frontiers | Research Topics

Co-use of medicines in surgery, 2nd edition

Edited by
Songwen Tan, Weiguo Li and Chuanpin Chen

Published in
Frontiers in Surgery

FRONTIERS EBOOK COPYRIGHT STATEMENT

The copyright in the text of individual articles in this ebook is the property of their respective authors or their respective institutions or funders. The copyright in graphics and images within each article may be subject to copyright of other parties. In both cases this is subject to a license granted to Frontiers.

The compilation of articles constituting this ebook is the property of Frontiers.

Each article within this ebook, and the ebook itself, are published under the most recent version of the Creative Commons CC-BY licence. The version current at the date of publication of this ebook is CC-BY 4.0. If the CC-BY licence is updated, the licence granted by Frontiers is automatically updated to the new version.

When exercising any right under the CC-BY licence, Frontiers must be attributed as the original publisher of the article or ebook, as applicable.

Authors have the responsibility of ensuring that any graphics or other materials which are the property of others may be included in the CC-BY licence, but this should be checked before relying on the CC-BY licence to reproduce those materials. Any copyright notices relating to those materials must be complied with.

Copyright and source acknowledgement notices may not be removed and must be displayed in any copy, derivative work or partial copy which includes the elements in question.

All copyright, and all rights therein, are protected by national and international copyright laws. The above represents a summary only. For further information please read Frontiers' Conditions for Website Use and Copyright Statement, and the applicable CC-BY licence.

ISSN 1664-8714
ISBN 978-2-8325-5876-8
DOI 10.3389/978-2-8325-5876-8

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Co-use of medicines in surgery, 2nd edition

Topic editors
Songwen Tan — Central South University, China
Weiguo Li — Harbin Institute of Technology, China
Chuanpin Chen — Central South University, China

Citation
Tan, S., Li, W., Chen, C., eds. (2025). *Co-use of medicines in surgery, 2nd edition*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5876-8

Publisher's note: This is a 2nd edition due to an article retraction.

Table of contents

frontiers in Surgery

ORIGINAL RESEARCH
published: 17 January 2022
doi: 10.3389/fsurg.2021.830571

Clinical Effectiveness of Pre-hospital and In-hospital Optimized Emergency Care Procedures for Patients With Acute Craniocerebral Trauma

Lili Wang[1] *and Rong Wu*[2]*

[1] *Department of Emergency, The Nanhua Affiliated Hospital, Hengyang Medical College, University of South China, Hengyang, China,* [2] *Department of Outpatients, The Nanhua Affiliated Hospital, Hengyang Medical College, University of South China, Hengyang, China*

Acute craniocerebral injury is a common traumatic disease in clinical practice, characterized by rapid changes in condition and a high rate of death and disability. Early and effective emergency care throughout the pre-hospital and in-hospital period is the key to reducing the rate of death and disability and promoting the recovery of patients. In this study, we conducted an observational study of 130 patients with acute craniocerebral injury admitted between May 2020 and May 2021. Patients were randomly divided into a regular group and an optimization group of 65 patients each, with patients in the regular group receiving the conventional emergency care model and patients in the optimization group receiving the pre-hospital and in-hospital optimal emergency care process for intervention. In this study, we observed and compared the time taken to arrive at the scene, assess the condition, attend to the patient and provide emergency care, the success rate of emergency care within 48 h, the interleukin-6 (IL-6), interleukin-8 (IL-8), and intercellular adhesion molecule-1 (ICAM-1) after admission and 1 day before discharge, the National Institute of Health Stroke Scale (NIHSS) and the Short Form 36-item Health Survey (SF-36) after resuscitation and 1 day before discharge, and the complications of infection, brain herniation, central hyperthermia, and electrolyte disturbances in both groups. We collected and statistically analyzed the recorded data. The results showed that the time taken to arrive at the consultation site, assess the condition, receive the consultation, provide first aid was significantly lower in the optimized group than in the regular group ($P < 0.05$); the success rate of treatment was significantly higher in the optimized group than in the regular group ($P < 0.05$). In both groups, IL-6, IL-8, and ICAM-1 decreased on the day before discharge compared with the day of rescue, with the levels of each index lower in the optimization group than in the regular group ($P < 0.05$); the NIHSS scores decreased and the SF-36 scores increased on the day before discharge compared with the successful rescue in both groups, with the NIHSS scores in the optimization group lower than in the regular group and the SF-36 scores higher than in the control group ($P < 0.05$). The overall complication rate in the optimization group was significantly lower than that in the regular group ($P < 0.05$).

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Wenjun Gu,
Shanghai Jiaotong University School of Medicine, China
Liang Hui,
Hainan General Hospital, China

****Correspondence:***
Rong Wu
240759384@qq.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *07 December 2021*
Accepted: *20 December 2021*
Published: *17 January 2022*

Citation:
Wang L and Wu R (2022) Clinical Effectiveness of Pre-hospital and In-hospital Optimized Emergency Care Procedures for Patients With Acute Craniocerebral Trauma. Front. Surg. 8:830571. doi: 10.3389/fsurg.2021.830571

This shows that optimizing pre-hospital and in-hospital emergency care procedures can significantly shorten the time to emergency care for patients with acute craniocerebral injury, increase the success rate, reduce inflammation, improve neurological function and quality of life, reduce the occurrence of complications, and improve patient prognosis.

Keywords: acute craniocerebral injury, pre-hospital and in-hospital full optimization, emergency care, inflammatory factors, quality of life

INTRODUCTION

Acute craniocerebral injuries are mainly caused by traffic accidents, accidental injuries and violence. With the contemporary development of industry, construction and transportation in China, the incidence of acute craniocerebral injury has increased significantly, and traumatic acute craniocerebral injury is the most common (1, 2). Epidemiological studies have shown that in recent years about 28.7% (about 370 million) of the population in China has been affected each year, and the incidence of acute craniocerebral injury has continued to increase, with heavy craniocerebral injury accounting for about 20% and death in nearly 10% of patients with the disease (3, 4). In acute craniocerebral injury, if the injury involves only the scalp and skull alone, the patient's prognosis is more likely to be good after aggressive treatment (5). In contrast, the condition of patients with brain injury is often complex and rapidly developing, and if the injury is not treated promptly and effectively, it often leads to more serious adverse consequences, threatening the life of the patient and causing injury-related death and permanent disability (6, 7).

The key to the treatment of acute craniocerebral injury is timing. Taking effective emergency measures as early as possible, making the chain of pre-hospital resuscitation, in-hospital emergency care, and surgical implementation more compact, with a clearer division of labor and more orderly steps, is the key to improving the effectiveness of emergency care (8, 9). The traditional emergency method for patients with acute severe craniocerebral injury is to consult and treat them in separate departments, which cannot achieve good articulation between various departments and delays the treatment time, which is not conducive to improving the survival rate of patients (10). Pre-hospital and in-hospital whole process optimization care further evolves on the traditional emergency mode, effectively perfecting the pre-hospital rescue network and trauma rescue mode, and making the whole emergency process procedural and standardized (11, 12). Currently this model of care has been widely used clinically in the emergency care of acute cerebral infarction (13), acute myocardial infarction (14) and other clinical emergencies, and good results have been achieved. In view of this, the present study applied the pre-hospital and in-hospital optimal nursing procedure to the emergency treatment of patients with acute craniocerebral injury, and used the emergency-related indexes, the success rate of treatment, the level of inflammatory factors in different periods, the neurological function and quality of life in different periods, and the occurrence of complications as the observation indexes to explore the effect of the pre-hospital and in-hospital optimal nursing procedure in the application of acute craniocerebral injury.

MATERIALS AND METHODS

Materials

One hundred and thirty cases of acute craniocerebral injury admitted to our hospital from May 2020 to May 2021 were selected as the study subjects. Patients were coded in order of admission for patients sorted from 1 to 130, and the enrolled patients were randomly divided into 65 cases each in the regular group and the optimized group according to the random number table method. Patients in the regular group received the conventional emergency care model and patients in the optimization group received the pre-hospital and in-hospital full optimization of emergency care procedures for intervention. General data such as age, gender, cause of injury, type of cranial injury and degree of injury [assessed according to the Glasgow Coma Scale (15), where 3–8 were classified as severe, 9–12 as moderate, and 13–15 as mild] were collected and compared between the two groups, and the differences were not statistically significant ($P > 0.05$, **Table 1**) and were comparable.

Inclusion Criteria

1. Age >18 years; 2. admission within 24 h of injury onset; 3. a clear history of trauma and a clear diagnosis of traumatic brain injury. 4. Patient and family understood the content of this study and voluntarily signed an informed consent form.

Exclusion Criteria

1. Patients who died in pre-hospital emergencies; 2. patients with other serious injuries in combination; 3. patients with previous neurological or limb movement dysfunction; 4. patients with a combined history of psychiatric disorders, hematological disorders and cancer in various organ systems. 5. Multiple trauma such as combined organ damage, fractures in other areas, severe shock, etc.

Care Methods

Patients in the regular group adopted the traditional emergency care model, as follows: after patients were transferred to the hospital by family members or lower hospitals, or by emergency vehicles, health care workers promptly assessed the patients' clinical symptoms, signs and past history to understand them. Patients were resuscitated according to the acute craniocerebral injury emergency procedures, including active management

TABLE 1 | Comparison of baseline demographic information for the regular group and optimization group.

Data		Regular group ($n = 65$)	Optimization group ($n = 65$)	χ^2 value	*P*-value
Gender (*n*, %)	Male	39 (60.00)	41 (63.08)	0.130	0.718
	Female	26 (40.00)	24 (36.92)		
Age (*n*, %)	18∼25 years	12 (18.46)	14 (21.54)	0.648	0.885
	25∼40 years	24 (36.93)	25 (38.46)		
	40∼55 years	18 (27.69)	18 (27.69)		
	55∼65 years	11 (16.92)	8 (12.31)		
Causes of injury (*n*, %)	Traffic accidents	27 (41.53)	25 (38.46)	0.301	0.960
	Drop	16 (24.62)	15 (23.08)		
	Hitting	15 (23.08)	17 (26.15)		
	Crush	7 (10.77)	8 (12.31)		
Degree of damage (*n*, %)	Mild	28 (43.08)	26 (40.00)	1.184	0.553
	Moderate	26 (40.00)	23 (35.38)		
	Severe	11 (16.92)	16 (24.62)		
Types (*n*, %)	Brain contusion and laceration	25 (38.46)	26 (40.00)	0.448	0.930
	Intracranial hematoma	20 (30.77)	18 (27.69)		
	Concussion	14 (21.54)	13 (20.00)		
	Skull base fracture	6 (9.23)	8 (12.31)		

of trauma, routine oxygenation, monitoring of signs, and symptomatic treatment, while the imaging department was contacted to improve imaging and assess the condition. Patients who required surgical treatment were treated preoperatively and finally admitted to the clinical operating theater or ward, and their families were contacted afterwards to educate them on the precautions to take in their daily self-care.

Patients in the optimization group adopted a pre-hospital and in-hospital whole process of optimizing emergency care, with the following details: 1. Construct a care pathway team consisting of senior emergency department nurses, emergency physicians and 3–4 paramedics. Develop optimal emergency care protocols throughout the process by searching the literature and seeking input from primary care providers. All members of the Emergency Department were trained by members of the team to regularly check and ensure that emergency equipment was in good standby condition. 2. Pre-departure optimization: the ambulance was dispatched within 3–5 min after receiving the call for dispatch. The experienced and professional ambulance driver will try to reach the scene of resuscitation in the shortest possible time according to the precise navigation system. The ambulance attendant keeps in touch with the patient's family or personnel at the scene by telephone to guide pre-hospital emergency care (16, 17). 3. On-site emergency optimization: On arrival, a brief assessment of the patient's condition was carried out and appropriate care measures were quickly developed and tailored to the patient's specific situation. Ensure that the head, trunk and limbs were at the same level during transport. 4. Optimization of transfer rescue: healthcare workers should maintain gentle movements during transport and monitor the patient's vital signs such as mental state, respiratory rate, and blood pressure in real time during transport. Communicate with the escort to understand the basic situation of the patient, as well as informing the escort of the treatment and care after admission. After a thorough assessment of the patient's condition, the hospital departments were contacted in a timely manner according to their specific conditions, and urged them to make various emergency preparations. 5. Optimization of in-hospital emergency care: patients were admitted to hospital and a simple and rapid initial judgement was made by the emergency physician, with nursing staff completing a series of procedures such as placement, administering oxygen, advising on intravenous circulation, retaining blood specimens, assisting with electrocardiography, and taking medical histories according to medical advice. The first aid measures were tailored to the patient's specific situation. If patients show symptoms such as headache, restlessness or high fever, the health care provider should analyse the cause of the symptoms and take different measures to treat them. Patients who required emergency surgery should be assisted in their preoperative preparation (18–20). 6. Optimize health education: After the completion of emergency treatment, nursing staff explained in detail to the patient's family about health knowledge such as nursing precautions and self-care capabilities, and instructed the family to help the patient carry out neurological function rehabilitation exercises and motor rehabilitation training.

Observation Indicators

Emergency Treatment Time

The indicators related to emergency care such as arrival time (the time between receiving the emergency call and the arrival of the emergency vehicle at the scene), assessment time (the time taken by the medical personnel to make a preliminary judgment on the patient's condition after reaching the emergency scene), receiving time (the time between arriving at the emergency scene and taking the patient to the hospital), emergency treatment time (the time between arriving at the emergency room of the emergency

department and the end of resuscitation) were counted and compared between the two groups.

Resuscitation Within 48 h

The success rate of emergency treatment within 48 h (21) was assessed in both groups, and the effect of treatment was classified into four grades: success, markedly effective, valid, and invalid, which was assessed according to the National Institute of Health Stroke Scale (NIHSS). Success was defined as patients with stable vital signs and complete resolution of clinical symptoms after resuscitation, with a reduction in NIHSS score of more than 90%. Markedly effective was defined as the patient's vital signs were stable after resuscitation, clinical symptoms were significantly improved and NIHSS scores were reduced by 51–90%. Valid means that the patient's vital signs were generally stable after resuscitation, and the patient's condition has improved, and the NIHSS score has been reduced by 21–50%. Invalid means that the patient's vital signs remained unstable after resuscitation, and his condition did not improve or even worsened, and the NIHSS score was reduced by no more than 20%. Resuscitation success rate = number of cases (success + markedly effective + valid)/total number of effective cases × 100%.

Serum Inflammatory Factor Levels

Five milliliter of fasting venous blood was collected from patients 1 day after admission and 1 day before discharge, and the supernatant was centrifuged at 3,000 r/min for 10 min and placed at −80°C for testing. The serum levels of inflammatory factors such as interleukin-6 (IL-6), interleukin-8 (IL-8), and intercellular adhesion molecule-1 (ICAM-1) were measured using an enzyme-linked immunoassay kit (ELISA) supplied by Wuhan Fien Biotechnology Co.

Neurological Function and Quality of Life

Patients were assessed on the NIHSS scale after resuscitation and 1 day before discharge, with a total score of 0–42, with higher scores indicating more severe neurological impairment. The Short Form 36-item Health Survey (SF-36) was used to assess the quality of life of the two groups of patients. The scale consists of eight components: physical function, physical function, physical pain, general health, vitality, social practice, emotional function, and mental health. The scale was scored on a scale of 0–100, with higher scores indicating better quality of life.

Complications

The occurrence of complications such as infection, brain herniation, central hyperthermia, and electrolyte disturbance were counted and compared between the two groups.

Statistical Methods

SPSS22.0 software was used for statistical analysis of the data, and Prism8.0 was used to draw the pictures. The measurement data conforming to normal distribution were expressed as mean ± standard deviation (mean ± SD), and t-test was performed for comparison between two groups; the count data were expressed as number of cases and composition ratio (n, %), and χ^2 test was used for comparison between groups. $P < 0.05$ indicated statistically significant difference.

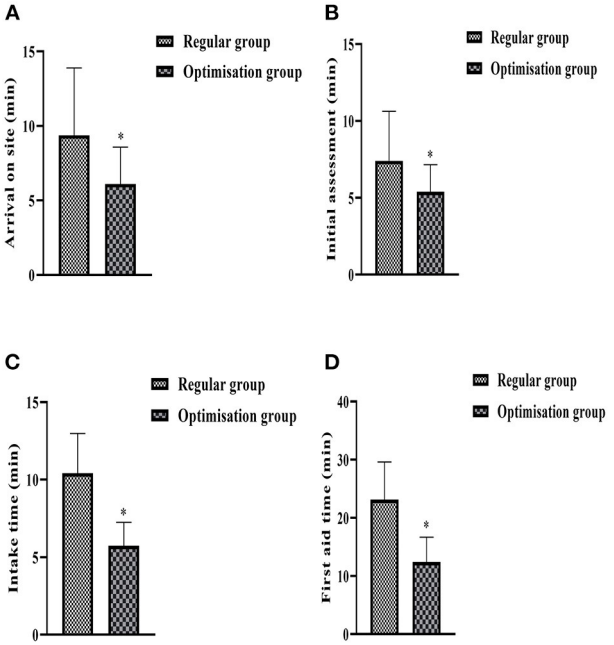


FIGURE 1 | Histogram comparing the indicators related to the two groups of first aid. **(A)** Shows the time spent on arrival at the scene. **(B)** Shows the time taken to assess the condition on site. **(C)** Shows the time taken to receive a consultation after admission to hospital. **(D)** Shows the time taken for first aid. *Denotes comparison with regular group, $P < 0.05$.

RESULTS

Comparison of First Aid-Related Indicators Between the Two Groups

The time spent on arrival at the scene, initial assessment, intake time and first aid in the two groups was counted, and the result of the comparison was that the time spent on arrival at the scene (**Figure 1A**), initial assessment (**Figure 1B**), intake time (**Figure 1C**), and first aid (**Figure 1D**) in the optimized group was lower than that in the regular group, and the difference was statistically significant ($P < 0.05$) (**Figure 1**).

Comparison of the Success Rate of First Aid Within 48 h Between the Two Groups

The first aid situation of the two groups within 48 h was counted. In the regular group, 20 cases were successfully treated, 14 cases were markedly effective, 19 cases were effective, 12 cases were ineffective, and 53 cases (81.54%) were successful in first aid. In the optimization group, 36 cases were successfully treated, 16 cases were markedly effective, 9 cases were effective, 4 cases were ineffective, and 61 cases (93.85%) were successful in first aid. The results of the comparison showed that the success rate of first aid in the optimization group was significantly higher than that of the regular group, and the difference was statistically significant ($P < 0.05$) (**Figure 2**).

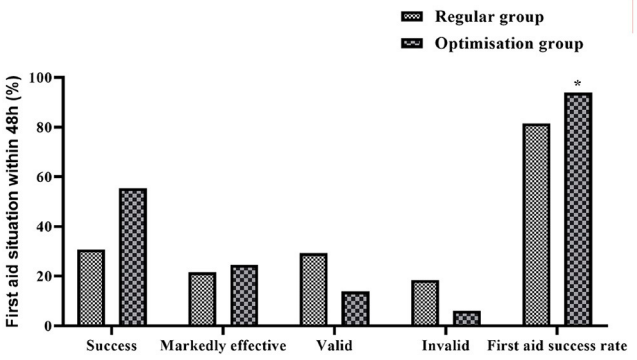


FIGURE 2 | Histogram comparing the success rate of resuscitation within 48 h between the two groups. *Denotes comparison with regular group, $P < 0.05$.

Comparison of Serum Inflammatory Factor Levels Between the Two Groups at Different Times

Blood specimens were collected from both groups on the first day after admission and the first day before discharge and their serum inflammatory factor levels were measured. The results showed that the differences in serum IL-6, IL-8, and ICAM-1 levels between the two groups on the first day after admission were not statistically significant ($P > 0.05$). The levels of IL-6 (**Figure 3A**), IL-8 (**Figure 3B**), and ICAM-1 (**Figure 3C**) in both groups 1 day before discharge were significantly lower than those on admission, with the optimized group being lower than the regular group, and the differences were all statistically significant ($P < 0.05$).

Comparison of Neurological Function and Quality of Life Scores Between the Two Groups at Different Times

The NIHSS and SF-36 were used to assess the neurological function and quality of life of the patients after resuscitation and before discharge, respectively. The difference between the NIHSS and SF-36 scores after resuscitation and awakening was not statistically significant ($P > 0.05$). In both groups, the pre-discharge NHISS scores (**Figure 4A**) decreased compared to the post-resuscitation awakening and the SF-36 scores (**Figure 4B**) increased compared to the post-resuscitation awakening, with the pre-discharge NHISS scores in the optimization group being lower than those in the regular group and the SF-36 scores being higher than those in the regular group, both with statistically significant differences ($P < 0.05$) (**Figure 4**).

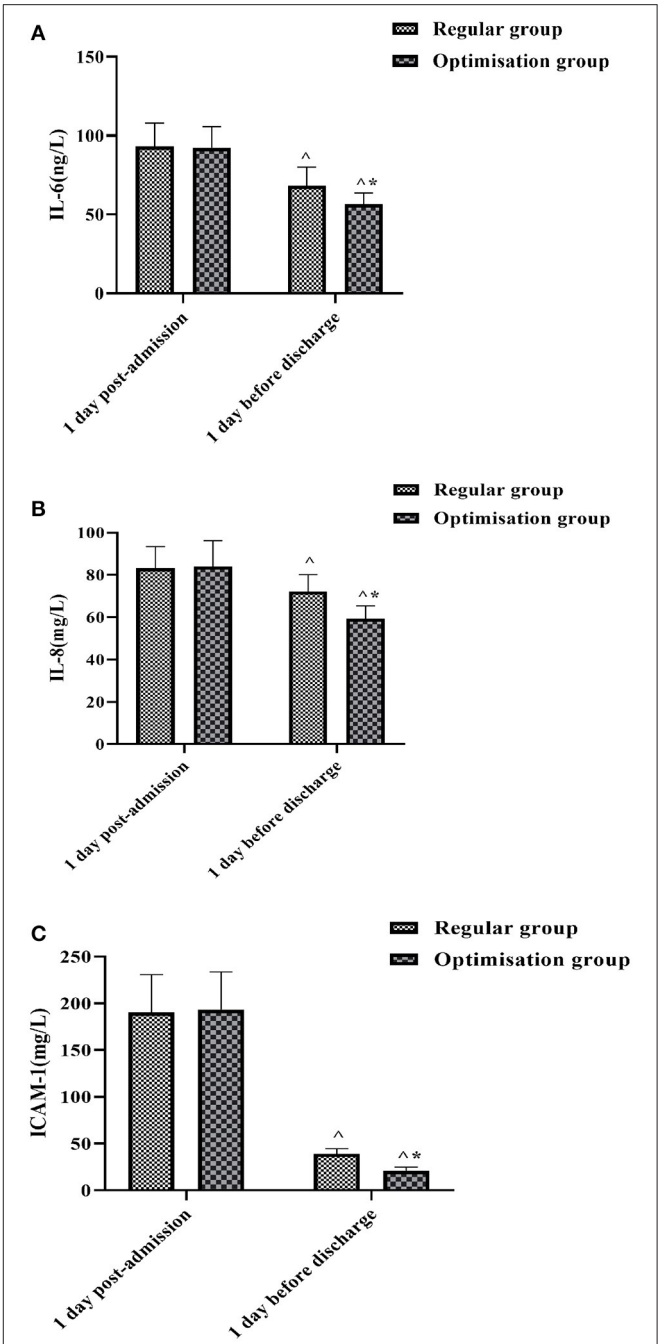


FIGURE 3 | Histogram comparing IL-6, IL-8, and ICAM-1 between the two groups at different times. **(A)** Shows the comparison of IL-6 levels. **(B)** Shows the comparison of IL-8 levels. **(C)** Shows the comparison of ICAM-1 levels. ^Denotes comparison with the same group 1 day post-admission, $P < 0.05$. *Denotes comparison with the regular group, $P < 0.05$.

Comparison of the Occurrence of Complications in the Two Groups

The overall incidence of complications such as infection (5 cases), brain herniation (2 cases), central hyperthermia (6 cases), and electrolyte disturbances (7 cases) in the regular group was 30.77% (20/65). In the optimization group, the overall complication rate of infection (1 case), brain herniation (1 case), central hyperthermia (3 cases), and electrolyte disturbances (3 cases) was 12.31% (20/65). The results of the comparison showed that the overall incidence of complications in the optimization group was lower than that in the regular group, with a statistically significant difference ($P < 0.05$) (**Figure 5**).

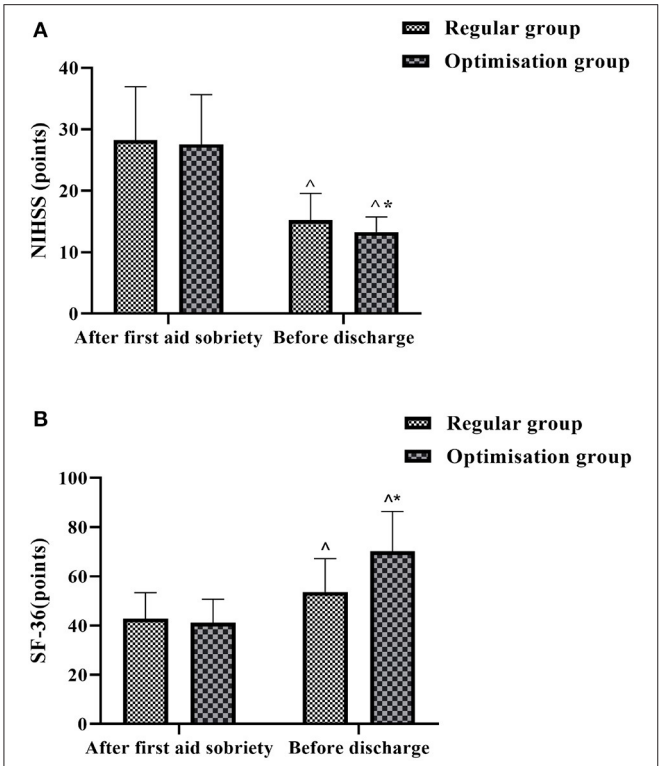


FIGURE 4 | Histogram comparing NIHSS scores and SF-36 scores between the two groups at different times. **(A)** Shows the comparison of NIHSS scores. **(B)** shows the comparison of SF-36 scores. ^Denotes comparison with the same group after first aid soberiety, $P < 0.05$. *Denotes comparison with the regular group, $P < 0.05$.

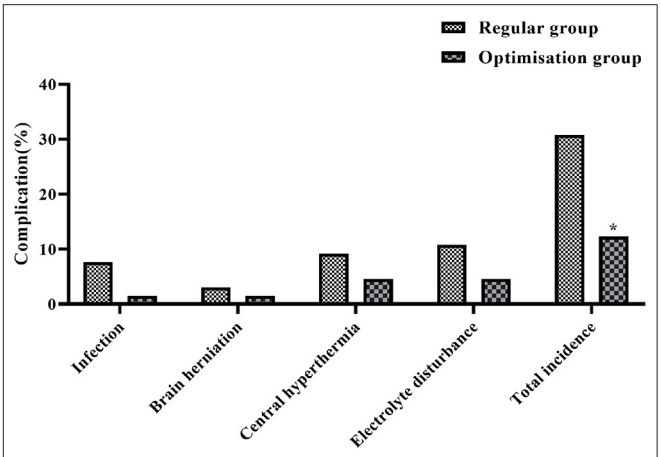


FIGURE 5 | Histogram comparing the incidence of complications between the two groups. *Denotes comparison with regular group, $P < 0.05$.

DISCUSSION

The Need for Timely Treatment of Acute Craniocerebral Injury

Acute craniocerebral injury is usually caused by traffic accidents or accidental injuries. After the injury, patients may experience a series of changes in the brain such as microcirculatory obstruction, cerebral blood circulation dysfunction, and rapid increase in intracerebral pressure, which may lead to respiratory depression, blurred consciousness, cerebral tissue ischemia, and electrolyte disorders if not rescued in time (22, 23). Patients with severe injuries are susceptible to rapid changes and complications that make treatment more difficult, so they need to be treated promptly and effectively after acute craniocerebral injury (24). The success of acute craniocerebral injury treatment is closely related to the severity of the injury, the timeliness of emergency care and treatment, the sophistication of the equipment and the professionalism of the medical staff (25). Pre-hospital and in-hospital optimal care is a combination of pre-hospital emergency care, emergency department resuscitation and in-hospital treatment, and is a nursing procedure developed on the basis of traditional emergency care (26). We have applied pre-hospital and in hospital optimized emergency care to the emergency treatment of patients with acute craniocerebral injury. By optimizing the five components of post-acute discharge, on-site emergency care, transport and rescue, in-hospital emergency care and health education, we have achieved a seamless integration of all components, greatly improving the efficiency of emergency care for patients with acute craniocerebral injury and gaining precious time for their treatment.

Impact of Pre-hospital and In-hospital Optimal Care Procedures Throughout on Indicators Related to Life-Saving Treatment

The results of the study showed that the time taken by the optimization group to reach the scene of the accident, the initial assessment of the condition, the time taken to receive treatment and in-hospital emergency care was significantly lower than that of the regular group ($p < 0.05$). Optimize every measure and operation from the dispatch of the ambulance to the completion of the handover, and regularly check the adequacy and perfection of the materials and equipment required for the first aid of acute brain injury, and dispatch the ambulance as soon as the call is received. When going to the accident site and transferring the ambulance, the most suitable route is chosen by combining the driver's rich experience and the accurate navigation system; before reaching the accident site, the medical personnel get in touch with the people around the patient, have a preliminary understanding of the basic situation of the patient through the telephone, and guide him/her to carry out scientific treatment, and at the same time prepare the relevant equipment and drugs according to the basic situation of the patient, and work out with the doctor The initial resuscitation plan, which can save a lot of time in on-site emergency care (27). On the way back to the hospital, the patient's vital signs are closely monitored, the patient's condition is comprehensively

assessed, and the corresponding department is contacted to prepare for consultation and consultation according to the trend of changes in the patient's condition, so that pre-hospital emergency and in-hospital emergency are seamlessly connected and the problem of pre-hospital and in-hospital disconnection is solved, which can also buy time for effective in-hospital emergency care for the patient (28). Therefore, the arrival time, initial assessment time, reception time and in-hospital resuscitation time of acute craniocerebral injury patients in the optimized group were all significantly reduced, suggesting that the optimized pre-hospital and in-hospital care procedure can effectively ensure that patients can be effectively treated within a shorter period of time and improve the efficiency of resuscitation.

Effect of Pre-hospital and In-hospital Optimized Care Procedures on the Success Rate of Emergency Care and Complication Rates

The results of the study showed that the success rate of emergency care within 48 h was significantly higher in the optimization group than in the regular group ($P < 0.05$). In the conventional resuscitation mode, although the rescue facilities are perfect and the medical level is better guaranteed, there is poor articulation between pre-hospital and in-hospital resuscitation, and in a panic emergency situation, the medical and nursing staff do not cooperate with the steps tightly enough, which easily causes the patient to miss the best time for rescue and treatment, resulting in deterioration of the condition and thus serious complications such as brain herniation and infection, and the patient's prognosis is poor (29). The pre-hospital and in-hospital optimization process saves a great deal of time through the optimization of post-visit trips, on-site emergencies, and transport ambulances, which is important for preserving the time window for acute craniocerebral injury treatment and can have a direct impact on the outcome of the patient. In addition, the overall complication rate in the optimization group was significantly lower than in the regular group ($P < 0.05$), which is probably due to the fact that the pre-hospital and in-hospital optimization process, with its scientific, effective, and timely care measures, has greatly improved the efficiency of the patients' follow-up treatment, thus reducing the possibility of complications.

Effect of Pre-hospital and In-hospital Optimal Care Procedures on Patients' Serum Inflammatory Factors, Neurological Function, and Quality of Life

The inflammatory response after acute craniocerebral injury is a major component of the pathological process and a leading factor in secondary brain injury after craniocerebral injury (30). After craniocerebral injury, the body can secrete and release large amounts of IL-6, IL-8, and other inflammatory factors into the blood, causing local vasodilatation and increased permeability, and extravasation into the plasma leading to the formation of tissue vasogenic oedema (31). In addition, ICAM-1 plays a role in the development of inflammation, and its elevated levels after craniocerebral injury can increase the adhesion of leukocytes to vascular endothelial cells, as well as directly into the surrounding tissue, exacerbating brain injury (32). By measuring serum IL-6, IL-8 and ICAM-1 levels in both groups at different times, we found that the levels of inflammatory factors in both groups decreased significantly in the first day before discharge compared with those at the time of admission, and the optimized group was lower than the regular group ($P < 0.05$). After timely and effective resuscitation, the patient's injuries and inflammatory response were well-controlled and the resuscitation was effective in helping to reduce the level of inflammatory factors. The results also showed that the NIHSS and SF-36 scores improved better in the optimization group than in the regular group, suggesting that the treatment of patients with acute craniocerebral injury under the guidance of a full optimized care program is more effective in improving neurological function and short-term quality of life.

CONCLUSION

It can be seen that optimizing the pre-hospital and in-hospital emergency care process can significantly shorten the time to emergency care, increase the success rate, reduce the inflammatory response, improve neurological function, and quality of life, reduce the occurrence of complications and improve the prognosis of the patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Nanhua Affiliated Hospital, Hengyang Medical College, University of South China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LW was mainly responsible for the formulation of the entire study and the inclusion of samples. RW was mainly responsible for the detection of results, statistics of data, and writing of the paper. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Claassen J, Doyle K, Matory A, Couch C, Burger KM, Velazquez A, et al. Detection of brain activation in unresponsive patients with acute brain injury. *N Engl J Med.* (2019) 380:2497–505. doi: 10.1056/NEJMoa1812757
2. Gregers MCT, Mikkelsen S, Lindvig KP, Brøchner AC. Ketamine as an anesthetic for patients with acute brain injury: a systematic review. *Neurocrit Care.* (2020) 33:273–82. doi: 10.1007/s12028-020-00975-7
3. Chen H, Song Z, Dennis JA. Hypertonic saline versus other intracranial pressure-lowering agents for people with acute traumatic brain injury. *Cochr Datab Syst Rev.* (2020) 1:1–57. doi: 10.1002/14651858.CD010904.pub3
4. Zhou Y, Yao Y, Sheng L, Zhang J, Zhang JH, Shao A. Osteopontin as a candidate of therapeutic application for the acute brain injury. *J Cell Mol Med.* (2020) 24:8918–29. doi: 10.1111/jcmm.15641
5. Murthy P, Zein H, Thomas S, Scott JN, Abou Mehrem A, Esser MJ, et al. Neuroprotection care bundle implementation to decrease acute brain injury in preterm infants. *Pediatr Neurol.* (2020) 110:42–8. doi: 10.1016/j.pediatrneurol.2020.04.016
6. Deng RM, Liu YC Li JQ, Xu JG, Chen G. The role of carbon dioxide in acute brain injury. *Med Gas Res.* (2020) 10:81–4. doi: 10.4103/2045-9912.285561
7. Caturegli G, Cho SM, White B, Chen LL. Acute brain injury in infant venoarterial extracorporeal membrane oxygenation: an autopsy study. *Pediatr Crit Care Med.* (2021) 22:297–302. doi: 10.1097/PCC.0000000000002573
8. Zimmerman A, Fox S, Griffin R, Nelp T, Thomaz EBAF, Mvungi M. An analysis of emergency care delays experienced by traumatic brain injury patients presenting to a regional referral hospital in a low-income country. *PLoS ONE.* (2020) 15:e0240528. doi: 10.1371/journal.pone.0240528
9. Reilly C, Zhang N, Babcock L, Wade SL, Rhine T. Emergency department care of young children at risk for traumatic brain injury: what are we doing and do parents understand? *Pediatr Emerg Care.* (2019) 35:468–73. doi: 10.1097/PEC.0000000000001042
10. Andersen SK, Hustveit R, Frøland E, Uleberg O, Krüger A, Klepstad P, et al. Improper monitoring and deviations from physiologic treatment goals in patients with brain injury in the early phases of emergency care. *J Clin Monit Comput.* (2021) 35:147–53. doi: 10.1007/s10877-019-00455-0
11. Li ZL, Jin P, Yuan HH, Xu JF, Chen YJ, Wang ZQ. Regional whole-course trauma care - experiences from a county-level hospital. *Chin J Traumatol.* (2018) 21:250–5. doi: 10.1016/j.cjtee.2018.08.001
12. Wu C, Wang Y. Application effect analysis of optimization of pediatric emergency nursing process in emergency treatment of children. *Minerva Med.* (2020). doi: 10.23736/S0026-4806.20.06679-3
13. Moreno-Carrillo A, Arenas LMÁ, Fonseca JA, Caicedo CA, Tovar SV, Muñoz-Velandia OM. Application of queuing theory to optimize the triage process in a tertiary emergency care ("ER") department. *J Emerg Trauma Shock.* (2019) 12:268–73. doi: 10.4103/JETS.JETS_42_19
14. Pendyal A, Rothenberg C, Scofi JE, Krumholz HM, Safdar B, Dreyer RP, et al. National trends in emergency department care processes for acute myocardial infarction in the United States, 2005 to 2015. *J Am Heart Assoc.* (2020) 9:1–10. doi: 10.1161/JAHA.120.017208
15. Enriquez CM, Chisholm KH, Madden LK, Krumholz HM, Safdar B, Dreyer RP, et al. Glasgow coma scale: generating clinical standards. *J Neurosci Nurs.* (2019) 51:142–6. doi: 10.1097/JNN.0000000000000448
16. Andersson SO, Lundberg L, Jonsson A, Tingström P, Abrandt Dahlgren M. Doctors' and nurses' perceptions of military pre-hospital emergency care - when training becomes reality. *Int Emerg Nurs.* (2017) 32:70–7. doi: 10.1016/j.ienj.2017.01.001
17. Scuffham PA, Moretto N, Krinks R, Burton P, Whitty JA, Wilson A, et al. Engaging the public in healthcare decision-making: results from a Citizens' Jury on emergency care services. *Emerg Med J.* (2016) 33:782–8. doi: 10.1136/emermed-2015-205663
18. Bin Zahid A, Hubbard ME, Dammavalam VM, Balser DY, Pierre G, Kim A, et al. Assessment of acute head injury in an emergency department population using sport concussion assessment tool - 3rd edition. *Appl Neuropsychol Adult.* (2018) 25:110–9. doi: 10.1080/23279095.2016.1248765
19. Benromano T, Defrin R, Ahn AH, Zhao J, Pick CG, Levy D. Mild closed head injury promotes a selective trigeminal hypernociception: implications for the acute emergence of post-traumatic headache. *Eur J Pain.* (2015) 19:621–8. doi: 10.1002/ejp.583
20. Karim N, Mumporeze L, Nsengimana VJP, Gray A, Kearney A, Aluisio AR, et al. Epidemiology of patients with head injury at a tertiary hospital in Rwanda. *West J Emerg Med.* (2021) 22:1374–8. doi: 10.5811/westjem.2021.4.50961
21. Chang R, Holcomb JB, Johansson PI, Pati S, Schreiber MA, Wade CE. Plasma resuscitation improved survival in a cecal ligation and puncture rat model of sepsis. *Shock.* (2018) 49:53–61. doi: 10.1097/SHK.0000000000000918
22. Lawati KA, Sharif S, Maqbali SA, Rimawi HA, Petrosoniak A, Belley-Cote EP, et al. Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials. *Intensive Care Med.* (2021) 47:14–27. doi: 10.1007/s00134-020-06279-w
23. Daly S, Thorpe M, Rockswold S, Hubbard M, Bergman T, Samadani U, et al. Hyperbaric oxygen therapy in the treatment of acute severe traumatic brain injury: a systematic review. *J Neurotrauma.* (2018) 35:623–9. doi: 10.1089/neu.2017.5225
24. Maegele M, Lefering R, Sakowitz O, Kopp MA, Schwab JM, Steudel WI, et al. The incidence and management of moderate to severe head injury. *Dtsch Arztebl Int.* (2019) 116:167–73. doi: 10.3238/arztebl.2019.0167
25. Wijdicks EFM. Recording neurogenic breathing patterns in acute brain injury. *Neurocrit Care.* (2021) 34:674–6. doi: 10.1007/s12028-020-00922-6
26. Oshida S, Komoribayashi N, Omama S, Mase T, Inoue Y, Ogasawara K. Severe traumatic brain injury due to repeated minor head injury while snowboarding: a report of two cases. *No Shinkei Geka.* (2020) 48:521–6. doi: 10.11477/mf.1436204222
27. Rastogi S. Coma with glasgow coma scale score 3 at admission following acute head injury: experiencing the complete recovery supported through ayurveda - a case report. *Complement Med Res.* (2019) 26:353–60. doi: 10.1159/000498912
28. Dingman AL, Stence NV, O'Neill BR, Sillau SH, Chapman KE. Seizure severity is correlated with severity of hypoxic-ischemic injury in abusive head trauma. *Pediatr Neurol.* (2018) 82:29–35. doi: 10.1016/j.pediatrneurol.2017.12.003
29. Mortimer DS, Berg W. Agitation in patients recovering from traumatic brain injury: nursing management. *J Neurosci Nurs.* (2017) 49:25–30. doi: 10.1097/JNN.0000000000000253
30. Dong X, Gao J, Zhang CY, Frank M, Wang Z. Neutrophil membrane-derived nanovesicles alleviate inflammation to protect mouse brain injury from ischemic stroke. *ACS Nano.* (2019) 13:1272–83. doi: 10.1021/acsnano.8b06572
31. Goetzl EJ, Peltz CB, Mustapic M, Kapogiannis D, Yaffe K. Neuron-derived plasma exosome proteins after remote traumatic brain injury. *J Neurotrauma.* (2020) 37:382–8. doi: 10.1089/neu.2019.6711
32. Lutton EM, Razmpour R, Andrews AM, Cannella LA, Son YJ, Shuvaev VV, et al. Acute administration of catalase targeted to ICAM-1 attenuates neuropathology in experimental traumatic brain injury. *Sci Rep.* (2017) 7:3846. doi: 10.1038/s41598-017-03309-4

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang and Wu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 24 January 2022
doi: 10.3389/fsurg.2021.826682

Risk Factors Analysis of Thoracic Trauma Complicated With Acute Respiratory Distress Syndrome and Observation of Curative Effect of Lung-Protective Ventilation

Xiaoyu Ma[1], *Zefang Dong*[1], *Yusuo Wang*[2], *Peidong Gu*[2], *Jinghua Fang*[2] *and Shaolin Gao*[1]*

[1] *Department of Thoracic Surgery, The Second Hospital of Hebei Medical University, Shijiazhuang, China,* [2] *Ningjin County Maternity and Childcare Hospital of Hebei Province Emergency Surgery, Xingtai, China*

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Fenglong Sun,
Capital University of Medical Sciences, China
Yang Liu,
The First Medical Center of Chinese PLA General Hospital, China

***Correspondence:**
Shaolin Gao
gaoshaolin1986@hb2h.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *01 December 2021*
Accepted: *14 December 2021*
Published: *24 January 2022*

Citation:
Ma X, Dong Z, Wang Y, Gu P, Fang J and Gao S (2022) Risk Factors Analysis of Thoracic Trauma Complicated With Acute Respiratory Distress Syndrome and Observation of Curative Effect of Lung-Protective Ventilation. Front. Surg. 8:826682. doi: 10.3389/fsurg.2021.826682

Purpose: To explore the risk factors of acute respiratory distress syndrome (ARDS) secondary to thoracic trauma and the therapeutic effect of protective lung ventilation in patients with acute respiratory distress syndrome complicated with thoracic trauma.

Methods: We collected 206 patients with thoracic trauma admitted to our hospital from September 2017 to March 2021, counted the incidence of ARDS and analyzed the risk factors of ARDS. To observe the clinical efficacy of the application of lung-protective ventilation therapy in patients with thoracic trauma combined with ARDS.

Results: Among 206 patients with thoracic trauma, there were 82 cases of combined ARDS, and its incidence was 39.81%. The 82 patients with ARDS were randomly divided into the control group and the observation group with 42 cases each, and different ventilation methods were used for treatment. The results showed that the mechanical ventilation time (MVT) was shorter in the observation group than in the control group, and the incidence of ventilator-associated lung injury (VALI) and case fatality rate (CFR) were lower than those in the control group ($P < 0.05$). Arterial partial pressure of oxygen ($Pa0_2$), arterial blood carbon dioxide partial pressure ($PaCO_2$), and Oxygenation index (arterial partial pressure of oxygen/Fraction of inspiration O_2, PaO_2/FiO_2) were significantly improved better in both groups after treatment; compared with the control group, patients in the observation group had higher Pa02 levels and lower $PaCO_2$ levels at 8 h and 24 h after ventilation ($P < 0.05$). Multivariate analysis revealed that blunt trauma, massive blood transfusion, procalcitonin (PCT) level, tumor necrosis factor-α (TNF-α) level, and acute physiology and chronic health score (APACHE II) were all risk factors for Thoracic trauma with ARDS.

Conclusion: Risk factors for the development of ARDS after thoracic trauma are blunt injuries, massive blood transfusion, high PCT and TNF-α levels, and high APACHE II scores, which can be given active interventions in the early stage of clinical practice to improve patient prognosis. The use of protective lung ventilation therapy can improve

the clinical outcome of patients with thoracic trauma combined with ARDS, which is important for improving the ventilation effect and respiratory function of patients.

Keywords: thoracic trauma, acute respiratory distress syndrome, risk factors, lung-protective ventilation, curative effect

INTRODUCTION

With the socio-economic development, the incidence of traumatic diseases is on a significant rise and the threat of trauma to human health is becoming more and more prominent. Trauma is now a global health problem and is one of the important causes of death in the young population (1). Thoracic trauma is a common site of involvement when the body is traumatized, and the lungs are the main organ involved in the early onset of severe thoracic trauma patients when they are admitted to the hospital (2). Acute respiratory distress syndrome (ARDS) is an acute diffuse lung injury that occurs within a short period of time and can cause severe hypoxemia leading to hypoxic damage to various organs throughout the body, and is the most common complication in patients with severe trauma (3). The current clinical treatment of severe thoracic trauma combined with acute respiratory distress syndrome mostly uses mechanical ventilation to ensure respiratory support. Therefore, reasonable and effective mechanical ventilation has an important impact on improving the treatment effect and reducing the mortality rate (4). Lung-protective ventilation therapy is a treatment with low tidal ventilation and permissive high carbon dioxide (CO_2) while meeting the patient's basic oxygenation, which can prevent pulmonary compression injury due to large tidal ventilation (5). Some studies (6, 7) have shown that the application of lun-protective ventilation therapy in the treatment of patients who have thoracic trauma combined with ARDS can achieve better therapeutic results.

Different from ARDS caused by infection, aspiration and other reasons, patients with ARDS secondary to trauma are usually younger, and effective interventions at an early stage of onset can lead to better outcomes and a good patient prognosis (8). Yet the difficulty in salvage lies in the early identification of severe trauma as secondary to ARDS, so screening for predictive risk factors to guide early clinical intervention is necessary (9). In this study, the basic data and pathophysiological characteristics of 206 patients with thoracic trauma treated in our hospital in the past 3 years were collected, and logistic regression models were used to analyze the risk factors for secondary ARDS after thoracic trauma. The clinical effects of different ventilation modalities in patients with ARDS combined with thoracic trauma were analyzed, aiming to provide a reference basis for clinical treatment.

INFORMATION AND METHODS

Case Sources and Basic Information

Total of 206 cases of thoracic trauma patients admitted to our hospital from September 2017 to March 2021 were selected as the study subjects. Eighty two patients with severe thoracic trauma combined with ARDS admitted during this period were taken as the main observation objects, and they were divided into 41 cases each in the observation group and the control group by double-blind randomization method, with the control group receiving conventional ventilation treatment and the patients in the observation group receiving lung-protective ventilation protocol. In the control group, 24 males and 17 females were aged from 34 to 60 years, with an average of (47.35 ± 10.37) years. In the observation group, 23 males and 18 females were aged from 35 to 59 years, with an average of (48.29 ± 10.52) years. The differences between the two groups in general data such as gender and age were not statistically significant ($P > 0.05$) and were comparable.

Diagnostic Criteria

Thoracic trauma (10): ① multiple rib fractures leading to a shackled chest; ② severe pulmonary contusion; ③ moderate or greater haemopneumothorax; ④ tracheobronchial rupture; ⑤ large vessel injury to the heart. The diagnosis can be made on the basis of one of the above.

The diagnosis of ARDS was made according to the Berlin-defined diagnostic criteria for ARDS (11): new onset of dyspnoea or worsening of pre-existing respiratory symptoms within 1 week of a known clinical diagnosis; and an arterial Oxygenation index (arterial partial pressure of oxygen/Fraction of inspiration O_2, PaO_2/FiO_2) <300.

Inclusion Criteria

① All patients met the diagnostic criteria for both thoracic trauma and ARDS and had an injury severity score (ISS) of ≥16, and the diagnosis was made by combining the patient's clinical symptoms, pulmonary infiltrative shadow, and oxygenation index; ② required mechanical ventilation; ③ age ≥ 18 years; ④ the only causative factor was trauma; ⑤ were admitted to the hospital within 24 h of the causative injury and were first seen in our hospital; ⑥ the patient's clinical information was complete and the patient or family had informed the study group and had signed the relevant consent form.

Exclusion Criteria

① patients with a long history of chronic lung disease; ② patients with a history of lung surgery; ③ those with autoimmune diseases; ④ those with infections; ⑤ those with ARDS due to non-traumatic causes or those who have been treated at other hospitals for a longer period of time and then transferred to our hospital; ⑥ those with active acute bleeding conditions.

METHODS

Treatment Method

First aid and basic treatment of trauma: Upon admission, the patient was thoroughly assessed and the management was tailored to the patient's individual circumstances. For patients with fractures, the ribs were first fixed with chest straps, and then internal fixation was performed after communication with the patient and family and obtaining consent. Patients with hemothorax were treated with thoracal closed drainage. For patients with shock, rehydration and blood transfusion were performed. For patients with inflammatory symptoms, corticosteroids were given to reduce tissue damage and improve microcirculation for 4–7 days and then reduced. Patients were given broad-spectrum antibiotics as necessary to prevent the development of infection. After emergency trauma management, all patients were orotracheally intubated or tracheotomized and connected to a ventilator for assisted breathing, with the control group on conventional ventilation and the observation group on lung protective ventilation.

The ventilator parameters for the conventional ventilation protocol were set as follows: positive end expiratory pressure (PEEP) of 3–10 cmH_2O, tidal volume (VT) of 10–15 mL/kg, respiratory rate of 15–18 breaths/min, inspiration-exhalation ratio (I:E) = 1:1.5–2.0, frequency was 12–16 breaths/min.

Lung-protective ventilation protocol: low tidal volume ventilation combined with optimal PEEP, and low tidal volume sequential pulmonary resuscitation (RM) when the abdominal pressure (IAP) has basically returned to normal (grade I abdominal hypertension, IAP $\leq$ 15 mmHg). The parameters were set as PEEP of 5–15 cmH_2O, I:E = 1:1.0–2.0; VT of 6–8 mL/kg, and frequency of 18–20 breaths/min.

Observed Indicators

The treatment status such as mechanical ventilation time (MVT), ventilator-associated lung injury (VALI) incidence and case fatality rate (CFR) were collected from both groups. The blood gas analysis indexes such as PaO_2, arterial blood carbon dioxide partial pressure ($PaCO_2$) and PaO_2/FiO_2 were observed and recorded at different times before and after treatment.

The gender, age, body mass index (BMI), causes of trauma, nature of injury, massive blood transfusion, acute physiology and chronic health score (APACHE II), ISS Score were collected from 206 patients with thoracic trauma. In addition, the following index were used: underlying disease, history of long-term smoking, history of alcohol abuse, serum C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6) and tumor

TABLE 1 | Univariate analysis of thoracic trauma combined with ARDS.

Influencing factors		Merged ARDS (n = 82)	Unconsolidated ARDS (n = 124)	t value or χ^2 value	P-value
Gender (n, %)	Male	47 (57.32)	69 (55.65)	0.056	0.813
	Female	35 (42.68)	55 (44.35)		
Age (years, Mean ± SD)		47.93 ± 10.45	45.69 ± 8.76	1.588	0.114
BMI (kg/m^2, Mean ± SD)		25.26 ± 4.26	25.19 ± 4.03	0.119	0.905
Causes of trauma (n, %)	Traffic Accidents	31 (37.80)	43 (34.68)	1.026	0.906
	Sharp objects	15 (18.29)	26 (20.97)		
	Falling	19 (23.17)	25 (20.16)		
	Crushing	12 (14.63)	19 (15.32)		
	Explosion	5 (6.10)	11 (8.87)		
Alcoholism (n, %)	Yes	20 (24.39)	38 (30.65)	0.955	0.329
	No	62 (75.61)	86 (69.35)		
Long-term smoking (n,%)	Yes	40 (48.78)	42 (33.87)	4.579	0.032
	No	42 (51.22)	82 (66.13)		
Underlying disease (n, %)	Diabetes	22 (26.83)	35 (28.23)	0.048	0.826
	High blood pressure	17 (20.73)	28 (22.58)	0.099	0.753
	Coronary heart disease	11 (13.41)	25 (20.16)	1.556	0.212
Nature of injury (n, %)	Blunt injury	57 (69.51)	44 (35.48)	22.870	<0.001
	Penetrating injury	25 (30.49)	80 (64.52)		
Massive blood transfusion (n, %)	Yes	37 (45.12)	32 (25.81)	8.267	0.004
	No	45 (54.88)	92 (74.19)		
APACHE II score (points, Mean ± SD)		22.26 ± 3.02	20.13 ± 2.41	5.607	<0.001
ISS score (points, Mean ± SD)		21.74 ± 3.25	20.86 ± 2.98	2.001	0.047
CRP (mg/L, Mean ± SD)		153.32 ± 31.25	138.59 ± 22.28	3.948	<0.001
PCT ($\times 10^9$/L, Mean ± SD)		28.47 ± 5.96	16.16 ± 2.04	13.572	<0.001
IL-6 (ng/L, Mean ± SD)		36.59 ± 11.04	27.52 ± 8.38	6.690	<0.001
TNF-α (ng/L, Mean ± SD)		46.74 ± 12.25	36.19 ± 11.77	6.196	<0.001

necrosis factor-alpha (TNF-α) levels within 1 week of admission. We compared the differences in the above indicators between patients who had a combined ARDS and those who did not have a combined ARDS in thoracic trauma, and used logistic regression to analyze the risk factors for combined ARDS in patients with thoracic trauma.

Statistical Methods

SPSS 22.0 software was used for data processing, and the measurement data were expressed as mean ± standard deviation (Mean ± SD), the *t*-test was used for two-by-two comparisons. The count data were expressed as (*n*, %) and the chi-square (χ^2) test was used. Logistic regression model was used for multi-factor analysis of thoracic trauma combined with ARDS. $P < 0.05$ was considered as a statistically significant difference.

RESULTS

Univariate Analysis of Thoracic Trauma in Combination With ARDS

Eventually, statistics revealed that 82 of 206 patients with thoracic trauma had combined ARDS, with an incidence of 39.81%; 124 patients without combined ARDS (60.29%). The basic data of patients with thoracic trauma in different conditions were analyzed, and the results showed that there were differences between patients with combined ARDS and those without combined ARDS in long-term smoking, nature of injury, massive blood transfusion, APACHE II score, ISS score, CRP, PCT, IL-6, TNF-α, etc. ($P < 0.05$). There were no differences in gender, age, BMI, causes of trauma, alcoholism and underlying diseases were not different ($P > 0.05$) (**Table 1**). This suggests that long-term smoking, blunt injuries, massive blood transfusion, high APACHE II, ISS score, high CRP, PCT, IL-6, and TNF-α levels may be associated in patients with thoracic trauma secondary to ARDS.

TABLE 2 | Assignment for multivariate analysis of factors.

Factors	Assignment
Blunt injury	Yes = 0, No = 1
Massive blood transfusion	Yes = 0, No = 1
APACHE II score	>25 = 0, 15–25 = 1, <15 = 2
PCT	>30 = 0, 15–30 = 1,<15 = 2
TNF-α	>60 = 0, 40–60 = 1, 20∼40 = 2,<20 = 3

Multi-Factor Analysis of Thoracic Trauma Combined With ARDS

Whether thoracic trauma patients had combined ARDS was used as the dependent variable (yes = 1, no = 0), and the relevant factors with statistically significant differences in the univariate analysis were used as independent variables for multifactor logistic regression analysis (Multi-factor assignments were shown in **Table 2**), which showed that blunt injury, massive blood transfusion, APACHE II score, PCT level, and TNF-α level were all independent risk factors affecting thoracic trauma patients with independent risk factors for secondary ARDS in patients with thoracic trauma ($P < 0.05$, **Table 3**).

Comparison of Clinical Efficacy

After different ventilation treatments in the two groups, the time to MVT, incidence of VALI and CFR were (10.26 ± 3.23) days, 26.83% (11/41) and 4.88% (2/41) in the control group, respectively; and (6.95 ± 2.51) days, 9.76% (4/41) and 12.20% (5/41) in the observation group, respectively. After analysis, the results showed that the MVT time in the observation group was shorter than that in the control group, and the incidence of VALI was lower than that in the control group ($P < 0.05$); the CFR in the observation group was slightly lower than that in the control group, although the difference between the two groups was not statistically significant ($P > 0.05$) (**Figure 1**).

Comparison of Blood Gas Analysis and Oxygenation Index Between the Two Groups Before and After Treatment

Comparison of the blood gas analysis and oxygenation index data collected from the two groups before treatment and at different times after ventilation showed no statistically significant differences in PaO_2, $PaCO_2$ and PaO_2/FiO_2 between the two groups before treatment ($P > 0.05$). PaO_2, $PaCO_2$ and PaO_2/FiO_2 at 8 h and 24 h after ventilation were higher than those before treatment in both groups, and the levels of PaO_2 and $PaCO_2$ detected at the same time points after treatment were significantly higher in the observation group than in the control group ($P < 0.05$); the difference in PaO_2/FiO_2 between the two groups at different time points after ventilation was not statistically significant ($P > 0.05$) (**Figure 2**).

TABLE 3 | Multifactorial analysis of ARDS in combination with thoracic trauma.

Influencing factors	*B*	*SE*	*Wald*χ^2	OR value	95%CI	*P*-value
Blunt injury	0.937	0.322	6.012	2.552	1.358–4.798	0.013
Massive blood transfusion	1.426	0.922	9.343	4.162	1.631–10.622	0.003
APACHE II score	0.712	0.250	11.324	2.038	1.249–3.327	0.001
PCT	0.878	0.305	6.352	2.406	1.323–4.375	0.017
TNF-α	1.254	0.530	5.235	3.504	1.240–9.903	0.031

Note: B is the regression coefficient, SE is the standard error, Wald is the test statistic, OR is the dominance ratio, and 95% CI is the 95% confidence interval.

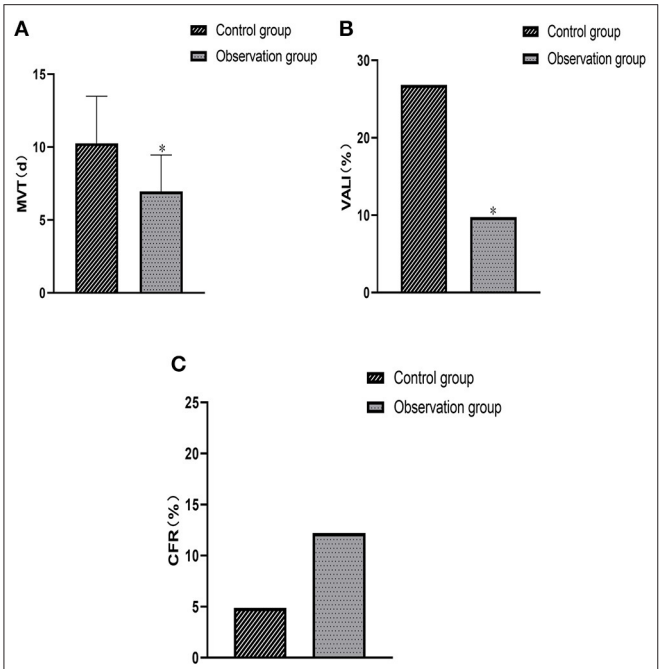


FIGURE 1 | Comparison of clinical efficacy between the two groups. **(A)** Comparison of average MVT. **(B)** Comparison of the occurrence of VALI. **(C)** Comparison of CFR. Compared with the control group, $^{*}P < 0.05$.

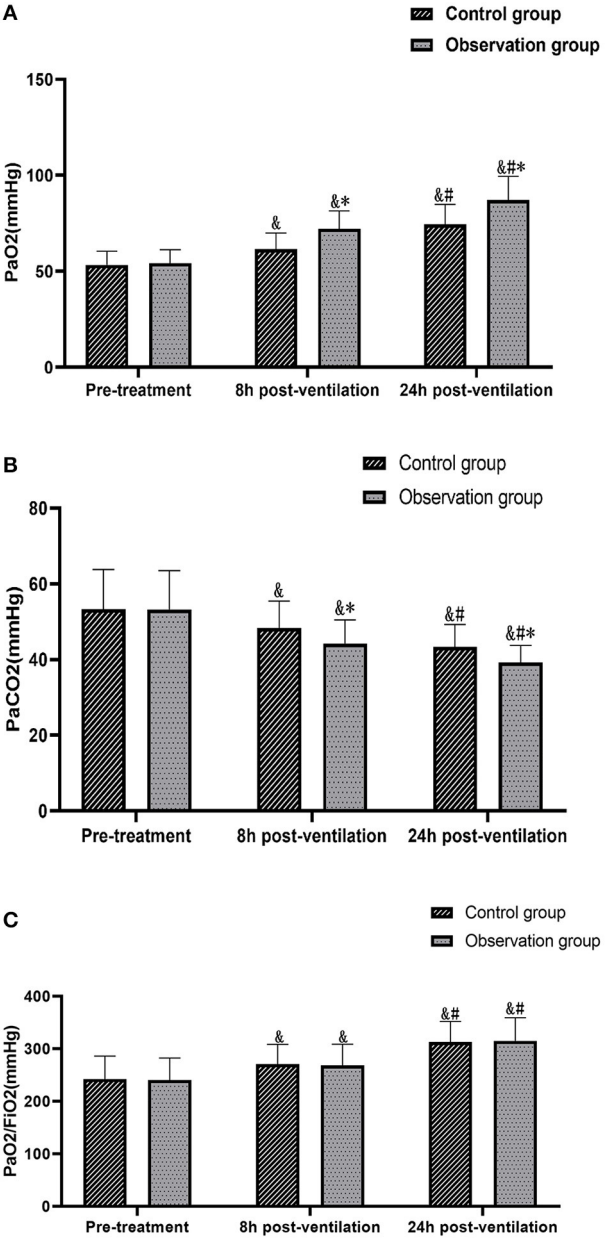


FIGURE 2 | Comparison of the changes in blood gas analysis values and oxygenation index between the two groups at different times. **(A)** Comparison of PaO_2. **(B)** Comparison of $PaCO_2$. **(C)** Comparison of $PaCO_2/FiO_2$. Compared with the same group pre-treatment, $^{\&}P < 0.05$. Compared with the same group 8 h post-ventilation, $^{\#}P < 0.05$. Comparison with control group over the same period, $^{*}P<0.05$.

DISCUSSION

Severe trauma is always a major problem in clinical treatment, among which the chest is a common site of trauma. Severe trauma to the patient's chest from multiple causes can often cause direct damage to the lungs, and if the trauma does not receive timely and effective intervention, the patient's condition can further develop into acute hypoxic respiratory failure, shock, and other symptoms, eventually leading to the development of ARDS (12, 13). However, the early recognition rate of severe thoracic trauma combined with ARDS is currently not high in clinical practice, so there is an urgent need to screen for independent risk factors for thoracic trauma combined with ARDS to guide early recognition and effective interventions (14, 15).

The results of this study showed that blunt injuries, massive blood transfusion, and APACHE II score were all independent risk factors for combined ARDS in patients with thoracic trauma and had some predictive value for ARDS secondary to thoracic trauma. Blunt injuries represent a significant proportion of traumatic injuries, and some studies (16) have pointed out their relationship with the development of ARDS. When a blunt blow occurs in the chest, the strong external force can cause rib fractures that can damage the integrity of the thorax or even produce a flail chest, and is often accompanied by hemothorax and pneumothorax at an early stage, leading to respiratory and circulatory dysfunction and then develop progressive dyspnea and refractory hypoxemia (17, 18). The infusion of a large number of blood products can induce inflammatory cells to activate in the lungs and secrete more inflammatory mediators, leading to capillary leakage and lung injury which in turn leads to ARDS (19). The APACHE II scoring system is used to evaluate the patient's condition based on the patient's vital signs and biochemical indicators, and an excessively high APACHE II score within 24 h of admission usually indicates that the patient's respiratory function is already significantly impaired (20). Moreover, the damage of trauma is mostly progressive, especially

in patients with thoracic trauma there are mostly pulmonary contusions, which are accompanied by a gradual increase in exudation and a further decrease in pulmonary ventilation aggravating hypoxemia, leading to the rapid development of ARDS (21). The results also showed that inflammatory cells such as PCT and TNF-α were also independent risk factors for ARDS secondary to thoracic trauma. To analyze the reasons for this, vascular endothelial damage after severe thoracic trauma can cause a large release of thrombomodulin (TM) and participate in regulating the coagulation process of the body, leading to microthrombus formation in the lung, microcirculatory blockage and structural damage, inducing pulmonary capillary spasm and increased permeability, activating inflammatory cells, and thus inducing the development of ARDS (22).

The results of this study showed that lung-protective ventilation therapy was more advantageous in improving oxygenation indices and protecting lung function in patients suffering from thoracic trauma combined with ARDS, and was able to reduce the duration of mechanical ventilation and the incidence of VALI in patients with a very low morbidity and mortality rate. At the present stage, ventilator-assisted ventilation is often used to treat patients with Thoracic trauma combined with ARDS on the basis of symptomatic treatment, which can precisely control oxygen therapy to avoid ventilator fatigue and obtain satisfactory treatment results (23). For the traditional conventional ventilation in clinical practice, patients are subjected to high airway pressure due to the large ventilation volume, which predisposes them to lung air pressure injury and thus has a serious impact on their prognosis. Lung-protective ventilation treatment can be used clinically according to the patient's specific situation, and this ventilation method with a lower tidal volume of 6–8 ml/kg and optimal PEEP can avoid overinflation and expansion of lung tissue, shorten expiratory time, ensure adequate ventilation, and help reduce the incidence of VALI (24).

Inconclusion, blunt injury, massive blood transfusion, APACHE II score, PCT, and TNF-α level are all risk factors for the occurrence of Thoracic trauma combined with ARDS, and early identification of these high-risk factors to guide clinical adoption of anticipatory treatment measures is expected to reduce the incidence of ARDS combined with Thoracic trauma. Lung-protective ventilation therapy is important to improve the ventilation effect of patients, reduce the occurrence of VALI and improve respiratory function.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of The Second Hospital of Hebei Medical University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

XM, ZD, YW, PG, and JF: collected the clinical datas, analyzed, and counted the datas. XM: wrote the manuscript. SG: modified the language and he is the Corresponding author. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Li L, Liang J, Fu H. An update on the association between traumatic brain injury and Alzheimer's disease: focus on tau pathology and synaptic dysfunction. *Neurosci Biobehav Rev.* (2021) 120:372–86. doi: 10.1016/j.neubiorev.2020.10.020
2. Dogrul BN, Kiliccalan I, Asci ES, Peker SC. Blunt trauma related chest wall and pulmonary injuries: an overview. *Chin J Traumatol.* (2020) 23:125–38. doi: 10.1016/j.cjtee.2020.04.003
3. Thompson BT, Chambers RC, Liu KD. Acute Respiratory Distress Syndrome. *N Engl J Med.* (2017) 377:562–72. doi: 10.1056/NEJMra1608077
4. Bertoni M, Spadaro S, Goligher EC. Monitoring patient respiratory effort during mechanical ventilation: lung and diaphragm-protective ventilation. *Crit Care.* (2020) 24:106. doi: 10.1186/s13054-020-2777-y
5. Abrams D, Schmidt M, Pham T, Beitler JR, Fan E, Goligher EC, et al. Mechanical ventilation for acute respiratory distress syndrome during extracorporeal life support. *Res Pract Am J Respir Crit Care Med.* (2020) 201:514–25. doi: 10.1164/rccm.201907-1283CI
6. Guérin C, Papazian L, Reignier J, Ayzac L, Loundou A, Forel JM. investigators of the Acurasys and Proseva trials. Effect of driving pressure on mortality in ARDS patients during lung protective mechanical ventilation in two randomized controlled trials. *Crit Care.* (2016) 20:384. doi: 10.1186/s13054-016-1556-2
7. O'Gara B, Talmor D. Perioperative lung protective ventilation. *BMJ.* (2018) 362:k3030. doi: 10.1136/bmj.k3030
8. Jabaudon M, Blondonnet R, Constantin JM, ARDS. in patients with chest trauma: better safe than sorry. *Anaesth Crit Care Pain Med.* (2019) 38:221–2. doi: 10.1016/j.accpm.2019.04.006
9. de Roulet A, Burke RV, Lim J, Papillon S, Bliss DW, Ford HR, et al. Pediatric trauma-associated acute respiratory distress syndrome: Incidence, risk factors, and outcomes. *J Pediatr Surg.* (2019) 54:1405–10. doi: 10.1016/j.jpedsurg.2018.07.005
10. Baker SP, O'Neill B, Haddon W, Long WB. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma.* (1974) 14:187–96. doi: 10.1097/00005373-197403000-00001
11. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA.* (2012) 307:2526–33. doi: 10.1001/jama.2012.5669
12. Fu PK, Wu CL, Tsai TH, Hsieh CL. Anti-inflammatory and anticoagulative effects of paeonol on LPS-induced acute lung injury in rats. *Evid Based Complement Alternat Med.* (2012) 2012:837513. doi: 10.1155/2012/837513
13. Ramin S, Charbit J, Jaber S, Capdevila X. Acute respiratory distress syndrome after chest trauma: Epidemiology, specific physiopathology and ventilation strategies. *Anaesth Crit Care Pain Med.* (2019) 38:265–76. doi: 10.1016/j.accpm.2018.09.009
14. Winkelmann M, Clausen JD, Graeff P, Schröter C, Zeckey C, Weber-Spickschen S, et al. Impact of accidental hypothermia on pulmonary complications in multiply injured patients with blunt chest trauma—a matched-pair analysis. *In Vivo.* (2019) 33:1539–45. doi: 10.21873/invivo.11634

15. Daurat A, Millet I, Roustan JP, Maury C, Taourel P, Jaber S, et al. Thoracic Trauma Severity score on admission allows to determine the risk of delayed ARDS in trauma patients with pulmonary contusion. *Injury.* (2016) 47:147–53. doi: 10.1016/j.injury.2015.08.031
16. Mommsen P, Zeckey C, Andruszkow H, Weidemann J, Frömke C, Puljic P, et al. Comparison of different thoracic trauma scoring systems in regards to prediction of post-traumatic complications and outcome in blunt chest trauma. *J Surg Res.* (2012) 176:239–47. doi: 10.1016/j.jss.2011.09.018
17. Moazed F, Hendrickson C, Conroy A, Kornblith LZ, Benowitz NL, Delucchi K, et al. Cigarette smoking and ARDS after blunt trauma: the influence of changing smoking patterns and resuscitation practices. *Chest.* (2020) 158:1490–8. doi: 10.1016/j.chest.2020.05.603
18. Kalbitz M, Karbach M, Braumueller S, Kellermann P, Gebhard F, Huber-Lang M, et al. Role of complement C5 in experimental blunt chest trauma-induced septic acute lung injury (ALI). *PLoS ONE.* (2016) 11:e0159417. doi: 10.1371/journal.pone.0159417
19. Robinson BRH, Cohen MJ, Holcomb JB, Pritts TA, Gomaa D, Fox EE, et al. PROPPR Study Group. Risk factors for the development of acute respiratory distress syndrome following hemorrhage. *Shock.* (2018) 50:258–64. doi: 10.1097/SHK.0000000000001073
20. Navarrete-Navarro P, Rivera-Fernández R, Rincón-Ferrari MD, García-Delgado M, Muñoz A, Jiménez JM, et al. GITAN multicenter project. Early markers of acute respiratory distress syndrome development in severe trauma patients. *J Crit Care.* (2006) 21:253–8. doi: 10.1016/j.jcrc.2005.12.012
21. Watkins TR, Nathens AB, Cooke CR, Psaty BM, Maier RV, Cuschieri J, et al. Acute respiratory distress syndrome after trauma: development and validation of a predictive model. *Crit Care Med.* (2012) 40:2295–303. doi: 10.1097/CCM.0b013e3182544f6a
22. Ehrnthaller C, Flierl M, Perl M, Denk S, Unnewehr H, Ward PA, et al. The molecular fingerprint of lung inflammation after blunt chest trauma. *Eur J Med Res.* (2015) 20:70. doi: 10.1186/s40001-015-0164-y
23. Qi Y. Clinical study on VATS combined mechanical ventilation treatment of ARDS secondary to severe chest trauma. *Exp Ther Med.* (2016) 12:1034–8. doi: 10.3892/etm.2016.3355
24. Dianti J, Matelski J, Tisminetzky M, Walkey AJ, Munshi L, Del Sorbo L, et al. Comparing the effects of tidal volume, driving pressure, and mechanical power on mortality in trials of lung-protective mechanical ventilation. *Respir Care.* (2021) 66:221–7. doi: 10.4187/respcare.07876

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Ma, Dong, Wang, Gu, Fang and Gao. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 25 January 2022
doi: 10.3389/fsurg.2021.832646

Effect of Dexmedetomidine-Assisted Intravenous Inhalation Combined Anesthesia on Cerebral Oxygen Metabolism and Serum Th1/Th2 Level in Elderly Colorectal Cancer Patients

Yixun Tang[1,2,3], *Jitong Liu*[1,3], *Xiaoling Huang*[1,3], *Huijuan Ding*[1,3], *Suhong Tan*[1,3] *and Yimin Zhu*[2,4*]

[1] *Department of Anesthesiology, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, China,* [2] *School of Life Sciences, Hunan Normal University, Changsha, China,* [3] *Clinical Research Center for Anesthesiology of ERAS in Hunan Province, Changsha, China,* [4] *Hunan Provincial Key Laboratory of Emergency and Critical Care Metabonomics, Institute of Emergency Medicine, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, China*

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Jianhua Xiao,
University of South China, China
Wenjie Song,
Fourth Military Medical University, China

***Correspondence:**
Yimin Zhu
zhuyimin1964@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *10 December 2021*
Accepted: *24 December 2021*
Published: *25 January 2022*

Citation:
Tang Y, Liu J, Huang X, Ding H, Tan S and Zhu Y (2022) Effect of Dexmedetomidine-Assisted Intravenous Inhalation Combined Anesthesia on Cerebral Oxygen Metabolism and Serum Th1/Th2 Level in Elderly Colorectal Cancer Patients. Front. Surg. 8:832646. doi: 10.3389/fsurg.2021.832646

Objective: To observe the effect of dexmedetomidine-assisted intravenous inhalation combined anesthesia on cerebral oxygen metabolism and serum Th1/Th2 levels in elderly patients with colorectal cancer.

Method: From April 2018 to May 2020,100 elderly patients undergoing elective laparoscopic radical resection of colorectal cancer were prospectively selected and randomly divided into observation group and control group. Before induction of anesthesia, the loading dose of dexmedetomidine was given at 0.5 μg/kg, and the infusion time was 15 min. After tracheal intubation, 0.4 μg/kg/h dexmedetomidine was continuously pumped, and the infusion was stopped 40 min before the end of the operation. In the control group, the same amount of 0.9% sodium chloride was injected intravenously in the same way. 30 min before induction of anesthesia (T_0), immediately before induction of anesthesia (T_1), immediately after tracheal intubation (T_2), 40 min before operation (T_3), and immediately after operation (T_4), record the blood oxygen content of the artery and internal jugular vein Difference ($D(a\text{-}jv)O_2$), brain oxygen uptake rate (COER%), brain oxygen saturation (rSO_2) mean. VAS scale, Ramsay scale, MoCA scale were taken at 6, 12, 24, and 48 h postoperatively to evaluate analgesia, sedation, and cognitive function. And monitor the levels of interferon-γ (IFN-γ), interleukin-4 (IL-4), myelin basic protein (MBP), neuron-specific enolase (NSE) and S100β. The occurrence of restlessness and adverse reactions during the recovery period of the two groups were compared.

Result: The levels of $D(a\text{-}jv)O_2$, COER%, and rSO_2 in the control group and observation group were higher than the preoperative basic values at T2, T3, and T4 ($P < 0.05$); The levels of $D(a\text{-}jv)O_2$, COER%, and rSO_2 in the observation group were lower than those

in the control group at T_2, T_3, and T_4 ($P < 0.05$). The VAS score and Ramsay score of the observation group were lower than those of the control group at 6, 12, 24, and 48 h after surgery, while the MoCA score was higher than that of the control group ($P < 0.05$). In addition, the serum IFN-γ, MBP, NSE and S100β levels of the observation group were lower than those of the control group ($P < 0.05$), and the ratio of IFN-γ/IL-4 was higher than that of the control group ($P < 0.05$). The overall incidence of adverse reactions in the observation group was lower than that in the control group [32.0% (16/50) vs. 12.0% (6/50), $P < 0.05$].

Conclusion: Dexmedetomidine-assisted combined intravenous and inhalation anesthesia is beneficial to reduce perioperative cerebral oxygen metabolism and improve postoperative immunosuppression in elderly patients with colorectal cancer. It has a certain protective effect on nerve injury after operation, thus improving the cognitive function of patients and reducing the occurrence of adverse reactions.

Keywords: elderly patients with colorectal cancer, dexmedetomidine, cerebral oxygen metabolism, cognitive impairment, immune function

INTRODUCTION

Colorectal cancer is one of the high-risk gastrointestinal malignant tumors, and more than 50% of patients die, ranking the third in malignant tumor deaths. Laparoscopic radical surgery is the main treatment of colorectal cancer, which greatly reduces the surgical trauma and ensures the smooth progress of postoperative rehabilitation. However, laparoscopic surgery establishes artificial pneumoperitoneum, and a large amount of CO_2 enters the peripheral blood circulation through the peritoneum, which affects brain metabolism and leads to nerve damage. Elderly patients have decreased body function and organ reserve function, and they are more likely to suffer from acute lung injury and postoperative cognitive dysfunction when receiving surgical treatment. Elderly patients are prone to cognitive dysfunction or delirium after surgery, and the selection of anesthetic methods and drugs is an important factors affecting the injury of brain neurons (1). Dexmedetomidine is an α2 receptor high-affinity agonist, especially for the α2A receptor located in the locus coeruleus nucleus in the brain, which has high selectivity. By inhibiting the release of sympathetic nerve excitatory transmitters and the upward transmission of peripheral pain signals, Produce sedation and analgesia (2). In addition, dexmedetomidine has a certain affinity for imidazoline I1 receptors located in brain stem and hippocampus, which inhibits the release of catecholamine and excitotoxic amino acids, reduces the sensitivity of neurons to glutamic acid, and thus plays a role in brain protection (3). At present, dexmedetomidine has been used in neurosurgery, thoracic surgery, cardiology surgery, pediatric surgery and other operations, but there are still few studies in the operation of abdominal tumor patients. Malignant tumor patients generally have disorders of immune system. Surgery and anesthesia may further inhibit the cellular immune function of the body, thus affecting the prognosis of patients (4). Dexmedetomidine is a commonly used auxiliary anesthetic in surgery, which has the effects of central nervous protection and cardiopulmonary function protection. This study was designed to observe the effects of dexmedetomidine combined with intravenous inhalation anesthesia on brain oxygen metabolism and serum Th1/Th2 levels in elderly patients with colorectal cancer, aiming to provide certain evidence-based evidence and reference for the clinical application of dexmedetomidine.

CLINICAL DATA AND METHODS

The Clinical Data Selected

From April 2018 to May 2020,100 elderly patients who underwent elective laparoscopic radical resection of colorectal cancer in the First Affiliated Hospital of Hunan Normal University were taken as the overall research object. Combined with clinical manifestations, related imaging manifestations and pathological first-stage biopsy, rectal cancer was diagnosed. Inclusion criteria: age 60–85 years old; Indications for laparoscopic radical resection of rectal cancer; American society of anesthesiologists (ASA) (5) grade I-II; There is no obvious contraindication to anesthesia. Exclusion criteria: those who have a history of neurological or mental illness; People with a history of drug allergy or long-term alcoholism; Those who took anticoagulants, sedatives, antidepressants, non-steroidal anti-inflammatory drugs or hormone drugs 3 months before operation; Eliminate those whose blood loss during the operation is > 20% of the basal blood volume; Those with intractable hypotension or anaphylactic shock. With the approval of the ethics committee of this hospital and the informed consent of the patients, 100 patients were divided into control group and observation group according to equal-length random sampling method with the approval of the ethics committee of the hospital and the informed consent of the patients. Comparing the age, gender composition, weight, body mass index (BMI), ASA classification, and cancer

type of the two groups of patients, the difference was not statistically significant ($P > 0.05$) and was comparable. As shown in **Table 1**.

Methods of Anesthesia

Routine fasting and drinking before operation lasted 6–8 h. After entering the room, open the venous channel to monitor the electrocardiogram, mean artery pressure (MAP), heart rate (HR), pulse oxygen saturation (SpO_2), and bispectral index (BIS). Patients in the observation group were given dexmedetomidine (Jiangsu Hengrui Pharmaceutical Co., Ltd., specification: 2 mL: 200 μg, batch number 190423BP) loading dose of 0.5 μg/kg before induction of anesthesia, and the infusion time was 20 min. After tracheal intubation, dexmedetomidine was continuously pumped at 0.4 μg/kg/h (prepared with normal saline to 4 μg/mL) until 40 min before the end of the operation. Patients in the control group were given an equal volume of 0.9% sodium chloride injection intravenously in the same way General anesthesia induction: intravenous infusion of propofol (1.5–2 mg/kg), after the patient's consciousness disappears, slow intravenous bolus of midazolam (0.02 mg/kg) and sufentanil citrate (2.0–3.5 μg/kg), etomidate (0.2 mg/kg) and cis-atracurium benzenesulfonate (0.1–0.2 mg/kg), the patients were subjected to sequential induction of general anesthesia; After the muscle relaxation takes effect, perform tracheal intubation, connect to anesthesia machine for mechanical ventilation, tidal volume 6–8 mL/kg, frequency 12–15 times/min, continuous inhalation of sevoflurane 1%-2%, target-controlled infusion C Poofol (4–10 mg/kg/h) was used for anesthesia maintenance, intermittent intravenous injection of cis-atracurium to relax the muscles. BIS is maintained between 40 and 60. Connect the intravenous analgesic pump after the operation. Patient controlled intravenous analgesia (PCIA) was used, dexmedetomidine (0.5 g/kg) + sufentanil (0.8 g/kg) was used, and normal saline was diluted into 100 ml solution. The dose is 1 mL, and the lock time is 15 min.

Observation Indicators

Cerebral Oxygen Metabolism

30 Minutes Before Induction of Anesthesia (T_0), Immediately Before Induction of Anesthesia (T_1), Immediately After Tracheal Intubation (T_2), 40 Min Before the Operation (T_3), and Immediately After the Operation (T_4), Collect Blood Samples From the Radial Artery and Internal Jugular Venous Bulb, and Calculate the Arterial-Internal Jugular Venous Blood Oxygen Difference ($D_{(a-Jv)}O_2$) and Cerebral Oxygen Uptake Rate (COER%) According to the Fick Formula (6). COER% = $[(CaO_2\text{-}CvO_2)/CaO_2] \times 100\%$, CaO_2 Is Arterial Blood Oxygen Content, CvO_2 Is Arterial Oxygen Consumption. At the Same Time, a Near-Infrared Photometer Was Used to Monitor the Mean Value of Cerebral Oxygen Saturation (RSO2) on Both Sides of the Frontal Line.

Postoperative Analgesia, Sedation Effect and Early Postoperative Cognitive Function

At 6, 12, 24, and 48 h after surgery, the visual analog scale (VAS) method was used to evaluate the analgesic effect. VAS scoring criteria: 0 point means no pain, 10 points means the most pain, < 3 points means good analgesia, and ≥5 points means poor analgesic effect. Ramsay score was used to evaluate the sedative effect. The total Ramsay score was 6 points. The higher the score was, the higher the degree of sedation would be. Montreal Cognitive Assessment (MoCA) score was also recorded. The MoCA scale included visual space and executive function, naming, memory, attention, language, abstraction, delayed memory and orientation, with a full score of 30. A lower score indicated lower cognitive function, < 26 indicated abnormal.

Postoperative Laboratory Index Monitoring

Serum samples were collected at the preoperative basic value and immediately after the operation, 6, 12, 24, and 48 h after the operation, and the ELISA kit was used to monitor interferon-γ (IFN-γ) and interleukin-4 (interleukin-4, IL-4), myelin basic protein (MBP), neuron-specific enolase (NSE), S100β content. The kit used was purchased from Shanghai Kanglang Biotechnology Co., Ltd.

Adverse Reactions

The incidence of restlessness, dizziness, nausea and vomiting, and respiratory depression in the two groups of patients during the recovery period was counted within 48 h after the operation.

Statistical Processing

Using SPSS19.0 statistical software, measurement data are expressed as mean ± standard deviation ($\bar{x} \pm s$), using repeated measures analysis of variance for intra-group comparison, and comparison between groups using LSD-t test; The count data is expressed as a percentage or rate (%), and the χ^2 test is performed. $P < 0.05$ indicates that the difference is statistically significant.

RESULTS

Comparison of Surgical Conditions Between the Two Groups

There was no significant difference in anesthesia induction time, operation time, anesthesia maintenance time, fluid replacement, blood loss during operation, directional recovery time, extubation time and observation time in PACU after anesthesia ($P > 0.05$). As shown in **Table 2**.

Changes in Cerebral Oxygen Metabolism Indexes of the Two Groups

The analysis of variance with repeated measures design was used to compare the levels of $D_{(a-jv)}O_2$, COER%, and rSO_2 at each time point of T_0-T_1 between the two groups. ①$D_{(a-jv)}O_2$, COER%, rSO_2 levels were statistically different at different time points ($F = 17.241, 8.260, 4.385$, $P < 0.05$), the control group and observation group patients $D_{(a-jv)}O_2$ COER% and rSO_2 levels at T_2, T_3, and T_4 were higher than the preoperative basic value ($P < 0.05$). ②The observation group and the control group had statistical differences in $D_{(a-jv)}O_2$, COER%, rSO_2 levels ($F = 16.451, 5.638, 8.799$, $P < 0.05$). The levels of $D_{(a-jv)}O_2$, COER%

TABLE 1 | Comparison of the general conditions of the two groups of patients ($\bar{x} \pm s$).

Group	*n*	Gender		Age (year)	BMI (kg/m^2)	ASA		Type		TNM stage		
		Male	Female			I	II	Colon cancer	Rectal cancer	I	II	III
Control group	50	38	12	70.68 ± 6.48	23.25 ± 1.38	24	26	34	16	19	26	5
Observation group	50	30	20	69.70 ± 6.58	22.75 ± 1.49	31	19	28	22	14	27	9
t value	-	2.941		0.750	1.741	1.980		1.528		1.919		
P value	-	0.086		0.455	0.085	0.159		0.216		0.383		

TABLE 2 | Comparison of surgical conditions between the two groups ($\bar{x} \pm s$).

Group	n	Anesthesia induction time (min)	Operation time (min)	Anesthesia maintenance time (min)	Rehydration volume (L)	Volume of blood loss (mL)	Orientation recovery time (min)	Extubation time (min)
Control group	50	10.94 ± 2.32	145.78 ± 43.27	163.84 ± 30.59	1.92 ± 0.73	389.76 ± 54.63	16.26 ± 4.58	20.48±5.67
Observation group	50	12.06 ± 3.75	161.52 ± 48.39	172.63 ± 28.95	2.07 ± 0.78	402.14 ± 64.85	15.44 ± 5.37	19.16±5.52
t-value	-	1.796	1.715	1.476	0.993	1.032	0.822	1.180
P-value	-	0.076	0.090	0.143	0.323	0.304	0.413	0.241

and rSO_2 of the observation group were lower than those of the control group at T_2, T_3, and T_4 ($P < 0.05$). ③There was a statistical difference in the trend of changes in the levels of $D_{(a-jv)}O_2$, COER%, and rSO_2 between the two groups of patients ($F = 38.757, 12.605, 9.374$, $P < 0.05$). As shown in **Figure 1**.

Comparison of Postoperative Analgesia, Sedation Effects and Cognitive Function Between the Two Groups

The analysis of variance with repeated measures design was used to compare the VAS score, Ramsay score, and MoCA score at each time point of 6, 12, 24, and 48 h after the operation of the two groups. 1. VAS score, Ramsay score, and MoCA score were statistically different at different time points ($F = 12.351, 5.462, 8.291$, $P < 0.05$). 2. There was a statistical difference between the observation group and the control group in VAS score, Ramsay score, and MoCA score ($F = 21.358, 27.642, 13.058$, $P < 0.05$). The observation group had VAS score and Ramsay score at 6, 12, 24, 48 h were lower than the control group, while the MoCA score was higher than the control group ($P < 0.05$). 3. There was a statistical difference in the trend of VAS score, Ramsay score, and MoCA score between the two groups ($F = 42.637, 27.814, 29.854$, $P < 0.05$). As shown in **Figure 2**.

Comparison of Laboratory Indicators Between the Two Groups

The analysis of variance with repeated measures design was used to compare the serum IFN-and ILIL-4els and IFN - γ/IL - 4 ratios of the two groups of patients before the operation, immediately after the operation, and at each time point of 6, 12, 24, and 48 h after the operation. 1. There were statistical differences in serum IFN-γ levels, IFN-γ/IL-4 ratio, serum MBP, NSE and S100β levels at different time points ($F = 8.410, 28.573, 37.258, 19.267, 4.851$, $P < 0.05$). There was no statistical difference in serum IL-4 levels at time points ($F = 2.059$, $P = 0.148$). 2. There were statistical differences in serum IFN-γ levels, IFN-γ/IL-4 ratio, serum MBP, NSE and S100β levels between the observation group and the control group ($F = 13.936, 37.815, 7.824, 9.673, 5.897$, $P < 0.05$). The serum IFN-γ levels, MBP and S100β levels of the observation group were lower than those of the control group immediately after the operation and at 6, 12, 24, and 48 h after the operation ($P < 0.05$). At the same time, IFN-γ The ratio of /IL-4 was higher than that of the control group ($P < 0.05$). Serum NSE levels in the observation group were lower than those in the control group at 6, 12, 24, and 48 h after surgery ($P < 0.05$). In addition, there was no significant difference in serum IL-4 levels between the two groups of patients ($F = 1.734$, $P = 0.325$). 3. There were statistical differences in the changes of serum IFN-γ levels, IFN-γ/IL-4 ratio, serum MBP, NSE and S100β levels between the two groups ($F = 43.218, 786.454, 118.379, 72.361, 28.504$, $P < 0.05$), while the comparison of the trend of changes in serum IL-4 levels between the two groups of patients, the difference was not statistically significant ($F = 0.927$, $P = 0.564$). As shown in **Figure 3**.

Comparison of Postoperative Adverse Reactions Between the Two Groups

All patients successfully completed the tracheal intubation, and no coughing or body odor movement occurred. The total incidence of adverse reactions (including restlessness in convalescence) in the control group and observation group was 32.0% (16/50) and 12.0% (6/50), respectively. The difference was statistically significant after the χ^2 test ($\chi^2 = 5.828$, $P = 0.016$), the overall incidence of adverse reactions in the observation group was slightly lower than that in the control group. As shown in **Figure 4**.

DISCUSSION

Postoperative cognitive dysfunction (POCD) refers to symptoms such as mental confusion, degeneration of mental function, and decreased social ability within a few days or months after surgery

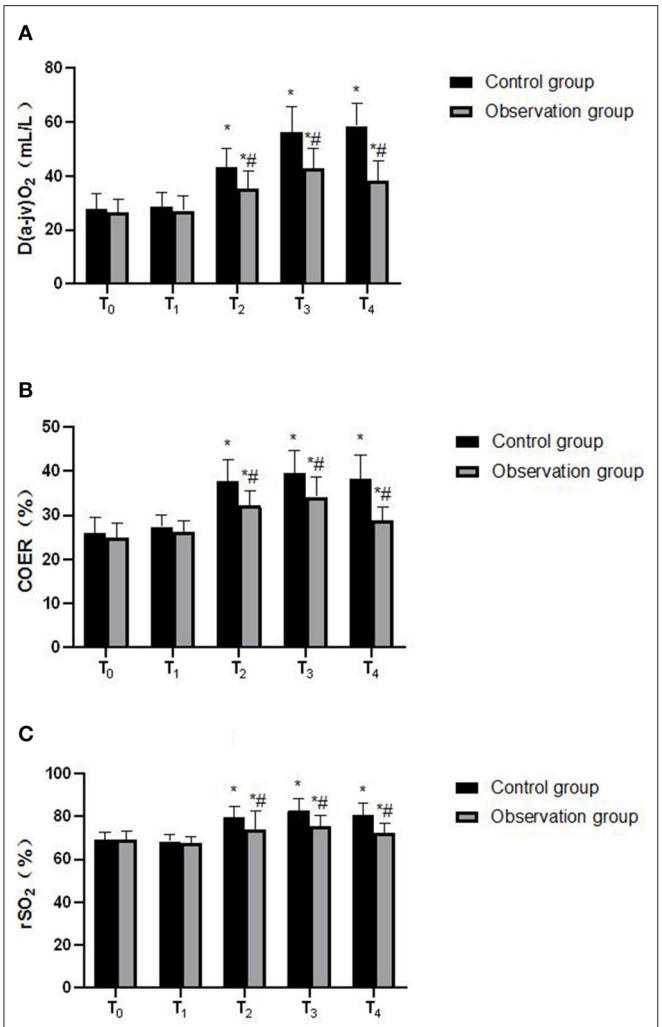


FIGURE 1 | Comparison of D(a-jv)O2, COER%, rSO2 at different time points between the two groups. **(A)** D(a-jv)O2; **(B)** COER% and **(C)** rSO2. Compared with T_0 in the samegroup, $^*P < 0.05$; compared with control group, $^\#P < 0.05$.

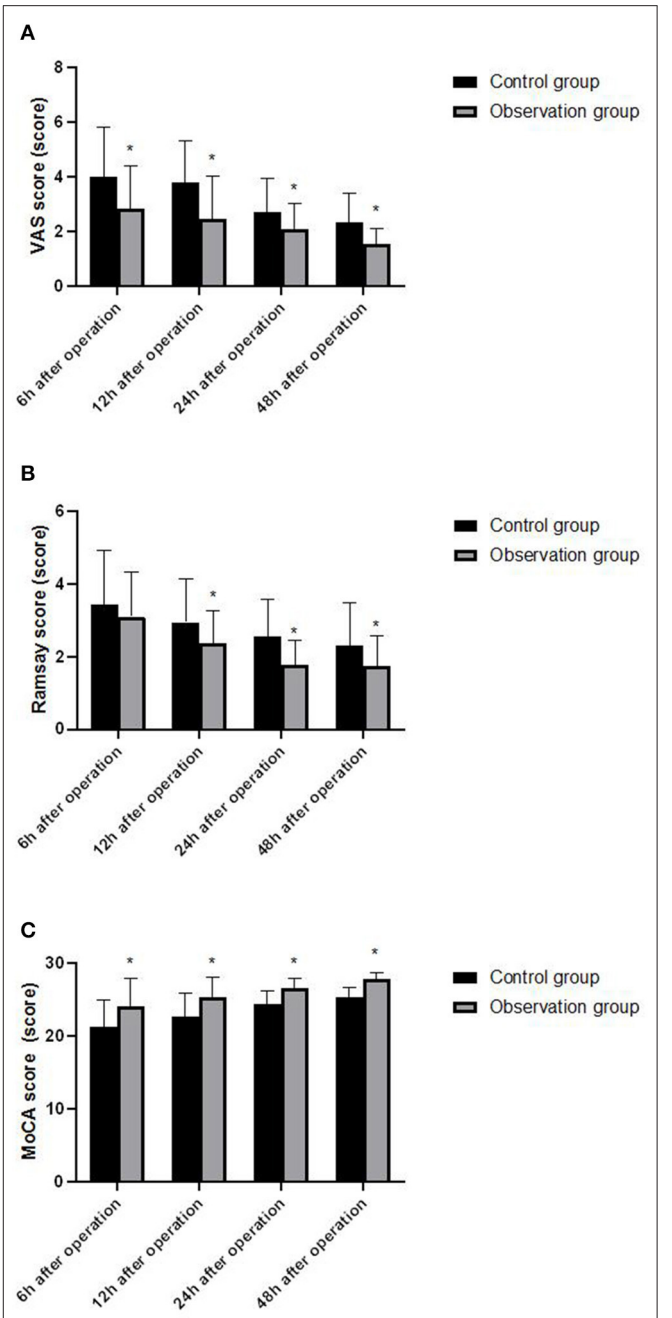


FIGURE 2 | Comparison of VAS score, Ramsay score and MoCA score between the two groups of patients at different time points. **(A)** VAS score; **(B)** Ramsay score and **(C)** MoCA score. Compared with the control group, $^*P < 0.05$.

(7), It is more common in patients undergoing major surgery such as cardiology, gastrointestinal surgery, trauma surgery, and tumor surgery. A small number of patients can even persist for a long time, It greatly increases the risk of postoperative complications and prolongs the hospital stay, which in turn affects the patient's prognosis and postoperative quality of life.

Old age is the risk factor that is closely related to POCD disease Scholars such as Czyz-Szypenbejl (8) found that the incidence of POCD in elderly patients over 60 years old within 7 days was about 17 ∼ 56%, and with the increase of age, the incidence of POCD increased. The incidence of POCD in elderly patients is higher than that of patients aged 60 to 69, and the proportion of patients with long-term persistent POCD has also increased greatly, and some patients may even progress to Alzheimer's disease. It is speculated that the principle lies in the degenerative changes in the brain structure and function of the elderly, the aging of neuronal nuclei, the increase in apoptosis rate, the decrease in neurotransmitter secretion, the deterioration of brain glucose metabolism and neural signal transmission functions, which makes the elderly population The brain is more susceptible to damage from anesthetics (9).

Besides age, anesthesia methods and narcotic drugs are also important factors that affect postoperative cognitive function. According to a multi-center study conducted by Wang Dongting and other scholars (10), 400 elderly patients who were to

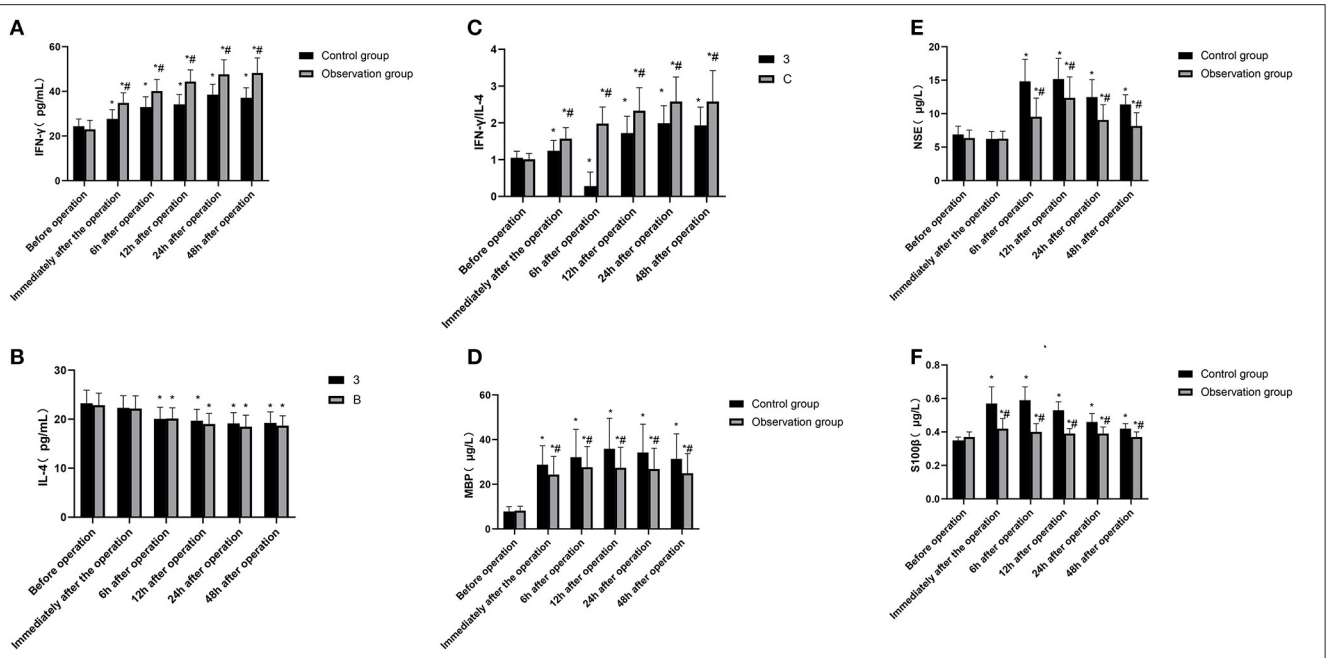


FIGURE 3 | Comparison of IFN-γ, IL-4, IFN-γ/IL-4, neurological impairment related indexes between the two groups of patients at different time points. **(A)** IFN-γ; **(B)** IL-4; **(C)** IFN-γ/IL-4; **(D)** MBP; **(E)** NSE and **(F)** S100β. Compared with the preoperative basic value of the same group, $^{*}P < 0.05$; compared with the control group, $^{\#}P < 0.05$.

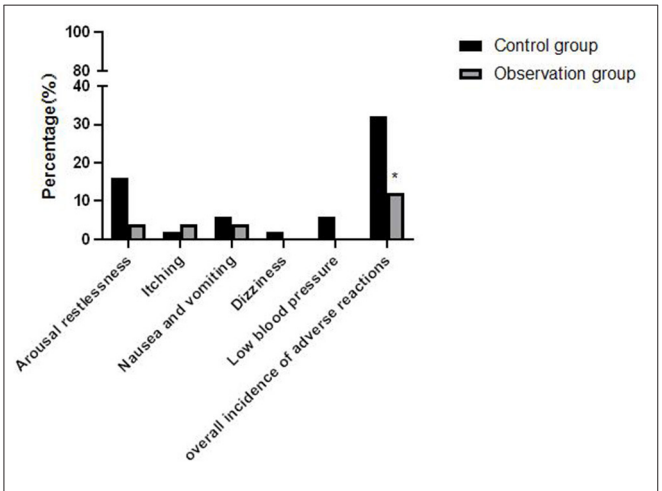


FIGURE 4 | Comparison of the incidence of adverse reactions between the two groups of patients. Compared with control group, $^{*}P < 0.05$.

undergo radical resection of colorectal cancer were followed up and observed. MoCA score is a common cognitive function screening tool, which is used as an auxiliary diagnostic method for POCD disease. The results showed that the incidence of POCD was about 15.6 %, and the duration of anesthesia and the proportion of general anesthesia are independent risk factors for the occurrence of POCD. In this study, the enrolled patients with colorectal cancer all used propofol-sevoflurane intravenous inhalation combined with general anesthesia. Propofol is a highly fat-soluble intravenous anesthetic. Its sedative mechanism and enhancement of γ-amino Butyrate A receptor activity, which in turn enhances the inhibitory postsynaptic current, is related (11). Gamma-aminobutyric acid receptor activity can lead to long-term potentiation (LTP) that inhibits the excitatory transmission of pyramidal neurons in the hippocampal CA 1 region, and then affect the learning and cognitive functions of patients (12). In addition, scholars such as Alkire MT (13) confirmed that inhalational anesthetics, such as sevoflurane and sevoflurane at the relative minimum alveolar concentration, within 24 h, the memory loss of nitrous oxide is more serious, but it is compared with other inhaled anesthetics. Sexual anesthetics, sevoflurane is metabolized quickly and has little effect on the nervous system, but it still cannot avoid the damage to the cognitive function of elderly patients after surgery.

Dexmedetomidine is an α 2 adrenergic receptor agonist with high selectivity and specificity. By inhibiting the activity of sympathetic nerves and the secretion of stress hormones such as cortisol and catecholamine, it can reduce the damage to hippocampus, thus reducing the influence of anesthetics on the early postoperative cognitive function of elderly patients (14). In this study, patients in the observation group were given dexmedetomidine-assisted intravenous inhalation combined anesthesia, and the postoperative VAS score and Ramsay score were significantly lower than those of the control group, indicating that dexmedetomidine-assisted combined intravenous inhalation anesthesia has good analgesia and sedation. In addition, the postoperative MoCA score of the observation group was higher than that of the control group, and the levels of $D_{(a-jv)}O_2$, COER%, and rSO_2 were lower than those of the control group. $D_{(a-jv)}O_2$, COER%, and rSO_2 reflect brain oxygen

An important indicator of metabolism and blood supply of brain tissue. If the oxygen uptake rate of brain decreases, the oxygen supply is greater than the oxygen consumption, indicating that the brain tissue has a normal aerobic metabolism. Therefore, the above results indicate that dexmedetomidine can effectively maintain the balance of cerebral oxygen supply and demand in elderly colorectal cancer surgery. In addition, MBP, NSE, S100β and other indicators are important marker molecules that reflect the damage of nerve cells, and have a certain effect on maintaining the proliferation and differentiation of neurons or glial cells (15). In this study, the levels of MBP, NSE, and S100β in the observation group were significantly lower than those in the control group, indicating that dexmedetomidine has a certain protective effect on nerve function damage caused by intravenous inhalation and combined anesthesia in elderly patients with colorectal cancer. Elderly patients with colorectal cancer often have autoimmune disorders, as well as surgical trauma, anesthesia stimulation, and postoperative stress, which further inhibit the body's humoral immune function (1, 16). Immune dysfunction is also one of the important reasons leading to cognitive dysfunction in patients (17). In this study, the postoperative IFN-γ/IL-4 ratio of the observation group was higher than that of the control group. IFN-γ and IL-4 were the most typical cytokines of Th1 and Th2 cells, and the ratio of IFN-γ/IL-4 increased Gao shows that under the action of dexmedetomidine, the Th1/Th2 response pattern gradually drifts to Th1 cells, which helps the recovery of the patient's immune function after surgery.

n summary, dexmedetomidine-assisted intravenous inhalation combined anesthesia is beneficial to reduce perioperative cerebral oxygen metabolism in elderly patients with colorectal cancer, improve postoperative immunosuppression status, and has a certain protective effect on postoperative neurological damage. In order to improve patients' cognitive function and reduce the occurrence of adverse reactions, this study provided evidence-based medical evidence support for the clinical application of dexmedetomidine.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hunan Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YT is mainly responsible for the writing of the paper. JL and XH are mainly responsible for the design of the study and the inclusion of cases. HD and ST are mainly responsible for the evaluation of results and data statistics, and YZ is mainly responsible for the guidance of the whole research process. All authors contributed to the article and approved the submitted version.

FUNDING

The current study was financially supported by following fund: Hunan Provincial Natural Science Foundation of China (Grant No. 2018JJ3296/Grant No. 2020JJ4404)/Fund of the Hunan Provincial Health Commission (Grant No. 20200758).

REFERENCES

1. Dang Y, Shi X, Xu W, Zuo M. The effect of anesthesia on the immune system in colorectal cancer patients. *Can J Gastroenterol Hepatol.* (2018) 1:7940603. doi: 10.1155/2018/7940603
2. Minnella EM, Carli F. Prehabilitation and functional recovery for colorectal cancer patients. *Eur J Surg Oncol.* (2018) 44:919–26. doi: 10.1016/j.ejso.2018.04.016
3. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS®) society recommendations: 2018. *World J Surg.* (2019) 43:659–95. doi: 10.1007/s00268-018-4844-y
4. Ren X, Chen B, Hong Y, Liu W, Jiang Q, Yang J, et al. The challenges in colorectal cancer management during COVID-19 epidemic. *Ann Transl Med.* (2020) 8:498. doi: 10.21037/atm.2020.03.158
5. Yu X, Li Z, Zheng H, Chan MT, Wu WK. NEAT1: a novel cancer-related long non-coding RNA. *Cell Prolif.* (2017) 50:12329. doi: 10.1111/cpr.12329
6. Farag E, Kot M, Podolyak A, Argalious M, Deogaonkar M, Mascha EJ, et al. The relative effects of dexmedetomidine and propofol on cerebral blood flow velocity and regional brain oxygenation: a randomised noninferiority trial. *Eur J Anaesthesiol.* (2017) 34:732–9. doi: 10.1097/EJA.0000000000000662
7. Li WX, Luo RY, Chen C, Li X, Ao JS, Liu Y, et al. Effects of propofol, dexmedetomidine, and midazolam on postoperative cognitive dysfunction in elderly patients: a randomized controlled preliminary trial. *Chin Med J.* (2019) 132:437–45. doi: 10.1097/CM9.0000000000000098
8. Czyz-Szypenbejl K, Medrzycka-Dabrowska W, Kwiecień-Jaguś K, Lewandowska K. The occurrence of postoperative cognitive dysfunction (POCD) - systematic review. *Psychiatr Pol.* (2019) 53:145–60. doi: 10.12740/PP/90648
9. Rengel KF, Pandharipande PP, Hughes CG. Special considerations for the aging brain and perioperative neurocognitive dysfunction. *Anesthesiol Clin.* (2019) 37:521–36. doi: 10.1016/j.anclin.2019.04.010
10. Ng C, Li H, Wu WKK, Wong SH, Yu J. Genomics and metagenomics of colorectal cancer. *J Gastrointest Oncol.* (2019) 10:1164–70. doi: 10.21037/jgo.2019.06.04
11. Gillis C, Buhler K, Bresee L, Carli F, Gramlich L, Culos-Reed N, et al. Effects of nutritional prehabilitation, with and without exercise, on outcomes of patients who undergo colorectal surgery: a systematic review and meta-analysis. *Gastroenterology.* (2018) 155:391–410. doi: 10.1053/j.gastro.2018.05.012
12. Tanos V, Berry KE, Seikkula J, Abi Raad E, Stavroulis A, Sleiman Z, et al. The management of polyps in female reproductive organs. *Int J Surg.* (2017) 43:7–16. doi: 10.1016/j.ijsu.2017.05.012
13. Alkire MT. Loss of effective connectivity during general anesthesia. *Int Anesthesiol Clin.* (2008) 46:55–73. doi: 10.1097/AIA.0b013e3181755dc6

14. Zhang H, Wu Z, Zhao X, Qiao Y. Role of dexmedetomidine in reducing the incidence of postoperative cognitive dysfunction caused by sevoflurane inhalation anesthesia in elderly patients with esophageal carcinoma. *J Cancer Res Ther.* (2018) 14:1497–502. doi: 10.4103/jcrt.JCRT_164_18
15. Yu X, Xie Y. Effect of dexmedetomidine combined with etomidate on IL-17A and S-100β expression levels in rats with postoperative cognitive dysfunction. *Exp Ther Med.* (2020) 20:275. doi: 10.3892/etm.2020.9405
16. Hasselager RP, Hallas J, Gögenur I. Inhalation or total intravenous anaesthesia and recurrence after colorectal cancer surgery: a propensity score matched Danish registry-based study. *Br J Anaesth.* (2021) 126:921–30. doi: 10.1016/j.bja.2020.11.019
17. Zhao J, Kang Z, Xie W, Lin H, Liu Y. Effects of depth of anesthesia monitored by ioc on patients undergoing laparoscopic radical resection of colorectal cancer. *Mol Ther Methods Clin Dev.* (2020) 18:304–11. doi: 10.1016/j.omtm.2020.05.032

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Tang, Liu, Huang, Ding, Tan and Zhu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 25 January 2022
doi: 10.3389/fsurg.2021.833288

Effect of CAD/CAM Guide Plate Combined With Socket-Shield Technique in Immediate Implantation of Anterior Teeth Aesthetic Area and Its Influence on Aesthetics

Zhigang Wang[1†], *Jianwei Liu*[2†], *Xinquan Wang*[3], *Ning Wang*[1] *and Min Teng*[4*]

[1] Department of Stomatology, Zibo Central Hospital, Zibo, China, [2] Department of Stomatology, People's Hospital of Changle County, Weifang, China, [3] Department of Stomatology, Rizhao Traditional Chinese Medicine Hospital, Rizhao, China, [4] Department of Stomatology, Tengzhou Central People's Hospital, Zaozhuang, China

Purpose: The purpose of this study is to discuss the effect of computer-aided design or computer-aided manufacturing (CAD/CAM) guide plate combined with socket-shield technique (SST) in immediate implantation of anterior teeth aesthetic area and its influence on aesthetics.

Methods: A total of 102 patients with immediate implantation in our hospital from March 2017 to March 2020 were selected. According to different repair methods, patients were divided into conventional group ($n = 51$) and observation group ($n = 51$). Traditional immediate implantation was performed in conventional group. The observation group underwent immediate implantation with CAD/CAM guides combined with SST. Immediately after operation and 12 months after operation, the success rate, implant deviation, periodontal index, absorption of labial bone plate, complications, aesthetic effects, and satisfaction of the two groups were observed.

Results: There was no significant difference in the success rate between the two groups ($p > 0.05$). The implant deviation values in the observation group were all lower than those in the conventional group ($p < 0.05$). PD, PLI, and SBI in the observation group were all lower than those in the conventional group ($p < 0.05$). The absorption value of labial bone plate in the observation group were all lower than those in the conventional group ($p < 0.05$). The total incidence of complications in the observation group (5.88%) was lower than that in the conventional group (19.61%) ($p < 0.05$). The PES and WES in the observation group were higher than those in the conventional group ($p < 0.05$). The total satisfaction in the observation group (92.16%) was higher than that in the conventional group (76.47%) ($p < 0.05$).

Conclusion : The application of CAD/CAM guide plate combined with SST in immediate implantation of anterior teeth aesthetic area has a good effect, which can improve the accuracy of implantation, improve the periodontal environment, reduce bone resorption, reduce complications, improve aesthetics, and have high patient's satisfaction.

Keywords: immediate implantation, anterior teeth, CAD/CAM guide plate, socket-shield technique, aesthetics

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Feng Qin,
Shanghai Jiao Tong University School of Medicine, China
Lihu Xie,
University of South China, China

***Correspondence:**
Min Teng
teng106@163.com

[†] *These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *11 December 2021*
Accepted: *22 December 2021*
Published: *25 January 2022*

Citation:
Wang Z, Liu J, Wang X, Wang N and Teng M (2022) Effect of CAD/CAM Guide Plate Combined With Socket-Shield Technique in Immediate Implantation of Anterior Teeth Aesthetic Area and Its Influence on Aesthetics. Front. Surg. 8:833288. doi: 10.3389/fsurg.2021.833288

INTRODUCTION

The aesthetic area of anterior teeth refers to any tooth-alveolar part that can be seen when laughing. Because of tooth defects, pulp diseases, trauma, and other factors, this area is easily damaged, which will greatly affect the patient's appearance, occlusion, pronunciation, physiological stimulation, and other functions and then affect the patient's mental health and social life (1). Immediate implantation is an oral repair technique that implants are implanted into the bone immediately after tooth extraction. It has the advantages of less trauma, short period, and fewer operations and can reduce the pain of patients and the social and economic burden of patients. It has been widely accepted by patients and doctors (2). The aesthetic area of anterior teeth, as an important position in oral cavity, has a special anatomical structure, and patients often have higher aesthetic requirements for this area. Therefore, it is undoubtedly a great challenge for most doctors to immediate implantation of aesthetic area of anterior teeth. The three-dimensional position and axial direction of the implant are the prerequisites for obtaining the long-term stability of the implant. However, the traditional implant operation mainly relies on the personal experience of doctors, which easily leads to the deviation between the implant position and the preoperative design position.

With the continuous development of information technology, computer-aided design or computer-aided manufacturing (CAD/CAM) is widely used in daily life. In 1970s, the team of French scholar Duret first introduced CAD/CAM technology into the design and manufacture of dental prostheses (3). The CAD/CAM technology uses CBCT data to reconstruct jaw information through professional software, designs and makes implant guide plate using CAD/CAM, and then guides each reaming drill and implant placement during implant operation (4). CAD/CAM guide plate can accurately control the three-dimensional direction of the implant, reduce the operation risk, shorten the operation time, and greatly promote the development of digital dental implant technology.

Clinical studies and animal experiments show that immediate implantation after tooth extraction cannot avoid vertical and horizontal bone resorption of surrounding bone tissue, especially the absorption of labial side, and the alveolar bone of labial side will collapse rapidly, resulting in alveolar ridge stenosis, which will adversely affect the healing of soft tissue, and then, it is difficult to achieve the ideal aesthetic requirements (5). In recent years, how to preserve alveolar bone with better repair methods has become a hot issue in the clinic. In the 1960's, root penetration technology became popular, mainly used to prevent alveolar bone resorption (6). In 2010, Hürzeler created the socket-shield technique (SST) based on the root penetration technique. The key points of this method are incomplete extraction of the affected teeth, preservation of cementum and periodontal ligament of labial dental tablets, and implantation of implants in the palatal side, which can reduce the risk of absorption of labial bone plate, resulting in long-term preservation of the alveolar ridge contour (7). Dayakar's team reported that the blood supply of periodontal membrane between tooth piece and buccal bone tissue was good, but no obvious absorption and reconstruction of labial bone plate were found. After the application of SST, there was new cementum between the implant and the retained root slice, which formed osseointegration. This technique is a good plan for implant restoration in the aesthetic area (8).

The implementation of SST has high technical sensitivity. As influenced by the improper operation of the operator and complicated anatomical structure, it is easy to cause the loosening and displacement of the labial dental shield, and even break and fall off, which leads to the failure of retaining the dental shield. In addition, there is a high probability of complications such as labial gingival recession after immediate implantation, and only patients with a thickness of the labial bone plate >1 mm can achieve better aesthetic results. Therefore, this research carried out SST based on the CAD/CAM guide plate, to provide some reference for clinical oral restoration.

MATERIALS AND METHODS

Research Object

A total of 102 patients with immediate implantation from March 2017 to March 2020 were selected. Inclusion criteria were as follows: age $\geq$18 years; single anterior tooth has no retention value; complete labial bone plate, thickness of labial bone plate $\geq$1 mm; the gingival biotype was a thick gingival type; periodontal tissue was normal, and there was no obvious inflammation at the root tip; do not smoke; good oral hygiene; no mouth opening limitation, the distance between the incisal edges of the upper and lower central incisors was $<$3.7 cm; can tolerate operation; informed consent to the study. Exclusion criteria were as follows: systemic diseases with contraindications for operation (such as leukemia, hemophilia, osteoporosis, systolic blood pressure $>$180 mmHg or diastolic blood pressure $>$100 mmHg in patients with hypertension, fasting blood glucose $>$8.88 mmol/L in patients with diabetes); accompanied by night bruxism, clenching teeth and other bad oral habits; mental disorders, unable to cooperate with the investigator; pregnancy or lactation; lost to follow-up or dropped out halfway. According to different repair methods, patients were divided into conventional group ($n = 51$) and observation group ($n = 51$). General data were equally comparable between the two groups ($p > 0.05$). See **Table 1** for specific general information.

Research Methods

Preoperative preparation: preoperative oral examination, imaging examination, and routine biochemical examination were carried out, and oral health education was carried out. Oral examination includes the followings: local soft and hard tissues of missing teeth, missing tooth space, occlusal relationship, periodontal condition of adjacent teeth, periodontal health of the whole mouth, joint condition, etc. It determined the implant plan and introduces the implant type, operation process, and possible complications to patients in detail. Imaging examination includes the followings: CBCT imaging, assessment of available

TABLE 1 | Comparison of general data between the two groups (n, %, $\bar{x} \pm s$).

Group	Gender		Average age (years)	Missing tooth position		Causes of dental disease		
	Male	Female		Loss of upper anterior teeth	Loss of lower anterior teeth	Lesions of tooth and Pulp	Tooth trauma	Other
Conventional group ($n = 51$)	25 (49.02%)	26 (50.98%)	40.67 ± 8.52	34 (66.67%)	17 (33.33%)	28 (54.90%)	17 (33.33%)	6 (11.76%)
Observation group ($n = 51$)	28 (54.90%)	23 (45.10%)	41.39 ± 8.06	33 (64.71%)	18 (35.29%)	30 (58.82%)	14 (27.45%)	7 (13.73%)
χ^2/t-value	0.353		0.438	0.043			0.436	
p-value	0.552		0.662	0.835			0.804	

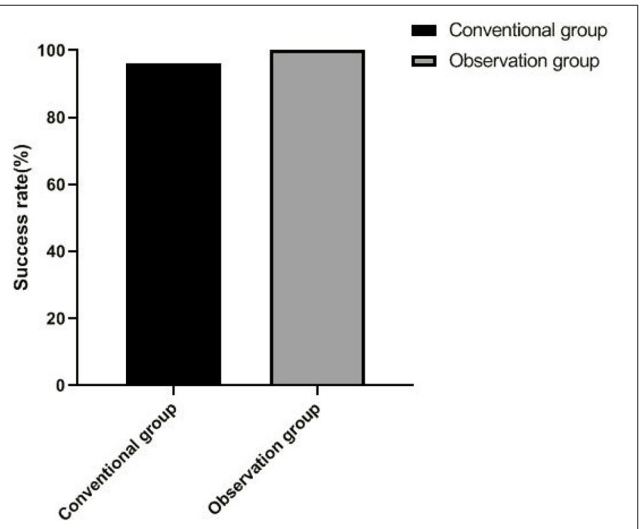


FIGURE 1 | Comparison of clinical efficacy between two groups.

bone width and bone height at the missing tooth, and adjacent to important anatomical structures.

Intraoperative operation: ① Traditional immediate implantation was performed in conventional group: As conventional disinfection and towel spreading, after local infiltration anesthesia, the implant cavity was prepared on the palatal side of the alveolar fossa. After the preparation of the hole was completed, a large amount of normal saline were used to flush the implant cavity and implanted the implant (Nobel Biocare, Sweden). The cover screws or healing abutments were placed, Bio-Oss bone powder (Geistlich, Switzerland) was filled into the labial jump gap of the implant, Bio-Gide barrier membrane was covered, and intermittent sutures were performed. ② The observation group underwent immediate implantation with CAD/CAM guides combined with SST: the data derived from CBCT were imported into Simplant Pro 2011 software (Materialize, Belgium), the target area was selected, the images of upper and lower dentition and bone tissue were extracted, and the high-quality three-dimensional jaw model was reconstructed. According to the condition of jaw and the position of prosthesis, the available bone width and available bone height in the missing tooth area were measured on the sagittal image, so as to determine the three-dimensional position, type, and size of the implant and design the surgical guide plate with accuracy exceeding millimeter level for patients. Finally, the CAD/CAM dental implant guide plate was manufactured using the dental guide plate forming machine. The upper and lower dentition models of patients were made with silicone rubber, and the super anhydrite model was poured and sent to the processing center. Conventional disinfection and towel spreading, after local infiltration anesthesia, SST was started. First, the labial apical fenestration, root removal, and alveolar fossa were performed. A U-shaped incision was made on the side of the lip from the incisor of the natural tooth, and the full-thickness flap was turned to expose the alveolar bone of the apical tooth. The labial side window was opened by high-speed turbine, and the root of the apical tooth was removed. The socket was cleaned with a spoon, and the socket was rinsed with plenty of saline. High-speed turbines were used to divide the root in the near and far directions to avoid alveolar bone damage. After the labial-palatal root was completely separated, the palatal root was removed, the labial-palatal slice was retained, the thickness was adjusted to 1 mm, and the shield shape was formed to 2 mm subgingival. The CAD/CAM guide plate prepared preoperatively was fixed in the dentistry, and the implant socket was prepared following the guide hole of the guide plate and implanted the implant (Nobel Biocare, Sweden). There was a 2-mm distance between the implant and the tooth piece. Bio-Oss bone powder (Geistlich, Switzerland) was filled into the labial jump gap of the implant, Bio-Gide barrier membrane was covered, and intermittent sutures were performed.

Postoperative treatment: after implantation, two groups of antibiotics were given for 3–5 days, 3 times a day, and two groups of chlorhexidine gargle were given for 14 days, 3 times a day. After 6 months of implantation, the superstructure was repaired, CBCT was taken to confirm the osseointegration of the implant, and the final model was taken for a permanent repair. All immediate implant operations were performed by the same operator. Patients were ordered to have regular checkups and informed of precautions for oral health maintenance. Patients in both groups were followed up for 12 months and the outcomes were evaluated. All evaluation items were completed by the same physician who did not participate in the operation.

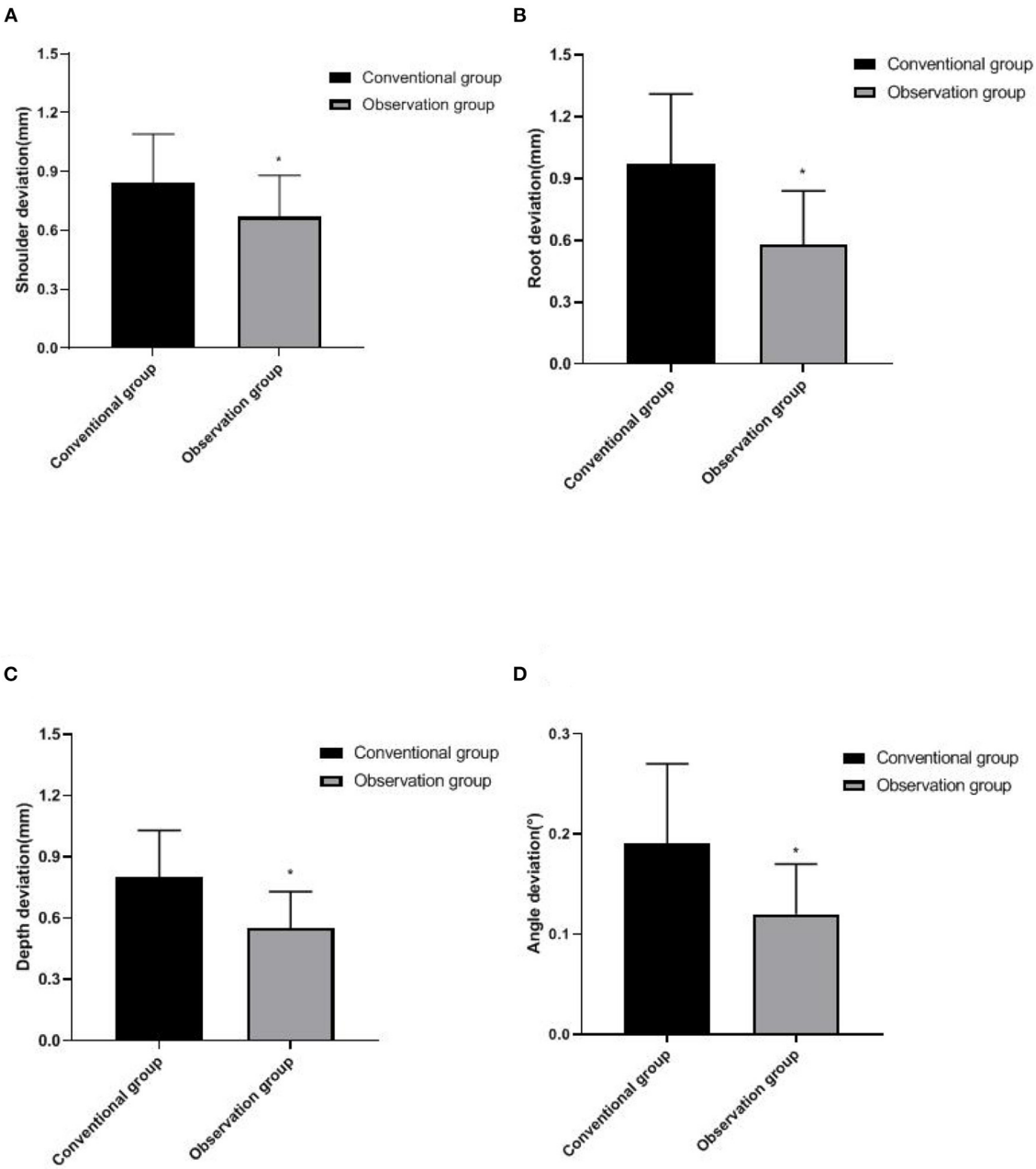


FIGURE 2 | Comparison of implant deviation between two groups. **(A)** Shoulder deviation, **(B)** Root deviation, **(C)** Depth deviation, and **(D)** Angle deviation. Compared with the conventional group, $^{*}p < 0.05$.

Observation Index

After 12 months of operation, the success rate of implant was evaluated according to Albrektsson standard (9), and the successful evaluation criteria were as follows: ① Implants did not loosen or fall off; ② No persistent or irreversible symptoms of the implant, including paresthesia, infection, pain, inflammation, etc.; ③ Imaging showed no transmission zone around the implant; ④ Implant neck bone resorption <2 mm in the first year and <0.2 mm every year thereafter.

Immediately after operation, the oral cavity of the two groups was scanned by the intraoral scanner to obtain the data information of the oral implants, and the image information was imported into the computer software for registration. The shoulder deviation, root deviation, depth deviation, and angle deviation between the preoperation design and the postoperation implant were measured for 3 times and averaged.

After 12 months of operation, the periodontal index was detected by periodontal probe, including 6 sites of each tooth:

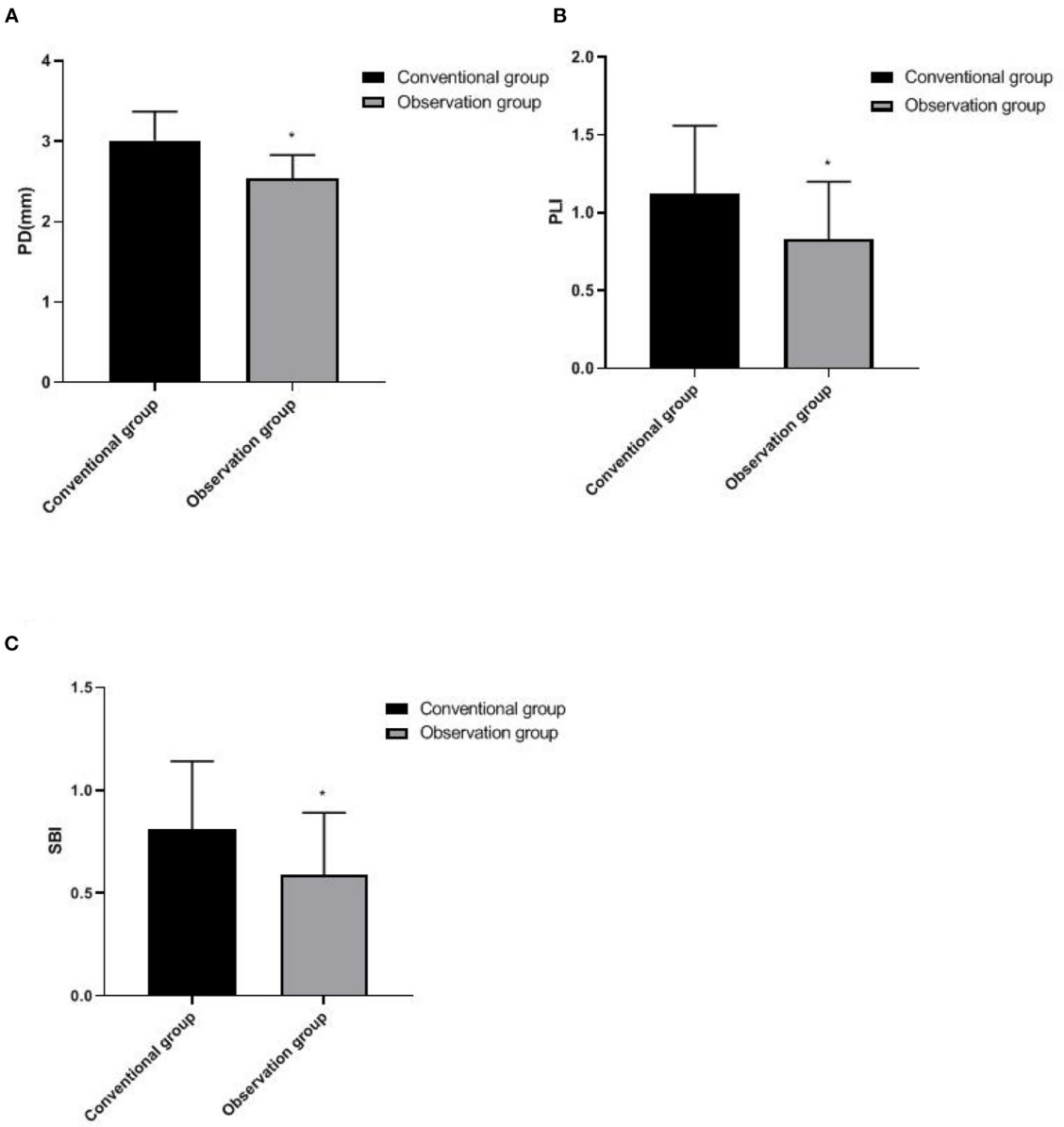


FIGURE 3 | Comparison of periodontal index between two groups. **(A)** PD, **(B)** PLI, and **(C)** SBI. Compared with the conventional group, $^*p < 0.05$.

the mesial, center, and distal of the buccal, and the mesial, center, and distal of the tongue. ① Probing depth (PD): the distance from the gingival margin to the bottom of the pocket or the bottom of the gingival groove was measured with a periodontal probe, and PD of healthy gingival was <2–3 mm. ② Plaque index (PLI): patients were instructed to gargle plaque for 2 min, blow-dry the tooth surface, and then lightly scratch the tooth surface with a probe. According to the amount and thickness of plaque on the tooth surface, the score method of 0–3 points was used. The higher the score, the more plaque. ③ Sulcular bleeding index (SBI): the periodontal probe was gently inserted into the gingival sulci, the probe was removed 30 s later, the gingival bleeding was observed, and the score method of 0–5 points was used. The higher the score, the greater the bleeding tendency.

Immediately after operation and 12 months after operation, the same doctor used the same CBCT to take photos of the two groups under the same parameters. The parameters were set as follows: the shooting voltage was 120 kV, the current was 5 mA, the effective exposure time was 8.9 s, and the resolution was 0.4 mm. Every time the patient took pictures, patients were sat upright, the occlusal plane was parallel to the horizontal plane, and the middle line was perpendicular to the horizontal plane. The built-in software KaVo-eXam Vision

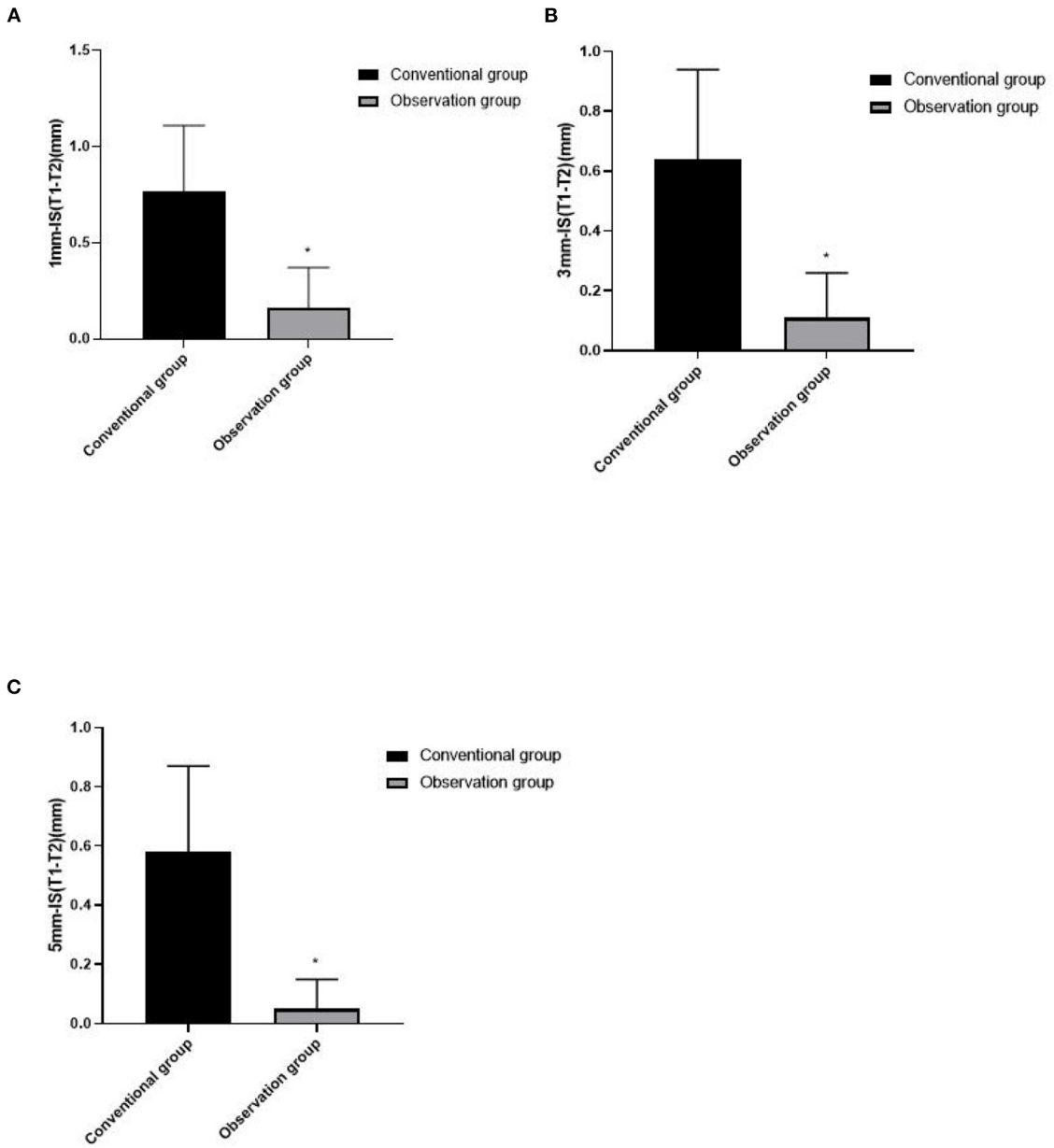


FIGURE 4 | Comparison of absorption of labial bone plate between two groups. **(A)** 1mm-IS(T1-T2), **(B)** 3mm-IS(T1-T2), and **(C)** 5mm-IS(T1-T2). Compared with the conventional group, $^*p < 0.05$.

was used to measure the multilevel labial bone plate thickness of 1, 3, and 5 mm of the root of the implant shoulder (IS). They were denoted as 1, 3, and 5 m-IS, respectively, the measurement images passed through the center of the implant, and the measurement accuracy was 0.01 mm and measured for 3 times and averaged. Labial plate absorption value = immediate postoperative labial plate thickness – 12 months postoperative labial plate thickness.

The complications that occurred in the two groups within 12 months after operation were recorded, including periimplant inflammation, crown fracture, gingival swelling, neuropathic pain, malocclusion, and other complications.

After 12 months of operation, the photos of the aesthetic area of the anterior teeth were taken, and the aesthetic effect was evaluated according to the pink aesthetic index (PES) and the white aesthetic index (WES). The score was obtained by comparing with the tooth of the same name on the opposite side. There were 12 members in the scoring group, who came from the Department of Stomatology, Implant Department, and

TABLE 2 | Comparison of complications between two groups (*n*, %).

Group	Periimplant inflammation	Crown fracture	Gingival swelling	Neuropathic pain	Malocclusion	Total incidence rate
Conventional group ($n = 51$)	2 (3.92%)	1 (1.96%)	5 (9.80%)	1 (1.96%)	1 (1.96%)	10 (19.61%)
Observation group ($n = 51$)	0 (0.00%)	0 (0.00%)	2 (3.92%)	1 (1.96%)	0 (0.00%)	3 (5.88%)
χ^2/t-value						4.320
p-value						0.038

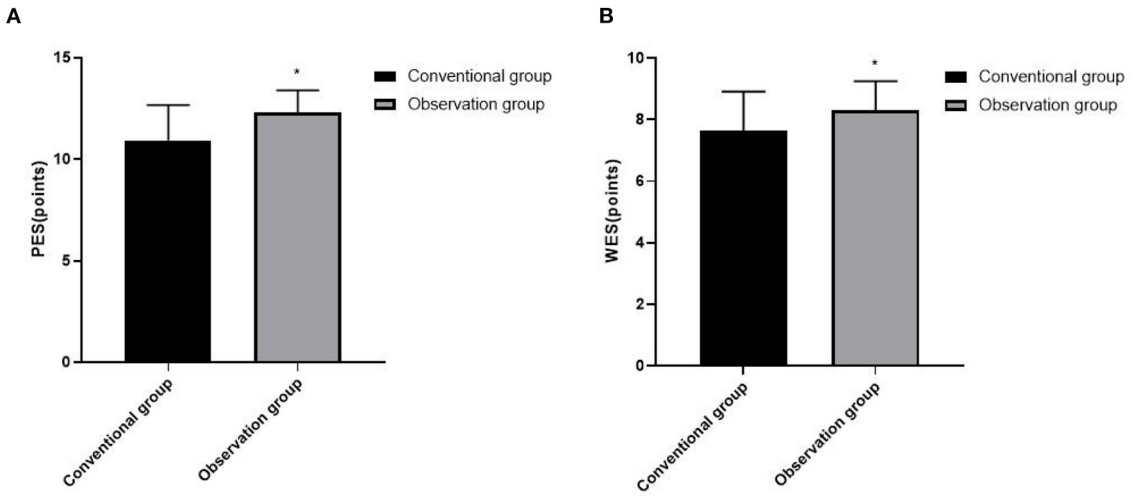


FIGURE 5 | Comparison of aesthetic effects between the two groups. **(A)** PES and **(B)** WES. Compared with the conventional group, $^*p < 0.05$.

Imaging Department, and the final score was scored by the total average. ① PES includes gingival margin level, alveolar process shape, soft tissue texture, soft tissue shape, soft tissue color, distal gingival papilla, and proximal gingival papilla, with a score of 0–2 points, with a full score of 14 points. The higher the score, the better the aesthetic effect of soft tissue. ② WES includes crown shape, crown outline, crown color, surface texture, and transparency, with a score of 0–2 points, with a full score of 10 points. The higher the score, the better the aesthetic effect of the restoration.

After 12 months of operation, the self-made questionnaire was used to evaluate the satisfaction of the two groups, including the overall appearance, occlusal ability, stability, comfort, etc. The total score was 100 points; 80–100 points denote very satisfied, 60–79 points denote satisfied, and <60 points denote dissatisfied. Total satisfaction = (very satisfied+satisfied)/total number of cases ×100%. The content validity index of our self-made questionnaire was 0.85, and the internal consensus reliability Cronbach's α coefficient was 0.779.

Statistical Methods

SPSS 22.0 software was used for the analysis, measurement data were expressed as mean ± standard deviation, and *t*-test was used to analyze the comparison. Count data were expressed as a ratio, and chi-square test was used to analyze the comparison. $p < 0.05$ was statistically significant.

RESULTS

Comparison of Clinical Efficacy Between Two Groups

There were 49 successful cases and the success rate was 96.08% in the conventional group, and there were 51 successful cases and the success rate was 100.00% in the observation group. There was no significant difference in the success rate between the two groups ($p > 0.05$), as shown in **Figure 1**.

Comparison of Implant Deviation Between Two Groups

The implant deviation values in the observation group were all lower than those in the conventional group ($p < 0.05$), as shown in **Figure 2**.

Comparison of Periodontal Index Between Two Groups

PD, PLI, and SBI in the observation group were all lower than those in the conventional group ($p < 0.05$), as shown in **Figure 3**.

Comparison of Absorption of Labial Bone Plate Between Two Groups

The absorption value of labial bone plate in the observation group was all lower than those in the conventional group ($p < 0.05$), as shown in **Figure 4**.

TABLE 3 | Comparison of satisfaction between the two groups (*n*, %).

Group	Very satisfied	Satisfied	Dissatisfied	Total satisfaction
Conventional group ($n = 51$)	22 (43.14%)	17 (33.33%)	12 (23.53%)	39 (76.47%)
Observation group ($n = 51$)	28 (54.90%)	19 (37.25%)	4 (7.84%)	47 (92.16%)
χ^2/t-value				4.744
p-value				0.029

Comparison of Complications Between the Two Groups

The total incidence of complications in the observation group (5.88%) was lower than that in the conventional group (19.61%) ($p < 0.05$), as shown in **Table 2**.

Comparison of Aesthetic Effects Between the Two Groups

The PES and WES in the observation group were higher than those in the conventional group ($p < 0.05$), as shown in **Figure 5**.

Comparison of Satisfaction Between the Two Groups

The total satisfaction in the observation group (92.16%) was higher than that in the conventional group (76.47%) ($p < 0.05$), as shown in **Table 3**.

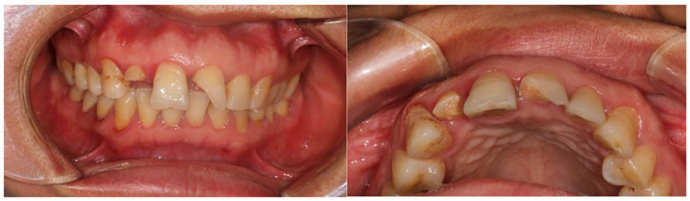
Typical Cases

A female patient who aged 35 years suffered from a traumatic injury to her upper left anterior tooth a month ago and came to our hospital for treatment because of the impact on the aesthetics of the teeth. The patient was physically healthy, denied a history of systemic disease, and denied a history of drug allergy. Extraoral examination showed that the patient's facial appearance was symmetrical, her mouth opening was normal, there was no buzzing, murmur, or tenderness in the temporomandibular joint area, and no enlarged lymph nodes were palpable in the submandibular, submental, and neck areas. Intraoral examination showed that the 21 mesial crown fracture defect, mesial and palatal side involving 1 mm subgingival, no loosening, tapping [-], gingival biologic pattern of medium thick gingival, root surface convexity consistent with the contralateral tooth of the same name, and median laughter line. Before the operation, CBCT showed that the 21 labial bone plate was continuous and complete, with a thickness of about 0.8 mm, the root of the tooth was close to the labial bone plate, and the height of apical bone was > 4 mm. It was diagnosed that 21 crown-roots were broken. The CAD/CAM guides combined with SST were performed on the patient. After the operation, the tooth was well repaired. The color of the restoration was similar to that of the adjacent teeth. The restoration was in harmony with the whole teeth, the gingival was in good condition, and the bone level at the edge of the implant was stable. The patient was satisfied with the restoration effect, as shown in **Figures 6 (A–K)**.

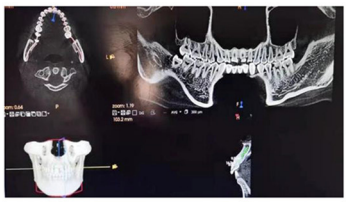
DISCUSSION

In recent years, with the improvement in economic level, people pay more and more attention to the problem of tooth health, and people are eager to repair the defect of anterior teeth aesthetic area and achieve ideal aesthetic effect. Immediate implantation, as a common clinical dental restoration method, is maturing in the development of artificial implantation technology, but its surgical accuracy and density can no longer meet the needs of patients. Because of the thin labial bone wall and thick palatal bone wall in the aesthetic area of anterior teeth, it is easy to cause the drill needle to shift to labial side when preparing the implant socket. In addition, immediate implantation cannot avoid alveolar bone absorption, especially in patients with thin labial bone plate, the probability of soft tissue retraction is obviously increased, resulting in a series of complications (10). Therefore, determining the three-dimensional position of the implant and maintaining the thickness of the labial bone wall play a vital role in the restoration of the aesthetic area of the anterior teeth, which has become an urgent problem to be solved in the current implant field.

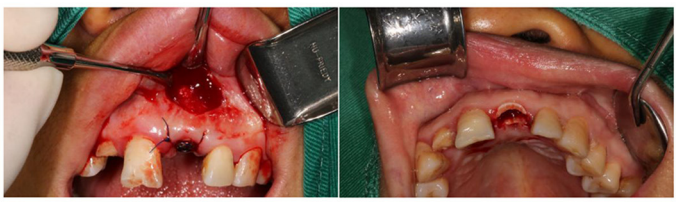
With the emergence of digital information technology, the application of CAD/CAM guide plate in clinic has been widely recognized. In this study, 102 patients with immediate implants were treated with CAD/CAM guide combined with SST, and finally, the success rate was 100.00%, and the deviation value of implants was small. The possible reason is that by importing the data derived from CBCT into professional software, deeply analyzing the three-dimensional data in the oral cavity and reconstructing the three-dimensional jaw model, the type, location, and depth of the implant can be determined (11). The dental implant guide plate manufactured by CAD/CAM greatly defines the angle and direction of implant implantation, which can provide more accurate positioning for immediate implant operation, significantly reduce the deviation value of empirical operation in space position and then improve the precision of implant and increase the probability of successful implant (12). In addition, during the implementation of SST, the surgeon divides the root of the tooth, extracts the root of the palatal tooth, and retains the dental slice shield, which is beneficial to enhance the resistance of the labial bone plate to external forces and maintain the blood supply of periodontal ligament to the labial bone plate (13). SST is a simple surgical procedure, which can preserve as many periodontal ligament cells as possible, reduce trauma of soft tissue and bone plate, reduce the risk of alveolar bone absorption and collapse, and play a positive role in increasing the stability of implants (14).



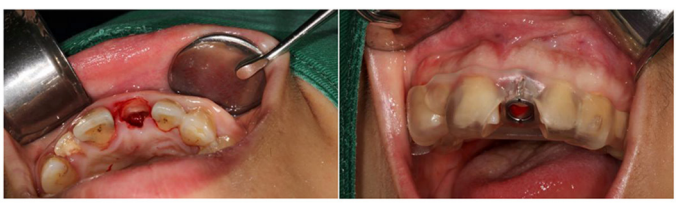
A Front view before operation **B** Maxillofacial view before operation



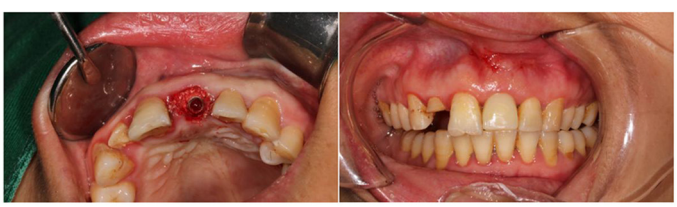
C CAD/CAM digital plan design before operation



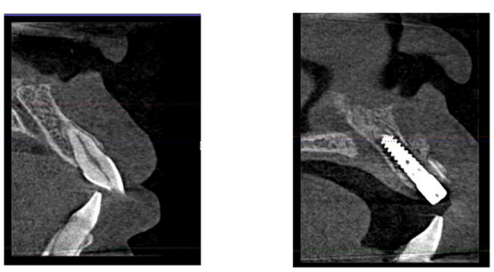
D The labial apical fenestration **E** The root was divided into labial-palatal sides



F The palatal root was removed **G** CAD/CAM digital guide plate in place



H Implant placement **I** 21 teeth restoration completed after operation



J CBCT image before operation **K** CBCT image after operation

FIGURE 6 | Typical cases. **(A)** Front view before operation, **(B)** Maxillofacial view before operation, **(C)** CAD/CAM digital plan design before operation, **(D)** The labial apical fenestration, **(E)** The root was divided into labial-palatal sides, **(F)** The palatal root was removed, **(G)** CAD/CAM digital guide plate in place, **(H)** Implant placement, **(I)** 21 teeth restoration completed after operation, **(J)** CBCT image before operation, and **(K)** CBCT image after operation.

We found that the absorption value of labial bone plate and the total incidence of complications in the observation group were lower than those in the conventional group. The results suggest that the application of CAD/CAM guide plate combined with SST in immediate implantation of anterior teeth aesthetic area can reduce the degree of bone resorption and complications. After applying CAD/CAM guide plate and SST in immediate implantation, it can induce the secretion of growth factors related to periodontal tissue regeneration and promote bone formation and reconstruction. At the same time, it can avoid squeezing the labial bone plate, increase blood supply, change the way that alveolar ridge bears stress, and stimulate the proprioceptor of periodontal membrane of anterior teeth, thereby reducing the absorption of labial bone plate. In the process of traditional immediate implant operation, the angle change and shaking of twist drill may lead to complications such as crown fracture and gingival swelling after operation, which will further affect the restoration effect. Compared with the traditional immediate implantation, SST based on CAD/CAM guide plate can prevent the twist drill from producing excessive impact and vibration by guiding the operator to determine the three-dimensional position of the implant and reduce the operation requirement of angle change, so that the implant can be implanted into the missing tooth more accurately and in a reasonable position. This surgical scheme has the advantages of less trauma and low risk, which can prevent the implant from touching the important nerves and blood vessels of periodontal tissue and reduce the occurrence of complications such as bleeding and peri implant inflammation. We also found that the application of CAD/CAM guide plate combined with SST can reduce PD, PLI, and SBI and promote periodontal health. Sun's team reported that the PD, PLI, and SBI in SST group were significantly lower than those in traditional group (15). After the implementation of SST, we applied CAD/CAM guide plate to implant, which made the oral structure, operation process, and other information clearer and more transparent, greatly reduced the surgical trauma, avoided damaging the periodontal tissue, and was more conducive to improve the postoperative periodontal environment.

For patients with defects in the aesthetic area of anterior teeth, they often have higher aesthetic restoration requirements. Not only the white aesthetics of restoration are the key part of this area, but also the pink aesthetics such as the shape, texture, color, and outline of gums are the focus of oral aesthetics (16). In this study, CAD/CAM guide plate combined with SST can improve the aesthetics of immediate implantation in the aesthetic area of anterior teeth and obtain higher satisfaction. In the process of CAD/CAM guide plate design, the operator and the patient communicate accurately and intuitively. After doctors know the patient's repair needs, they can extract oral information through CBCT, reconstruct the three-dimensional jaw image, and measure the available bone width and the available bone height in the missing tooth area, so as to determine the three-dimensional position of the implant. This can obtain good initial stability, which is beneficial to achieve accurate and beautiful implant restoration effect (17). The design and manufacture of CAD/CAM guide plate plays a certain restrictive role in implant operation, which is beneficial to avoid the poor implant position caused by the operator's lack of experience, and makes the tooth position structure after operation close to the normal physiological state, thus meeting the aesthetic requirements of immediate implant patients (18). SST is beneficial to preserve the amount of labial alveolar bone, maintain the thickness and contour of bone plate, improve the shape and position of gingival margin, and provide conditions for the regeneration of soft and hard tissues, so that the immediate implant site can obtain a stable aesthetic effect (19, 20). SST is easy to operate, less surgical trauma, no excessive surgical intervention, and relatively low repair cost, which is easily accepted by patients (21).

It is worth noting that although the implementation of CAD/CAM guide plate has high accuracy, there is still some deviation in clinical application, which is the result of superposition of many factors, and the deviation may occur in any operation. At the same time, SST has the limitation of narrow indications, and it cannot be applied to cases with chronic apical infection. Additionally, the development of SST still has some problems such as tooth position, tooth outcome, curved root, and so on, and there may be potential risks in practical application. Therefore, it is necessary for clinicians to master professional knowledge and clinical skills, minimize the controllable deviation factors during implantation, and carefully implement SST to protect dental tablets.

CONCLUSION

To sum up, the application of CAD/CAM guide plate combined with SST in immediate implantation of anterior teeth aesthetic area has a good effect, which can improve the accuracy of implantation, improve the periodontal environment, reduce bone resorption, reduce complications, improve aesthetics, and have high patient satisfaction. The results of this study still need to be further verified by a larger sample size data, and the long-term effects need to be discussed.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

ZW and JL mainly responsible for data statistics and paper writing. XW and NW are mainly responsible for the inclusion and treatment of cases and the detection of results. MT is mainly responsible for the guidance of the whole study. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2021.833288/full#supplementary-material

REFERENCES

1. Rupawat D, Maiti S, Nallaswamy D, Sivaswamy V. Aesthetic outcome of implants in the anterior zone after socket preservation and conventional implant placement: a retrospective study. *J Long Term Eff Med Implants.* (2020) 30:233–9. doi: 10.1615/JLongTermEffMedImplants.2020035942
2. Vidigal GM Jr, Groisman M, Clavijo VG, Barros Paulinelli Santos IG, Fischer RG. Evaluation of pink and white esthetic scores for immediately placed and provisionally restored implants in the anterior maxilla. *Int J Oral Maxillofac Implants*. (2017) 32:625–32. doi: 10.11607/jomi.5149
3. Duret F, Blouin JL, Duret B, CAD-CAM in dentistry. *J Am Dent Assoc.* (1988) 117:715–20. doi: 10.14219/jada.archive.1988.0096
4. Rosentritt M, Raab P, Hahnel S, Stöckle M, Preis V. In-vitro performance of CAD/CAM-fabricated implant-supported temporary crowns. *Clin Oral Investig.* (2017) 21:2581–7. doi: 10.1007/s00784-017-2057-7
5. Yuan X, Pei X, Zhao Y, Li Z, Chen CH, Tulu US, et al. Biomechanics of immediate postextraction implant osseointegration. *J Dent Res.* (2018) 97:987–94. doi: 10.1177/0022034518765757
6. Choi S, Yeo IS, Kim SH, Lee JB, Cheong CW, Han JS, et al. A root submergence technique for pontic site development in fixed dental prostheses in the maxillary anterior esthetic zone. *J Periodontal Implant Sci.* (2015) 45:152–5. doi: 10.5051/jpis.2015.45.4.152
7. Hürzeler MB, Zuhr O, Schupbach P, Rebele SF, Emmanouilidis N, Fickl S. The socket-shield technique: a proof-of-principle report. *J Clin Periodontol.* (2010) 37:855–62. doi: 10.1111/j.1600-051X.2010.01595.x
8. Dayakar MM, Waheed A, Bhat HS, Gurpur PP. The socket-shield technique and immediate implant placement. *J Indian Soc Periodontol.* (2018) 22:451–5. doi: 10.4103/jisp.jisp_240_18
9. Albrektsson T, Zarb G, Worthington P, Eriksson AR. The long-term efficacy of currently used dental implants: a review and proposed criteria of success. *Int J Oral Maxillofac Implants.* (1986) 1:11–25.
10. AlKudmani H, Al Jasser R, Andreana S. Is Bone graft or guided bone regeneration needed when placing immediate dental implants? A systematic review. *Implant Dent.* (2017) 26:936–44. doi: 10.1097/ID.0000000000000689
11. Vafiadis D, Goldstein G, Garber D, Lambrakos A, Kowalski B. Immediate implant placement of a single central incisor using a CAD/CAM crown-root form technique: provisional to final restoration. *J Esthet Restor Dent.* (2017) 29:13–21. doi: 10.1111/jerd.12265
12. Pang JH, Brooke S, Kubik MW, Ferris RL, Dhima M, Hanasono MM, et al. Staged Reconstruction (Delayed-Immediate) of the Maxillectomy Defect Using CAD/CAM Technology. *J Reconstr Microsurg.* (2018) 34:193–9. doi: 10.1055/s-0037-1607394
13. Abd-Elrahman A, Shaheen M, Askar N, Atef M. Socket shield technique vs conventional immediate implant placement with immediate temporization. Randomized clinical trial. *Clin Implant Dent Relat Res.* (2020) 22:602–11. doi: 10.1111/cid.12938
14. Nguyen VG, Flanagan D, Syrbu J, Nguyen TT. Socket shield technique used in conjunction with immediate implant placement in the anterior maxilla: a case series. *Clin Adv Periodontics.* (2020) 10:64–8. doi: 10.1002/cap.10087
15. Sun C, Zhao J, Liu Z, Tan L, Huang Y, Zhao L, et al. Comparing conventional flap-less immediate implantation and socket-shield technique for esthetic and clinical outcomes: a randomized clinical study. *Clin Oral Implants Res.* (2020) 31:181–91. doi: 10.1111/clr.13554
16. Al-Harbi F, Ahmad I. A guide to minimally invasive crown lengthening and tooth preparation for rehabilitating pink and white aesthetics. *Br Dent J.* (2018) 224:228–34. doi: 10.1038/sj.bdj.2018.121
17. Noharet R, Van Dooren E. Combination of cone beam computed tomography and CAD-CAM techniques for maintaining natural emergence profile in immediate extraction and/or implant placement and restoration of a central incisor: a dental technique. *J Prosthet Dent.* (2019) 122:193–7. doi: 10.1016/j.prosdent.2018.12.003
18. Johnson AC, Jain V, Ahuja S. Modified technique for CAD/CAM guided implant planning in the presence of existing hopeless teeth. *J Dent (Shiraz).* (2020) 21:69–72.
19. Mourya A, Mishra SK, Gaddale R, Chowdhary R. Socket-shield technique for implant placement to stabilize the facial gingival and osseous architecture: a systematic review. *J Investig Clin Dent.* (2019) 10:e12449. doi: 10.1111/jicd.12449
20. Bramanti E, Norcia A, Cicciù M, Matacena G, Cervino G, Troiano G, et al. Postextraction dental implant in the aesthetic zone, socket shield technique versus conventional protocol. *J Craniofac Surg.* (2018) 29:1037–41. doi: 10.1097/SCS.0000000000004419
21. Bäumer D, Zuhr O, Rebele S, Hürzeler M. Socket shield technique for immediate implant placement - clinical, radiographic and volumetric data after 5 years. *Clin Oral Implants Res.* (2017) 28:1450–8. doi: 10.1111/clr.13012

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang, Liu, Wang, Wang and Teng. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 31 January 2022
doi: 10.3389/fsurg.2022.838848

Evaluation of Implementation Effect of Cervical Cancer Comprehensive Treatment Patients With Whole-Course High-Quality Care Combined With Network Continuation Care

Jing Chen[1] *and Hui Bai*[2]*

[1] Department of Gynaecology, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, China, [2] Department of Nephrology, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, China

Purpose: Discuss the implementation effect of cervical cancer comprehensive treatment patients applying whole-course high-quality care combined with network continuation care.

Methods: From August 2020 to August 2021, 120 patients who met the inclusion criteria for comprehensive treatment of cervical cancer were divided into the regular group ($n = 60$) who received conventional care and the joint group ($n = 60$) who received whole-course high-quality care combined with network continuation care, according to the method of care. The comprehensive treatment cognition level, comprehensive treatment compliance, adverse reaction rate, quality of life questionnaire (QLQ-C30) score, self-rating anxiety/depression scale (SAS/SDS) score, and nursing satisfaction were compared between the two groups.

Results: After care, the comprehensive treatment cognition score and comprehensive treatment compliance score were higher in the joint group than in the regular group ($P < 0.05$). After care, the incidence of radiation cystitis and radiation proctitis was lower in the joint group than that in the regular group ($P < 0.05$). After care, QLQ-C30 scores on symptom domains, functional domains, and single questions were higher in both groups than before care, and were higher in the joint group than in the regular group ($P < 0.05$). After care, SAS and SDS scores were lower in both groups than before care, and were lower in the joint group than in the regular group ($P < 0.05$). After care, the joint group was more satisfied with care than the regular group ($P < 0.05$).

Conclusion: The implementation of cervical cancer comprehensive treatment patients with whole-course high-quality care combined with network continuation care has an ideal implementation effect, which can significantly increase the patient's cognition and compliance with treatment, the incidence of adverse reactions is less, the quality of life and emotional state have also improved significantly, and care satisfaction has also increased accordingly.

Keywords: cervical cancer, comprehensive treatment, whole-course high-quality care, network continuation care, implementation effect

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Yan Zou,
University of South China, China
Li Zhu,
Central South University, China

***Correspondence:**
Hui Bai
baihui512@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *18 December 2021*
Accepted: *03 January 2022*
Published: *31 January 2022*

Citation:
Chen J and Bai H (2022) Evaluation of Implementation Effect of Cervical Cancer Comprehensive Treatment Patients With Whole-Course High-Quality Care Combined With Network Continuation Care. Front. Surg. 9:838848. doi: 10.3389/fsurg.2022.838848

INTRODUCTION

Cervical cancer is a malignant tumor of the cervical canal and uterus and vagina associated with multiple factors such as human papillomavirus (HPV) infection, unclean sex, smoking, young age at first birth, prolificacy, immunosuppression, etc. (1, 2). Squamous carcinoma, adenocarcinoma, and adenosquamous carcinoma are their common pathological types (3). Its *in situ* carcinoma is more likely to occur in women aged 30–35 years, and invasive carcinoma is more likely to occur in women aged 45–55 years, and both of which have a tendency to develop at a lower age in recent years (4). The earlier the disease is treated and the earlier the clinical stage, the higher the survival rate of patients. The current 5 year survival rate worldwide is about 55.50%, which can pose a great threat to the life safety and physical and mental health of patients (5). A comprehensive treatment plan based on surgery and radiotherapy, supplemented by chemotherapy, is usually adopted clinically after considering the patient's age, physical condition, fertility needs, and cancer stage. However, there is a high risk of complications such as pain, radiation cystitis, radiation proctitis, bone marrow suppression, skin damage, hair loss, and gastrointestinal symptoms after surgery or during radiotherapy or chemotherapy, which affects patients' physical and mental status and treatment compliance (6, 7). However, the lack of scientific medical guidance and standardized nursing management after patients leave the hospital makes them more prone to a series of near and long-term complications and sequelae. Therefore, how to improve the physical and mental status and treatment compliance of cervical cancer patients, enhance the quality of post-treatment survival, and reduce the occurrence of adverse reactions has become an urgent issue for medical professionals to address. The whole-course high-quality care is to give maximum high-quality nursing support in the whole stage of patients' admission, protect patients' personal privacy and respect patients' dignity and value, so as to maximize the treatment effect and minimize adverse reactions. The network continuous care is an out of hospital extension of in-hospital nursing service with wechat and other information tools as communication media to help patients solve nursing problems after discharge. It has the characteristics of low cost and high efficiency. In recent years, our department has applied the whole-course high-quality care combined with network continuation care to the care service of cervical cancer comprehensive treatment patients, and the effect is ideal, which is reported as follows.

MATERIALS AND METHODS

Research Object

From August 2020 to August 2021, 120 patients with cervical cancer who met the inclusion criteria were enrolled in this study. Inclusion criteria: All met the diagnostic criteria of American Society for Colposcopy and Cervical Pathology for cervical cancer (8) and the staging criteria of International Federation of gynecology and obstetrics for cervical cancer (9); Clinical stage I–III; All received comprehensive anti-cancer treatment in our hospital; Junior high school education and above; Proficiency in the application of WeChat; All met the follow-up conditions. Exclusion criteria: Previous neurological or psychiatric history; Pregnancy and lactation; Presence of significant organ damage; Presence of malignancy at other sites; Presence of cognitive and communication impairment. All study subjects were divided into the regular group ($n = 60$) and the joint group ($n = 60$) according to the different methods of care. There was no significant difference in age, clinical stage, type of pathology, and education level between the two groups, which were comparable ($P > 0.05$) (**Table 1**).

TABLE 1 | Comparison of baseline information between the two groups (n, $\bar{x}\pm s$, %).

Items	Regular group ($n = 60$)	Joint group ($n = 60$)	t/χ^2 value	P-value
Age (years old)	49.42±6.49	50.24±6.49	0.703	0.483
Clinical stage (n, %)			0.586	0.746
Period I	18 (30.00)	20 (33.33)		
Period II	23 (38.33)	19 (31.67)		
Period III	19 (31.67)	21 (35.00)		
Type of pathology (n, %)			1.097	0.578
Squamous carcinoma	45 (75.00)	48 (80.00)		
Adenocarcinoma	14 (23.33)	10 (16.67)		
Adenosquamous carcinoma	1 (1.67)	2 (3.33)		
Education level (n, %)			0.391	0.532
Middle School–High School	46 (76.67)	43 (71.67)		
University and above	14 (23.33)	17 (28.33)		

Research Methods

Both groups received comprehensive treatment for cervical cancer. That was, for patients with stage Ia1–Ib1 cervical cancer, the cervix or uterine body should be surgically removed as appropriate + pelvic lymph node dissection and/or paraaortic lymph node dissection, for those with high-risk factors, adjuvant radiotherapy and chemotherapy; For patients with stage Ib2–IIa2 cervical cancer, radical hysterectomy + pelvic lymph node dissection and/or paraaortic lymph node dissection and radiotherapy and chemotherapy were performed; For patients with stage IIb–IIIb cervical cancer, concurrent chemoradiotherapy with radiotherapy as the core was implemented. On this basis, the regular group received conventional care interventions and the joint group received whole-course high-quality care combined with network continuation care interventions.

Conventional care: In other words, according to the comprehensive treatment process of cervical cancer, patients were given verbal health education about cervical cancer; they were informed of the precautions and examination items during surgery and radiotherapy; they were advised to complete daily basic care; they were strictly supervised to take medication and receive treatment on time; the hygiene and room temperature of wards and treatment rooms were maintained; and the changes of patients' vital signs were strictly monitored and recorded.

Whole-course high-quality care: ①Before comprehensive treatment: Medical and nursing staff should actively communicate with patients and their families, patiently inform patients or their families of the rationale, necessity, effects and possible adverse reactions of the treatment. Through conversations, letting them fully understand the basic knowledge and precautions related to treatment, so that they had good self-management skills and ability to respond to emergencies. For example, radiotherapy maybe cause burning, redness, swelling and other damage to the skin of the patient's healthy parts. Therefore, medical staff should inform patients or their families in advance to prepare soft, cotton underwear to reduce contact with the skin of the affected area. For patients with psychological stress or their family members, they should be informed that anxiety, tension, fear, etc. are all normal psychological emotions, and should be addressed squarely and actively relieved. Through verbal communication, understand the reasons for the patients' negative emotions and provide targeted psychological counseling to make the patients face treatment with an optimistic attitude. ②During comprehensive treatment: Recording the patient's vital signs changes and adverse reactions in detail, and giving targeted treatment measures to them. In addition, strengthenning the screening of patients' pain and other problems, timely intervene in case of abnormality. At the same time, medical staff stilled need to pay close attention to the patient's psychological state and source of negative emotions. The discomfort of the patient or the psychological defense mechanism could be eliminated in time through methods such as psychological suggestion and attention shift, so as to obtain the cooperation and trust of the patient as much as possible, thereby improving the compliance to receive treatment. ③After comprehensive treatment: Actively dealing with treatment-related adverse reactions and complications. For example, for patients with skin burns, they should be told to keep their skin dry, keep away from light, do not touch vigorously, and do not use drugs without authorization. Patients with gastrointestinal symptoms should be encouraged to eat consistently, and medical staff can work with the patient's family to establish a scientific, reasonable and rich and diverse healthy diet for the patient. Instruct patients to increase their drinking water appropriately after radiotherapy and chemotherapy to accelerate the metabolism and excretion of drugs. Eat more fresh ingredients that can boost immunity every day, and try to maintain or enhance the flavor of the food during preparation to stimulate the appetite of the patient. It was also possible to reduce gastrointestinal discomfort in patients by eating small meals and frequent meals. For patients with radiation cystitis, gauze could be filled in the vagina to reduce radiation damage, and dexamethasone, gentamicin and other drugs could also be appropriately treated. For patients with radiation proctitis, bismuth carbonate should be taken orally in time, and the patients should be instructed to reduce the intake of crude fiber to reduce the secondary irritation to the intestinal tract. After the patient was discharged from the hospital, the researchers followed up by telephone twice a month to understand their physical and mental status and health problems, supervised patient's treatment progress and health management, etc., actively corrected patients' misunderstandings about disease and health, and patiently answered patients' health problems and treatment confusion.

Network continuation care: Using WeChat as the medium of implementation. First, the department established a WeChat group of network continuation care, and drew the members of the department into the group. Then posted the admission QR code in the department, and patients could scan the code to join the group upon admission. Arranging a full-time nurse to develop a treatment cycle schedule for each patient, so that patients can obtain information such as consultation appointments, discharge instructions, return treatment time, follow-up time, treatment progress, departmental contact information, and other relevant information within the group. At the same time, the group regularly pushed related articles about common complications and treatment methods after cervical cancer radiotherapy and chemotherapy, and dietary precautions, which patients could download and read by themselves. Every day, a physician and a full-time nurse were arranged to provide professional answers and guidance to patients' doubts and problems. Questions related to personal privacy such as sex life could be reported and answered privately. At the same time, patients could also communicate or give feedback on their own in the group, share their anti-cancer experience or nursing improvement opinions, etc. The department held a forum once a month to summarize the problems and feedback collected and discuss solutions, so as to continuously improve the group management process and service process of network continuation care.

Observation Index

(1) Comprehensive treatment cognitive score: After care, the "Questionnaire for Comprehensive Treatment Cognitive Level of Cervical Cancer," which was developed by our hospital, was used for assessment. The total score was 0–100, and the higher the score, the higher the cognitive level.

(2) Comprehensive treatment compliance score: After care, the "Questionnaire for Comprehensive Treatment Adherence of Cervical Cancer," which was developed by our hospital, was used for assessment. The total score was 0–100, the higher the score, the better the compliance.

(3) Incidence of adverse reactions: The treatment-related adverse reactions such as radiation cystitis, radiation proctitis, bone marrow suppression and digestive symptoms during care were recorded in both groups.

(4) Quality of life questionnaire (QLQ-C30) score: Before and after care, the QLQ-C30 was used to assess the overall quality of life of both groups, including symptom domains, functional domains, and single-item problems. The total score of each item was 0∼100, and the higher the score, the better the quality of life.

(5) Self-rating anxiety/depression scale (SAS/SDS) score: Before and after care, the emotional status of both groups was assessed by SAS/SDS. The former group was classified as having anxiety symptoms with a standard score of $\geq$50, and the latter group was classified as having depressive symptoms with a standard score of $\geq$53.

(6) Nursing satisfaction: After nursing care, the "Nursing Satisfaction Questionnaire for Cervical Cancer Patients," which

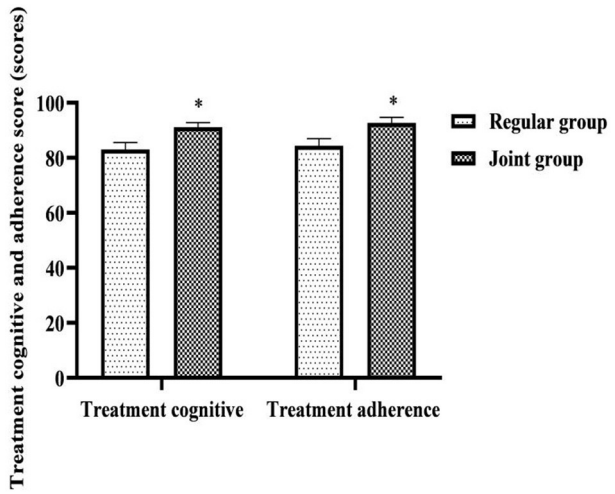


FIGURE 1 | Comparison of cognitive and adherence scores of comprehensive treatment of the two groups. Compared with the same item in the regular group, $^*P < 0.05$.

was developed by our hospital, was used for assessment. The total score of 90–100 was very satisfied, 60–89 was satisfied and <60 was unsatisfied.

Statistical Methods

SPSS 22.0 software was applied, and the measurement data were expressed as mean ± standard deviation and compared by *t*-test. Count data were expressed as ratio, and the χ^2 test was used for comparison. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of Cognitive and Adherence Scores of Comprehensive Treatment of the Two Groups

After care, the comprehensive treatment cognition score and comprehensive treatment compliance score were higher in the joint group than in the regular group ($P < 0.05$) (**Figure 1**).

Comparison of the Incidence of Adverse Reactions of the Two Groups

After care, the incidence of radiation cystitis and radiation proctitis was lower in the joint group than that in the regular group ($P < 0.05$) (**Table 2**).

Comparison of QLQ-C30 Scores of the Two Groups

After care, QLQ-C30 scores on symptom domains, functional domains, and single questions were higher in both groups than before care, and were higher in the joint group than in the regular group ($P < 0.05$) (**Figure 2**).

Comparison of SAS and SDS Scores of the Two Groups

After care, SAS and SDS scores were lower in both groups than before care, and were lower in the joint group than in the regular group ($P < 0.05$) (**Figure 3**).

Comparison of Nursing Satisfaction of the Two Groups

After care, the joint group (96.67%) was more satisfied with care than the regular group (83.33%) ($P < 0.05$) (**Table 3**), 60–89 was satisfied and <60 was unsatisfied.

DISCUSSION

In recent years, with the popular use of HPV vaccine and cervical cytology screening, the incidence of cervical cancer and its precancerous lesions has been greatly reduced by early prevention, diagnosis and treatment, but patient survival is still low (10). In the implementation of comprehensive treatment for cervical cancer patients, the clinical approach mostly adopts staged treatment. That is, cervical cancer patients with stage Ia1–IIa2 are treated with comprehensive treatment measures mainly with surgery and supplemented with radiotherapy; patients with stage ≥IIb are treated with simultaneous radiotherapy and chemotherapy with radiotherapy as the core (7, 11). However, it has been observed that after cervical cancer surgery, the sense of experience such as pain or incompleteness caused by surgical resection can lead to a range of negative emotions such as low self-esteem, loss, and depression (12, 13); Damage to adjacent organs, fatigue or bone marrow suppression caused by radiotherapy can cause further damage to the patient's health status and quality of life (14, 15); Moreover, the damage to the digestive tract caused by chemotherapy can lead to decreased appetite, nausea and vomiting, and even rejection of food, and the patient's nutrient intake is insufficient, and the body's immunity can be further reduced (16, 17). These problems can lead to non-compliance or intolerance of patients to later radiotherapy and chemotherapy, and patients end up in the unfavorable situation of short survival time and low survival probability because they cannot complete their treatment. In addition, according to our clinical observation, under the conventional nursing mode, medical staff lack advance judgment and prevention of patients' treatment adverse reactions or negative emotions, so they often fall into a panic and passive situation when problems appear, which is not conducive to the maintenance of nurse-patient relationship and the establishment of nurse-patient trust. Based on the above, it is obviously not enough to provide only routine nursing support for patients receiving comprehensive treatment for cervical cancer, and more humane and comprehensive high-quality nursing services are urgently needed to be implemented.

This study implemented the whole-course high-quality care combined with network continuation care for patients with comprehensive treatment of cervical cancer. Both of them follow the concept of "patient-centered" and strive to provide quality and humanized nursing care throughout the whole stage of

TABLE 2 | Comparison of the incidence of adverse reactions of the two groups (*n*, %).

Groups	Radiation cystitis	Radiation proctitis	Digestive symptoms	Bone marrow suppression	Others
Regular group ($n = 60$)	14 (23.33)	10 (16.67)	22 (36.67)	47 (78.33)	27 (45.00)
Joint group ($n = 60$)	3 (5.00)	2 (3.33)	18 (30.00)	40 (66.67)	18 (30.00)
χ^2value	8.292	5.926	0.600	2.048	2.880
P-value	0.004	0.015	0.439	0.152	0.090

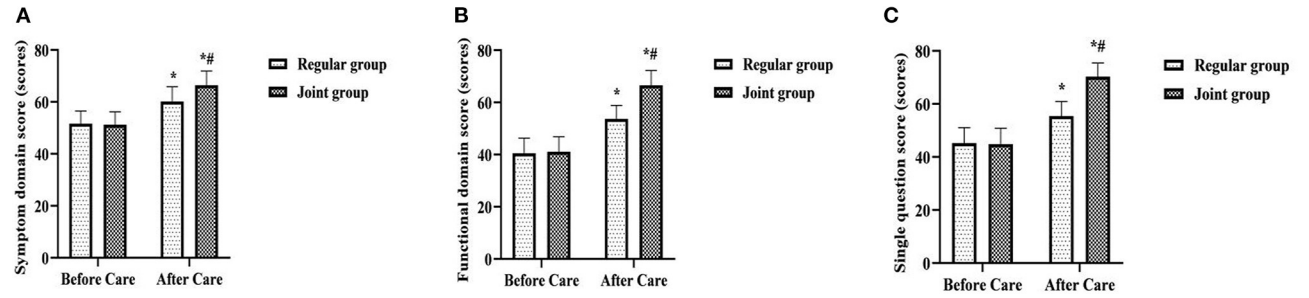


FIGURE 2 | Comparison of QLQ-C30 scores of the two groups. **(A)** Symptom domain score; **(B)** Functional domain score; **(C)** Single question score. Compared with the same group before care, $^{*}P < 0.05$; Compared with the regular group after care, $^{\#}P < 0.05$.

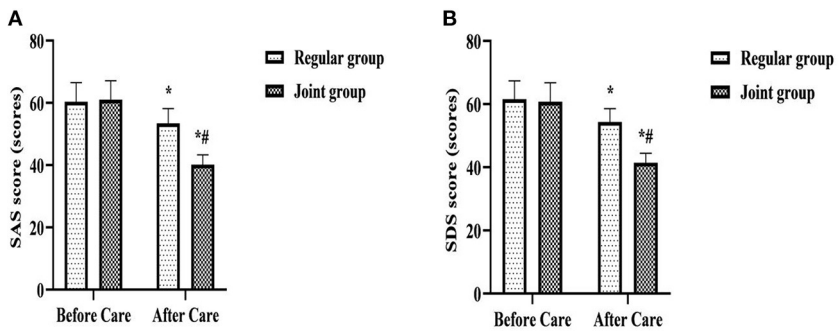


FIGURE 3 | Comparison of SAS and SDS scores of the two groups. **(A)** SAS score; **(B)** SDS score. Compared with the same group before care, $^{*}P < 0.05$; Compared with the regular group after care, $^{\#}P < 0.05$.

TABLE 3 | Comparison of nursing satisfaction of the two groups (*n*, %).

Groups	Very satisfied	Satisfied	Unsatisfied	Overall satisfaction rate
Regular group ($n = 60$)	22 (36.67)	28 (46.67)	10 (16.67)	50 (83.33)
Joint group ($n = 60$)	37 (61.67)	21 (35.00)	2 (3.33)	58 (96.67)
χ^2value				5.926
P-value				0.015

in-hospital and out-of-hospital treatment. The implementation results show that after care, the comprehensive treatment cognition score and comprehensive treatment compliance score were higher in the joint group than in the regular group; the incidence of radiation cystitis and radiation proctitis was lower in the joint group than that in the regular group; QLQ-C30 scores on symptom domains, functional domains, and single questions were higher in both groups than before care, and were higher in the joint group than in the regular group ($P < 0.05$). In clinical care, almost all patients have varying degrees of lack of basic knowledge related to treatment (18). This may lead to poor treatment cooperation or improper self-care, which ultimately aggravates the occurrence of treatment-related complications or adverse effects and affects the quality of life and health status of patients after treatment (19). During the whole-course high-quality care in this study, before comprehensive treatment, medical staff explained to the patient the principle, necessity, effect and possible adverse reactions of the treatment. This was not only an early prediction and prevention by medical staff of possible problems during and after comprehensive treatment of patients, but also helped patients to be psychologically prepared. In order to reduce the occurrence of unfavorable expectations, patients entered the preparation state in advance to cooperate with medical staff for treatment and nursing, and actively learned basic knowledge and precautions related to treatment. Furthermore, its treatment

cognition level, treatment compliance, self-management ability and emergency response ability had been greatly improved, which would ultimately help reduce treatment-related adverse reactions and improve the prognostic quality of life. During the comprehensive treatment, medical staff not only paid attention to the targeted care of the patient's existing vital signs changes and various adverse reactions, but also paid attention to the comprehensive screening and protection of the patients' possible problems. Early detection and treatment of the direct or indirect damage that surgery or radiotherapy and chemotherapy might bring to the body would also help patients maintain their quality of life and health. After comprehensive treatment, the focus of medical staff's care was to actively treat complications and maintain the treatment effect. After the comprehensive treatment in this study, the patient's daily diet and daily life were intervened by combining with the patient's family members. The family members could play an auxiliary role in helping, supervising and reminding. This could better meet the treatment needs of patients and enhance their confidence in disease resistance, which would ultimately help improve the anti-cancer effect of comprehensive treatment. In addition, the application of network continuation care in patients' home treatment, which provided information, consultation and out-of-hospital reminders to patients with the interactive information function of WeChat. This made patients no longer limited to the time and space constraints of inconvenient to answer the phone, unclear speech, or unable to understand the content of the communication in a timely manner under the conventional care model, it had also changed the past model that patients need to integrate and screen effective information to cooperate with treatment during home treatment on their own. Medical staff could also learn about the patient's disease dynamics and treatment needs in real time through the patient's condition feedback and consultation questions, and updated and improved the nursing content accordingly. This helped to maintain the coordination and continuity of care during home treatment of patients, and was an effective way to foster patients' healthy self-reflection behavior and ensure patient treatment compliance and safety.

When the patient has misunderstandings about the disease or treatment, it can not only affect the treatment compliance and treatment effect, but also easily cause psychological imbalance, leading to a series of bad emotions such as anxiety, depression, worry, resistance, etc., which in turn can also affect the patient's compliance and effect with treatment (20). After care in this study, SAS and SDS scores were lower in both groups than before care, and were lower in the joint group than in the regular group; After care, the joint group was more satisfied with care than the regular group ($P < 0.05$). It is suggested that whole-course high-quality care combined with network continuation care is an effective initiative to improve patients' psychological stress level and nursing satisfaction, and to maintain patients' good therapeutic mindset. Analyzing the reasons, all stages of the whole-course high-quality care in this study focused on the control and enlightenment of patients' psychological state. Among them, the meticulous care and patient guidance of medical staff, and the involvement of family relationships are all helpful to the establishment of patients' confidence in treatment and the relief of negative emotions. In addition, in network continuation care, patients can discuss embarrassing problems encountered in daily life without having to meet with medical staff, which is an effective way to relieve patients' psychological burden and psychological defense mechanism, enhance nurse-patient trust and promote mutual understanding. It enables patients to communicate more candidly about psychological problems and receive psychological counseling from medical staff.

CONCLUSION

To sum up, after the implementation of the whole-course high-quality care combined with network continuation care, patients with comprehensive cervical cancer treatment have greatly improved their cognition and compliance with treatment, and treatment-related side effects have been greatly reduced. This is helpful to the overall solution of the patients' physical, psychological and social problems, so their quality of life is significantly improved, and the patient's nursing satisfaction is high.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Jinzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JC is mainly responsible for research results testing, data statistics, and paper writing. HB is mainly responsible for research design and guidance of the entire research process. Both authors contributed to the article and approved the submitted version.

REFERENCES

1. Kuroki LM, Massad LS, Woolfolk C, Thompson T, McQueen A, Kreuter MW. Cervical cancer risk and screening among women seeking assistance with basic needs. *Am J Obstet Gynecol.* (2021) 224:368. doi: 10.1016/j.ajog.2020.12.018
2. Ogilvie GS, van Niekerk D, Krajden M, Smith LW, Cook D, Gondara L, et al. Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA.* (2018) 320:43-52. doi: 10.1001/jama.2018.7464
3. Frumovitz M, Obermair A, Coleman RL, Pareja R, Lopez A, Ribero R, et al. Quality of life in patients with cervical cancer after open versus minimally invasive radical hysterectomy (LACC): a secondary outcome of a multicentre, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol.* (2020) 21:851–60 doi: 10.1016/S1470-2045(20)30081-4
4. Canfell K, Saville M, Caruana M, Gebski V, Darlington-Brown J, Brotherton J, et al. Protocol for compass: a randomised controlled trial of primary HPV testing versus cytology screening for cervical cancer in HPV-unvaccinated and vaccinated women aged 25-69 years living in Australia. *BMJ Open.* (2018) 8:e016700. doi: 10.1136/bmjopen-2017-016700
5. Chung HC, Ros W, Delord JP, Perets R, Italiano A, Shapira-Frommer R, et al. Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: results from the phase II KEYNOTE-158 study. *J Clin Oncol.* (2019) 37:1470–78. doi: 10.1200/JCO.18.01265
6. Aghili M, Andalib B, Karimi Moghaddam Z, Maddah Safaie A, Amoozgar Hashemi F, Mousavi Darzikolaie N. Concurrent Chemo- radiobrachytherapy with cisplatin and medium dose rate intra- cavitary brachytherapy for locally advanced uterine cervical cancer. *Asian Pac J Cancer Prev.* (2018)19:2745-50. doi: 10.22034/APJCP.2018.19.10.2745
7. Jing H, Xiuhong W, Ying Y, Zhenrong L, Xiyun C, Deping L, et al. Neoadjuvant chemotherapy combined with radical surgery for stage IB2/IIA2 cervical squamous cell carcinoma: a prospective, randomized controlled study of 35 patients. *World J Surg Oncol.* (2021) 19:209. doi: 10.1186/s12957-021-02318-y
8. Perkins RB, Guido RS, Castle PE, Chelmow D, Einstein MH, Garcia F, et al. 2019 ASCCP risk-based management consensus guidelines for abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis.* (2020) 24:102–31. doi: 10.1097/LGT.0000000000000525
9. FIGO Committee on Gynecologic Oncology. FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. *Int J Gynaecol Obstet.* (2014) 125:97–8. doi: 10.1016/j.ijgo.2014.02.003
10. Wright TC Jr, Parvu V, Stoler MH, Kodsi S, Eckert K, Yanson K, et al. HPV infections and cytologic abnormalities in vaccinated women 21-34 years of age: results from the baseline phase of the Onclarity trial. *Gynecol Oncol.* (2019) 153:259–65. doi: 10.1016/j.ygyno.2019.02.016
11. Benson R, Pathy S, Kumar L, Mathur S, Dadhwal V, Mohanti BK. Locally advanced cervical cancer - neoadjuvant chemotherapy followed by concurrent chemoradiation and targeted therapy as maintenance: a phase II study. *J Cancer Res Ther.* (2019) 15:1359–64. doi: 10.4103/jcrt.JCRT_39_18
12. Liu X, Wang X, Zhao W, Wei L, Zhang P, Han F. A prospective, randomized, double-blind, placebo-controlled trial of acute postoperative pain treatment using opioid analgesics with intravenous ibuprofen after radical cervical cancer surgery. *Sci Rep.* (2018) 8:10161. doi: 10.1038/s41598-018-28428-4
13. Shi Y, Cai J, Wu Z, Jiang L, Xiong G, Gan X, et al. Effects of a nurse-led positive psychology intervention on sexual function, depression and subjective well-being in postoperative patients with early-stage cervical cancer: a randomized controlled trial. *Int J Nurs Stud.* (2020) 111:103768. doi: 10.1016/j.ijnurstu.2020.103768
14. Delia P, Sansotta G, Pontoriero A, Iati G, De Salvo S, Pisana M, et al. Clinical evaluation of low-molecular-weight hyaluronic acid-based treatment on onset of acute side effects in women receiving adjuvant radiotherapy after cervical surgery: a randomized clinical trial. *Oncol Res Treat.* (2019) 42:217–23 doi: 10.1159/000496036
15. Alcântara-Silva TR, de Freitas-Junior R, Freitas NMA, de Paula Junior W, da Silva DJ, Machado GDP, et al. Music therapy reduces radiotherapy-induced fatigue in patients with breast or gynecological cancer: a randomized trial. *Integr Cancer Ther.* (2018) 17:628–35. doi: 10.1177/1534735418757349
16. Abdollahi R, Najafi S, Razmpoosh E, Shoormasti RS, Haghighat S, Raji Lahiji M, et al. The effect of dietary intervention along with nutritional education on reducing the gastrointestinal side effects caused by chemotherapy among women with breast cancer. *Nutr Cancer.* (2019) 71:922–30. doi: 10.1080/01635581.2019.1590608
17. Pfister C, Gravis G, Flvention along with nutritional educa, et al. Randomized phase iii trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin, or gemcitabine and cisplatin as perioperative chemotherapy for patients with muscle-invasive bladder cancer. Analysis of the GETUG/AFU V05 VESPER trial secondary endpoints: chemotherapy toxicity and pathological responses. *Eur Urol.* (2021) 79:214–21. doi: 10.1016/j.eururo.2020.08.024
18. Wang B, Luo QQ, Li Q, Cheng L, Chen SL. Daily short message service reminders increase treatment compliance and efficacy in outpatients with functional dyspepsia: a prospective randomized controlled trial. *J Gen Intern Med.* (2020) 35:2925–31. doi: 10.1007/s11606-020-06088-3
19. Tong P, Bu P, Yang Y, Dong L, Sun T, Shi Y. Group cognitive behavioural therapy can reduce stigma and improve treatment compliance in major depressive disorder patients. *Early Interv Psychiatry.* (2020) 14:172–8.doi: 10.1111/eip.12841
20. Cai H, Xu S. A randomized trial of psychological intervention on perioperative anxiety and depression of patients with severe blepharoptosis undergoing autologous fascia lata frontal muscle suspension. *Ann Palliat Med.* (2021) 10:3185–93. doi: 10.21037/apm-21-345

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Chen and Bai. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 01 February 2022
doi: 10.3389/fsurg.2021.829227

Clinical Observation of Comfort Nursing Combined With Continuous Nursing Intervention After Discharge on Improving Pressure Ulcers, Falls, Quality of Life, and Prognosis in Patients With Intracerebral Hemorrhage

Ji Min Wang[1], *Zhen Liu*[2†] *and Hongxia Liu*[2*†]

[1] *Department of Traditional Chinese Medicine, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, China,* [2] *Department of Neurology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, China*

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Li Zhang,
University of South China, China
Jing Xu,
Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, China

***Correspondence:**
Hongxia Liu
lhx8891@sina.cn

[†] *These authors have contributed equally to this work and share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *05 December 2021*
Accepted: *15 December 2021*
Published: *01 February 2022*

Citation:
Wang JM, Liu Z and Liu H (2022) Clinical Observation of Comfort Nursing Combined With Continuous Nursing Intervention After Discharge on Improving Pressure Ulcers, Falls, Quality of Life, and Prognosis in Patients With Intracerebral Hemorrhage. Front. Surg. 8:829227. doi: 10.3389/fsurg.2021.829227

In this prospective study, we randomly divided 131 patients with intracerebral hemorrhage (ICH) who met the inclusion criteria into two groups. One group received routine nursing during hospitalization, and the "Stroke Prevention Knowledge Manual" was issued before discharge, and was recorded as the control group ($n = 61$); one group received comfort nursing during hospitalization, and implemented continuous nursing after discharge, and was recorded as the research group ($n = 70$). The indicators we observed were the occurrence of pressure ulcers and falls during the hospitalization of the two groups of patients and the improvement in neurological function, limb function, quality of life, ability of daily living, and emotional state after the intervention. We also compared the disability degree of the two groups 6 months after discharge, the readmission status within 6 months of discharge, and the nursing satisfaction after the intervention. Our conclusion is that comfort nursing combined with continuous nursing intervention after discharge can effectively reduce the occurrence of pressure ulcers and falls during the nursing period of patients with ICH and contribute to the improvement of their quality of life and prognosis. It is worthy of clinical promotion.

Keywords: intracerebral hemorrhage, comfort nursing, continuous nursing, pressure ulcers, falls, quality of life, prognosis

INTRODUCTION

Intracerebral hemorrhage (ICH) is an acute hemorrhagic stroke in which non-traumatic factors cause the rupture of cerebral arteries and the accumulation of blood around the brain tissue, which damages the normal nerve function of the brain, and it accounts for about 10–30% of all patients with stroke (1, 2). The clinical symptoms of the disease are complex and the treatment cycle is long. In addition to the limbs and nerve dysfunction caused by the disease itself, some patients who

need to receive long-term bed treatment due to coma, intracranial hypertension, or large bleeding are also prone to pressure sores, pulmonary infection, and other immobile complications, which complicates the condition (3). In addition, falls are also a common adverse event in patients with ICH, and the cause may be related to the decline in cognitive level of patients with ICH and motor and sensory functions (4). For the treatment of ICH, surgical puncture and drainage is the ideal way to remove hematoma, relieve intracranial hypertension, prevent occupying lesions, and reduce brain herniation in a timely manner. However, 75% of patients may still have different degrees of disability after surgery, so a longer rehabilitation period is required. However, patients with prolonged illness and long-term reduced mobility are very prone to anxiety and depression, which affect the rehabilitation process (5, 6). Under the traditional nursing model, the focus of nursing for patients during hospitalization is mostly on the physiological level, and after discharge, patients can only obtain phased knowledge of rehabilitation treatment by returning to the hospital for follow-up visits, so it is difficult to achieve a harmony of physical, mental, and social health. Comfort nursing, as an extension of the connotation of holistic nursing, focuses on the harmonization of comfort and satisfaction at the physical, psychological, social, and spiritual levels compared to traditional care and is an effective care model to help patients achieve a relaxed and comfortable state and eliminate pain and fatigue symptoms, etc. (7). As an out-of-hospital extension of holistic care in the hospital, continuous nursing is a community and family service model that ensures that patients can still enjoy continuous and coordinated rehabilitation care during the recovery period after discharge, and it has the effect of promoting the rehabilitation process and reducing the need for readmission (8). In this study, comfort nursing and continuous nursing were combined in the nursing management of ICH, and its effects on pressure ulcers, falls, quality of life, and prognosis of patients with ICH were observed. The report is as follows.

MATERIALS AND METHODS

General Information

From March 2018 to December 2019, 131 patients with ICH who were admitted to this hospital were randomly divided into the control group ($n = 61$) and the study group ($n = 70$). There was no statistical difference between the two groups in general information such as gender, age, bleeding site, hematoma volume, diabetes mellitus, and caregivers ($p > 0.05$), as shown in **Table 1**.

TABLE 1 | Comparison of two groups of general information [*n* (%), (M±SD)].

Types	Control group ($n = 61$)	Study group ($n = 70$)	χ^2/t	*p*
Gender			0.026	0.871
Male	34 (55.74)	40 (57.14)		
Female	27 (44.26)	30 (42.86)		
Age (year old)	64.52 ± 7.86	63.39 ± 7.67	0.831	0.407
Bleeding site			0.297	0.862
Basal ganglia	36 (59.02)	38 (54.28)		
Brain lobe	18 (29.51)	23 (32.86)		
Thalamus	7 (11.47)	9 (12.86)		
Hematoma volume (mL)	48.73±10.29	49.38±9.90	0.368	0.713
Diabetes			0.283	0.595
Yes	10 (16.39)	14 (20.00)		
No	51 (83.61)	56 (80.00)		
Caregiver			0.412	0.814
Spouse	35 (57.38)	38 (54.29)		
Children	18 (29.51)	20 (28.57)		
Other	8 (13.11)	12 (17.14)		

Inclusion Criteria

The inclusion criteria included the followings: ① patients who met the diagnostic criteria for spontaneous ICH in Guidelines for the Management of Spontaneous Intracerebral Hemorrhage (9); ② age <75 years; ③ first onset; ④ patients with soft channel puncture and drainage to remove hematoma; ⑤ patients who met the requirements for home visits; ⑥ patients who had signed an informed consent.

Exclusion Criteria

The exclusion criteria included the followings: ① ICH caused by trauma; ② secondary ICH; ③ patients with brainstem hemorrhage or brainstem failure; ④ patients with vascular dementia, Parkinson's disease, and psychosis; ⑤ patients with malignant tumors.

Nursing Methods

Both groups were treated with minimally invasive soft channel puncture and drainage after admission to the hospital, and vital signs were monitored and maintained after the operation. Basic treatments such as lowering intracranial pressure, brain-protective agents, control of blood pressure and blood sugar, and prevention of complications were given according to the specific conditions of the patients. Based on this, the control group was received with routine nursing intervention during hospitalization, that was, in-hospital health education, guidance on diet, life and medication, oral, respiratory, and psychological care, and after 48 h of stable illness, routine functional training and active and passive activities of the limbs were carried out. The "Knowledge Handbook of Stroke Prevention and Treatment" was distributed before discharge and rehabilitation training was ordered and returned to the hospital for follow-up treatment 6 months after discharge.

On the basis of the above, the research group was received with comfort nursing intervention during hospitalization. Specifically, (1)Comfortable environment: Keep the ward well-ventilated, well-lit, clean and tidy, suitable for room temperature and humidity, place green plants, and use warm color decorations to provide a comfortable hospital environment for the rehabilitation of patients. (2) Comfortable bedtime: Based on the routine bedtime management (3–4 w), combined with evidence-based nursing basis and expert advice, targeted bedtime guidance was

implemented to prevent adverse events such as rebleeding and falls. In other words, for those who had basically disappeared with positive signs of the nervous system and symptoms, they could gradually sit up and get out of bed after 5–7 days of bed rest; for those with mild positive signs of the nervous system and no symptoms of intracranial hypertension, they could perform self-care activities such as dressing, sitting up, eating, and washing in bed after 2 weeks of bed rest and gradually got out of bed after half a month; for severe condition of patients with heavy bleeding or intracranial hypertension, they stayed in bed strictly for 3–4 w; and for subarachnoid hemorrhage, they stayed in bed absolutely for 4–6 w. Those who did not listen to discussion should have patiently explained the reasons and consequences. (3) Comfortable posture: Raise the head of the bed 15–30°, use an antidecubitus air mattress, and assist the patient to turn over and knock their back once every 2.5 h. In the treatment of the affected limbs and joints, put a small soft pillow to keep the affected limbs in a functional position and assist the caregiver to massage the bony processes and compressed areas. Wipe the skin with warm water every day, especially to keep the skin clean at the vulva, buttocks and cornea. Put foot boards on the soles of the feet or wore hard shoes to prevent edema, shoulder and back pain, joint deformities, pressure sores, and foot drop; for people with unconsciousness or agitation, guardrails should be added by the bed to prevent falls hurt. (4)Comfortable sleep: Keep the ward quiet, arrange reasonable time for diagnosis, treatment and nursing activities, and create favorable conditions for the patient's normal sleep–wake cycle, which could soak feet in hot water at night, empty your urinary bladder before going to bed, drink hot milk, listen to light music, etc. For those who suffered from insomnia caused by pain, we should deal with symptoms promptly; for those who were accompanied by anxiety and depression, we should strengthen psychological counseling and give more comfort and companionship. If necessary, oral sedative hypnotic drugs were administered. (5) Comfortable defecation: the reasons and importance of defecating in bed needed to be explained to the patient. The bed should be covered with a sheet, kept dry and clean, and changed in a timely manner. When the ward had many people, a screen was set up to shield and give psychological comfort to the patients. When the patients had difficulty in defecating, the researchers could help them defecate by massaging the lower abdomen appropriately. (6) Comfortable infusion: Use intravenous indwelling needles for infusion, when infusion, keep warm and use a thermostat to warm to about 35°C before infusion, appropriate massage during needle insertion to relieve discomfort, during the infusion, observe closely for redness, swelling, and leakage of the infusion limb. (7)Mental comfort: Medical staff should be confident and calm, communicate actively with patients in friendly language, and introduce past successful cases to patients to ease their panic, respect and understand patients, listen patiently to their main complaints, and promptly resolve the psychological problems that cause their unhappiness. (8)Social comfort: understand the patient's family members and social relationships, communicate with the patient's family more often, and do a good job of psychological counseling for them. It was suggested that the patients should be tolerant and understand each other and strive for effective family and social support for the patients as much as possible.

Continuous nursing care during the rehabilitation period after discharge from the hospital was carried out. Specifically, (1) Conduct targeted bedside teaching or video drills before discharge, and print out the key content and precautions of rehabilitation training and prevention of complications and distribute them to patients. The content mainly included the guidance of language and physical function training, the guidance of medication, diet and daily life, the treatment of spastic hemiplegia, and the prevention and treatment of pressure sores, falls, and emotional guidance. (2) Establishing a "patient rehabilitation group" by WeChat to push knowledge about stroke and its prevention and treatment of complications. Conduct video visits to guide patients' rehabilitation skills and guide communication between patients-to-patients. Organize and record the patient's rehabilitation data and answer the patient's rehabilitation questions. (3) Telephone followed-up once for every 2 w to know the patient's rehabilitation progress and to provide targeted rehabilitation guidance. Nursing staff could help patients build confidence in recovery through psychological hints or examples of successful cases. (4) The first home visit was after 1 month of discharge and once for every 3 months thereafter. Based on the degree of completion of the patient's rehabilitation plan, the patient's subsequent rehabilitation goals were analyzed and revised, and on-site rehabilitation drills were implemented until the patient and caregiver fully master them. The results were compared between the two groups 6 months after discharge.

Observe Indicators

(1) The occurrence of pressure sores and falls during the nursing period of the two groups was recorded. (2) The neurological function of the two groups before nursing and 6 months after discharge was evaluated by the National Institutes of Health Stroke Scale (NIHSS). It contained 11 items. The total score was 42, the higher the score, the more impaired the neurological function. (3) The limb function of the two groups before nursing and 6 months after discharge was assessed by Fugl-Meyer Scale (FMA). It was divided into upper limb motor function scale (33 subitems) and lower limb motor function scale (17 subitems). The total score was 100, the higher the score, the better the limb motor function. (4) The quality of life of the two groups before nursing and 6 months after discharge was assessed by the Stroke Special Quality of Life Scale (SS-QOL). It contained 12 aspects. The total score was 49–245 points, and the score was directly proportional to the quality of life. (5) The daily living ability of the two groups before nursing and 6 months after discharge was evaluated by the Modified Barthel Index (MBI). It contained 10 items. The total score was 100, the higher the score, the better the life skills. (6) The emotional state of the two groups before nursing and 6 months after discharge was evaluated by the Hospital Anxiety Depression Scale (HAD-A/HAD-D). Both are 7 items, which used Likert 3-level scoring method; 0–7 points, 8–10 points, 11–21 points represented the three emotional states of no anxiety/depression, borderline anxiety/depression, and obvious anxiety/depression,

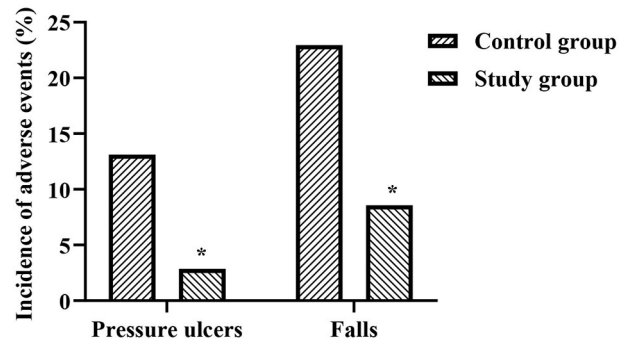


FIGURE 1 | Comparison of the incidence of pressure ulcers and falls between the two groups. *Represents that there was a statistical difference in the control group and the study group.

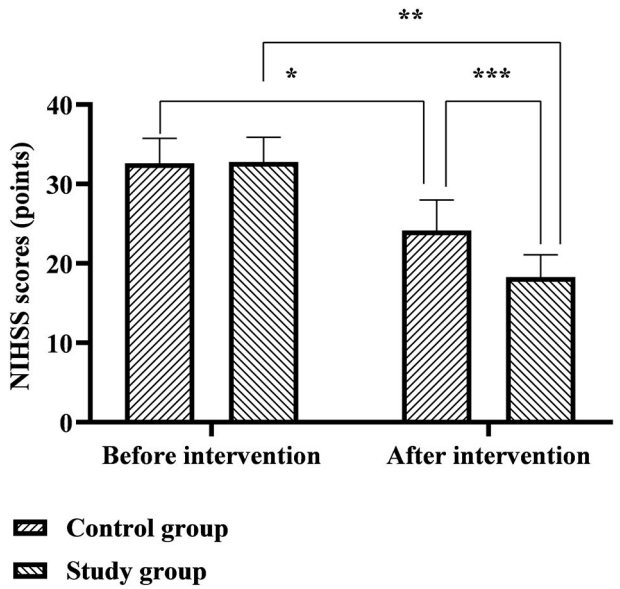


FIGURE 2 | Comparison of NIHSS scores between the two groups. *Represents that there was a statistical difference in the NIHSS scores before and after the intervention in the control group ($t = 13.390$, $p < 0.001$); **represents that there was a statistical difference in the NIHSS scores before and after the intervention in the study group ($t = 29.212$, $p < 0.001$); ***represents that there was a statistical difference in the NIHSS scores of the control group and the study group after the intervention ($t = 10.076$, $p < 0.001$).

respectively. (7) The degree of disability of the two groups 6 months after discharge was assessed by the Glasgow Outcome Scale (GOS). A five-level scoring method was adopted for grading. Among them, Grade I, Grade II, Grade III, Grade IV, and Grade V represented the five disability states of namely death, plant survival, severe disability, moderate disability, and good disability, respectively. Disability rate = (Grade II + III + IV)/total number of cases. The readmissions within 6 months of discharge from the two groups were recorded. (8) The satisfaction of the two groups after nursing was evaluated by the self-made nursing satisfaction questionnaire. It was divided into three levels: very satisfied, basically satisfied, and unsatisfied (85–100 points, 60–84 points, and 0–60 points). The content validity index of this questionnaire was 0.890, the Cronbach's alpha coefficient was 0.896, and the reliability and validity were good. Satisfaction rate = (very satisfied + basically satisfied) number/total number × 100%.

Statistical Methods

The SPSS 22.0 software was used, the counting data are expressed as (%), the comparison is performed by chi-square test, the measurement data are expressed as (±s), and t analysis is carried out for comparison. $p < 0.05$ indicates that the difference is statistically significant.

RESULTS

Comparison of the Incidence of Pressure Ulcers and Falls Between the Two Groups

During the nursing period, the incidence of pressure ulcers in the study group (2.86%) was significantly lower than that in the control group (13.11%) ($p < 0.05$), and the incidence of falls in the study group (8.57%) was significantly lower than the control group (22.95%) ($p < 0.05$), as shown in **Figure 1**.

Comparison of NIHSS and FMA Scores Between the Two Groups

The NIHSS scores of the control group before and after the intervention were 32.62 ± 3.13 and 24.14 ± 3.83 points, respectively, and the NIHSS scores of the study group before and after the intervention were 32.80 ± 3.08 and 18.29 ± 2.79 points, respectively. The FMA scores of the control group before and after the intervention were 31.41 ± 6.63 and 75.86 ± 7.14 points, respectively, and the FMA scores of the study group before and after the intervention were 30.65 ± 6.72 and 81.82 ± 8.06 points, respectively. Six months after discharge, the NIHSS scores of the two groups were significantly lower than before nursing, the FMA scores were significantly higher than before nursing, and the study group was significantly better than the control group ($p < 0.05$), as shown in **Figures 2**, **3**.

Comparison of SS-QOL and MBI Scores Between the Two Groups

The SS-QOL scores of the control group before and after the intervention were 143.57 ± 9.83 and 154.34 ± 12.78 points, and the SS-QOL scores of the study group before and after the intervention were 142.89 ± 9.64 and 172.22 ± 13.61 points. The MBI scores of the control group before and after the intervention were 35.43 ± 5.61 and 63.48 ± 6.50 points, and the MBI scores of the study group before and after the intervention were 34.96 ± 5.77 and 69.06 ± 7.19 points. Six months after discharge, the SS-QOL and MBI scores of the two groups were significantly higher than before nursing, and the study group was significantly higher than the control group ($p < 0.05$), as shown in **Figures 4**, **5**.

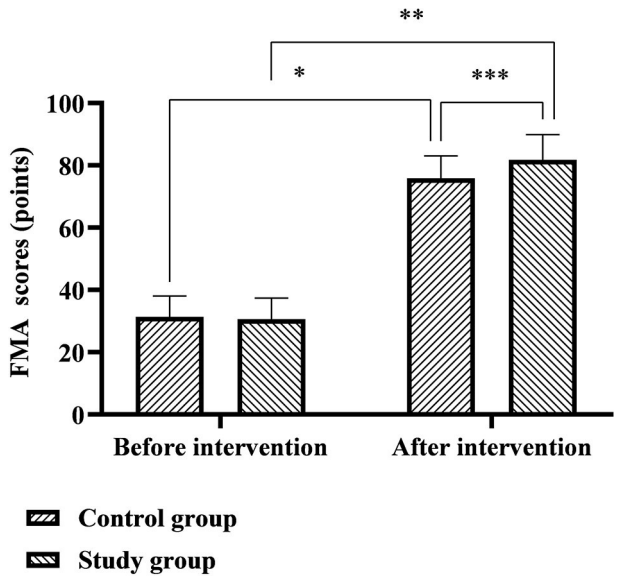


FIGURE 3 | Comparison of FMA scores between the two groups. *Represents that there was a statistical difference in the FMA scores of the control group before and after the intervention ($t = 35.630$, $p < 0.001$); **represents that there was a statistical difference in the FMA scores of the study group before and after the intervention ($t = 40.797$, $p < 0.001$); ***represents that there was a statistical difference in the FMA scores of the control group and the study group after the intervention ($t = 4.450$, $p < 0.001$).

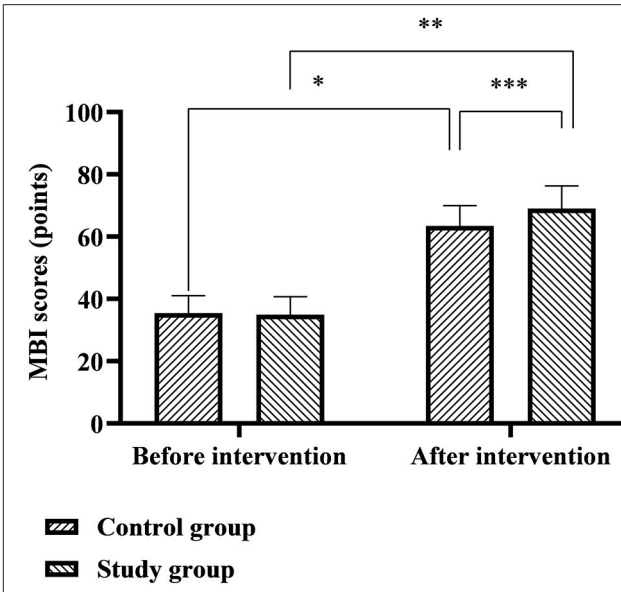


FIGURE 5 | Comparison of MBI scores between the two groups. *Represents that there was a statistical difference in the MBI score of the control group before and after the intervention ($t = 25.515$, $p < 0.001$); **represents that there was a statistical difference in the MBI score of the study group before and after the intervention ($t = 30.947$, $p < 0.001$); ***represents that there was a statistical difference in the MBI scores of the control group and the study group after the intervention ($t = 4.632$, $p < 0.001$).

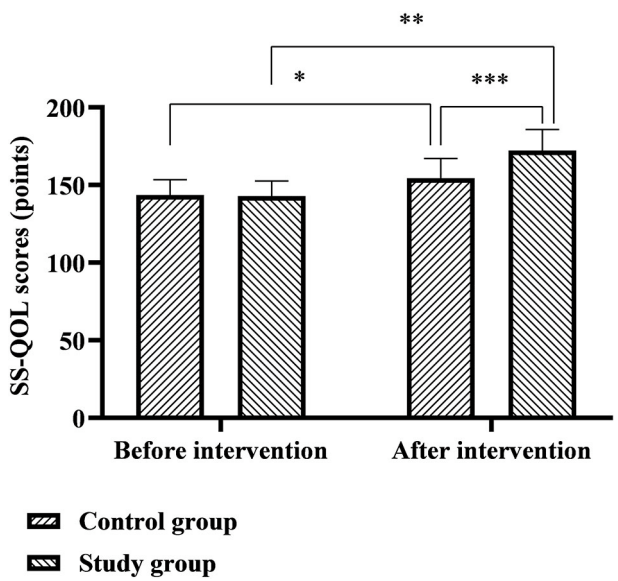


FIGURE 4 | Comparison of SS-QOL scores between the two groups. *Represents that there was a statistical difference in the SS-QOL score of the control group before and after the intervention ($t = 5.217$, $p < 0.001$); **represents that there was a statistical difference in the SS-QOL score of the study group before and after the intervention ($t = 14.713$, $p < 0.001$); ***represents that there was a statistical difference in the SS-QOL scores of the control group and the study group after the intervention ($t = 7.716$, $p < 0.001$).

Comparison of HAD-A and HAD-D Scores Between the Two Groups

The HAD-A scores of the control group before and after the intervention were 9.64 ± 2.68 and 6.77 ± 2.35 points, and the HAD-A scores of the study group before and after the intervention were 9.58 ± 2.71 and 5.87 ± 2.01 points. The HAD-D scores of the control group before and after the intervention were 8.53 ± 2.32 and 6.73 ± 1.72 points, and the HAD-D scores of the study group before and after the intervention were 8.60 ± 2.29 and 5.84 ± 1.46 points. Six months after discharge, the HAD-A and HAD-D scores of the two groups were significantly lower than before nursing, and the study group was significantly lower than the control group ($p < 0.05$), as shown in **Figures 6**, **7**.

Comparison of Disability Rate and Readmission Rate Between the Two Groups

Six months after discharge, the disability rate of the study group (62.86%) was lower than that of the control group (75.41%), but there was no statistical difference between the two groups ($p > 0.05$). Within 6 months of discharge, the readmission rate of the study group (7.14%) was lower than that of the control group (18.03%), but there was no statistical difference between the two groups ($p > 0.05$), as shown in **Table 2**.

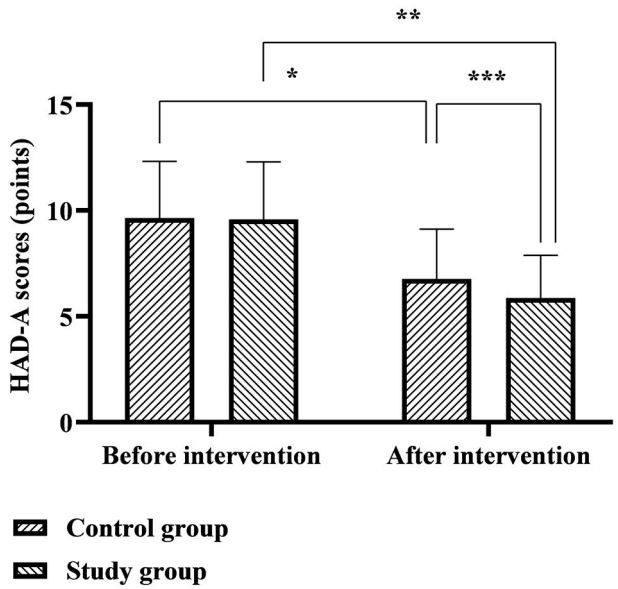


FIGURE 6 | Comparison of HAD-A scores between the two groups. *Represents that there was a statistical difference in the HAD-A scores of the control group before and after the intervention ($t = 6.289$, $p < 0.001$); **represents that there was a statistical difference in the HAD-A scores of the study group before and after the intervention ($t = 9.200$, $p < 0.001$); ***represents that there was a statistical difference in the HAD-A scores of the control group and the study group after the intervention ($t = 2.363$, $p < 0.05$).

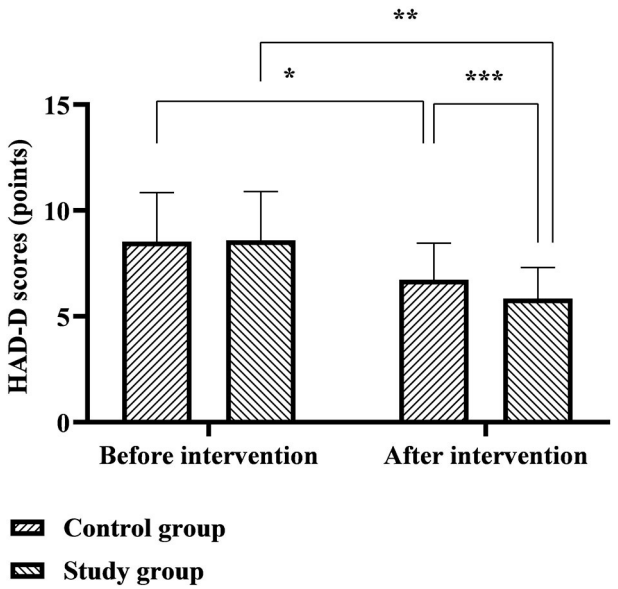


FIGURE 7 | Comparison of HAD-D scores between the two groups. *Represents that there was a statistical difference in the HAD-D scores of the control group before and after the intervention ($t = 4.868$, $p < 0.001$); **represents that there was a statistical difference in the HAD-D scores of the study group before and after the intervention ($t = 8.503$, $p < 0.001$);***represents that there was a statistical difference in the HAD-D score between the control group and the study group after the intervention ($t = 3.203$, $p < 0.05$).

Comparison of Nursing Satisfaction Rate Between the Two Groups

The nursing satisfaction rate of the study group (98.57%) was significantly higher than that of the control group (88.52%) ($p < 0.05$), as shown in **Table 3**.

DISCUSSION

According to Kolcaba's comfort theory, when the disease deprives the integrity of the patient's body or deprives the normal functioning of the brain and body functions, the patient can have a strong demand for treatment and comfort due to all the current experience (10). But in the regular care mode, there is a gap between the patient's comfort needs and the caregivers meeting their needs, and there is a gap between the effect of hospital nursing and the effect of out-of-hospital nursing. Based on this, this study applied comfort nursing to the nursing management of patients with ICH during the hospitalization period and applied continuation nursing to the nursing management of patients with ICH during the rehabilitation period after discharge from the hospital. It aimed to help patients with ICH achieve the maximum effect of nursing and treatment.

(1). Comfort nursing combined with continuous nursing intervention can effectively prevent the occurrence of pressure sores and falls in patients with ICH. Pressure ulcers are the long-term compression of local skin or soft tissues and then a kind of ischemia, hypoxia, or malnutrition ulcer necrosis, and it is one of the common complications of patients with coma, hemiplegia, or postural restriction caused by ICH (11). Falls are more common in patients with impaired motor and cognitive function and are also an important mechanism of injury leading to ICH (12, 13). During the nursing period of this study, the incidence of pressure sores and falls in the study group were significantly lower than that in the control group. Analyzing the reasons, under the guidance of comfort nursing and continuous nursing, the application of antidecubitus air mattresses for patients in hospitals and homes can automatically change the patient's pressure position, avoid continuous pressure on local skin tissues, and assist in turning over and knocking back regularly, and massage the bones and joints, etc., which can effectively promote blood circulation and reduce the occurrence of necrosis (14). In addition, a wealth of antifall knowledge can enhance the patient's antifall awareness and improve the ability to respond to fall behavior (15). However, because patients with ICH often have different degrees of motor and cognitive dysfunction, in this study, researchers used health education before discharge, such as on-site teaching, video exercises, health manuals, WeChat push, etc. to strengthen patients' memory, which is conducive to the improvement of patients' fall prevention behavior.

(2). Comfort nursing combined with continuous nursing intervention after discharge can effectively improve the quality of life of patients with ICH. Impairment of neurological function is an important feature of ICH, which creates physical and language dysfunction in patients, severely impaired cognition

TABLE 2 | Comparison of disability rate and readmission rate between the two groups [*n* (%)].

Group	*n*	Degree of disability						Readmission rate
		Grade I	Grade II	Grade III	Grade IV	Grade V	Disability rate	
Control group	61	1 (1.64)	2 (3.28)	10 (16.39)	34 (55.74)	14 (22.95)	46 (75.41)	11 (18.03)
Study group	70	1 (1.43)	1 (1.43)	9 (12.86)	34 (48.57)	25 (35.71)	44 (62.86)	5 (7.14)
χ^2							2.389	3.605
P							0.122	0.058

TABLE 3 | Comparison of nursing satisfaction rate between the two groups [*n* (%)].

Group	*n*	Very satisfied	Basically satisfied	Dissatisfied	Satisfaction rate
Control group	61	26 (42.62)	28 (45.90)	7 (11.48)	54 (88.52)
Study group	70	57 (81.43)	12 (17.14)	1 (1.43)	69 (98.57)
χ^2					5.738
P					0.017

and quality of life, and further promotes the generation of negative emotions such as anxiety, depression, pessimism, and world-weariness (16, 17). The results of this study showed that 6 months after discharge from the hospital, the FMA, SS-QOL, and MBI scores of the two groups of patients were significantly higher than before nursing, the NIHSS, HAD-A, and HAD-D scores were significantly lower than before nursing, and the study group both were significantly better than the control group. It is suggested that the effect of comfort nursing combined with continuous nursing intervention after discharge on patients' neurological function, motor function, self-care ability, and mental health level is significantly better than that of conventional nursing. Analyzing the reasons, in the comfort nursing of this study, based on the conventional bed rest management, combined with evidence-based nursing basis and expert advice to implement targeted bedtime guidance, it will help not only to avoid the occurrence of rebleeding in the acute phase, but also to cultivate the ability of self-care in early life for people with mild symptoms and signs. In the comfort management of the lying position, paying attention to the maintenance of the functional position of the affected limb during the acute phase of the patient's disease will help to provide conditions for the later rehabilitation training. During the recovery period after discharge from the hospital, the patients are guided one by one through multiple channels such as online WeChat and offline home visits to expand the rehabilitation plan and training content, which not only solves the problem of patients' difficulty in obtaining systematic knowledge of rehabilitation nursing at home and in the community, but also improves timeliness and effectiveness of communication between nurses and patients, which provides convenience for the patient's rehabilitation process. In addition, the comfort nursing in this study also focused on providing comfort interventions to patients from environmental, sleep, defecation, infusion, and psychological and social aspects. Among them, the warm and comfortable inpatient environment is conducive to the improvement of the patient's mood and the recovery of the disease; adequate and good sleep quality is conducive to the recovery of the patient's nerve function; comfortable defecation care is conducive to reducing the embarrassment of patients with defecation in bed; comfortable infusion care is conducive to alleviation patients suffering from pain and discomfort during infusion therapy; psychological comfort care can provide patients with psychological support and stimulate their self-recovery potential and self-exercise perseverance; social comfort care can help to create a positive recovery atmosphere and reduce patients' psychological barriers. It can be seen from the above that the two nursing models used in this study are effective models that fully meet the comfort needs and rehabilitation needs of patients from the physical, psychological, and social levels.

(3). Comfort nursing combined with continuous nursing intervention after discharge can improve the short-term prognosis of patients with ICH to a certain extent. ICH is a type of stroke related to the highest disability rate and the highest mortality rate, and active and effective functional rehabilitation training during the rehabilitation period is an important measure to improve the function of the patient's affected limb and reduce the degree of disability (18). However, the negative emotions caused by the disease and the cohesion and compliance of out-of-hospital nursing after discharge from the hospital are the important reasons that affect the completion of the rehabilitation training of patients (19, 20). Based on this, in the nursing design of this study, the positive psychological assistance to patients and the creation of a rehabilitation atmosphere run through the hospital and out-of-hospital nursing. In terms of realization form, through the communication and interaction between nurses and patients, nurses can timely understand the patient's psychological changes and the crux of the problem and provide symptomatic counseling and interpretation to improve the degree of cooperation in treatment; through the communication and mutual assistance between patients-to-patients, it is helpful to increase patients' recovery enthusiasm and social behavior, so that patients can consciously participate in rehabilitation activities. The results showed that the disability rate and readmission rate of the study group were lower than those of the control group, but there was no statistical difference between the two groups, suggesting that comfort nursing combined with continuous nursing intervention can reduce the patient's brain to a certain extent the degree of injury and reduce the readmission rate. In this study, the nursing satisfaction rate of the study group was significantly higher than that of the control group. It shows

that the combination of comfort nursing and continuous nursing intervention improves patients' satisfaction with the nursing effect and has certain application prospects.

CONCLUSION

To sum up, the combination of comfort nursing and continuous nursing intervention after discharge can effectively reduce the occurrence of pressure ulcers and falls during the care of patients with ICH and contribute to the improvement of their quality of life and prognosis. It is worthy of clinical promotion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZL is responsible for the collection of cases and the evaluation of relevant results. JW is responsible for the statistics of data and the writing of papers. HL is responsible for the guidance of the research process. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

REFERENCES

1. Choy KW, Tsai AP, Lin PB, Wu MY, Lee C, Alias A, et al. The role of urocortins in intracerebral hemorrhage. *Biomolecules.* (2020) 10:96. doi: 10.3390/biom10010096
2. Lattanzi S, Di Napoli M, Ricci S, Divani AA. Matrix metalloproteinases in acute intracerebral hemorrhage. *Neurotherapeutics.* (2020) 17:484–96. doi: 10.1007/s13311-020-00839-0
3. Naito Y, Kamiya M, Morishima N, Ishikawa T. Association between out-of-bed mobilization and complications of immobility in acute phase of severe stroke: a retrospective observational study. *J Stroke Cerebrovasc Dis.* (2020) 29:105112. doi: 10.1016/j.jstrokecerebrovasdis.2020.105112
4. Madhuranga PVH, Mathangasinghe Y, Anthony DJ. Improving balance with wobble board exercises in stroke patients: single-blind, randomized clinical trial. *Top Stroke Rehabil.* (2019) 26:595–601. doi: 10.1080/10749357.2019.1645439
5. de Oliveira Manoel AL. Surgery for spontaneous intracerebral hemorrhage. *Crit Care.* (2020) 24:45. doi: 10.1186/s13054-020-2749-2
6. Ahmed ZM, Khalil MF, Kohail AM, Eldesouky IF, Elkady A, Shuaib A. The prevalence and predictors of post-stroke depression and anxiety during COVID-19 pandemic. *J Stroke Cerebrovasc Dis.* (2020) 29:105315. doi: 10.1016/j.jstrokecerebrovasdis.2020.105315
7. Oliveira SM, Costa KNFM, Santos KFOD, Oliveira JDS, Pereira MA, Fernandes MDGM. Comfort needs as perceived by hospitalized elders: an analysis under the light of Kolcaba's theory. *Rev Bras Enferm.* (2020) 73:e20190501. doi: 10.1590/0034-7167-2019-0501
8. Xia L. The effects of continuous care model of information-based hospital-family integration on colostomy patients: a randomized controlled trial. *J Cancer Educ.* (2020) 35:301–11. doi: 10.1007/s13187-018-1465-y
9. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* (2015) 46:2032–60. doi: 10.1161/STR.0000000000000069
10. Berntzen H, Bjørk IT, Storsveen AM, Wøien H. "Please mind the gap": a secondary analysis of discomfort and comfort in intensive care. *J Clin Nurs.* (2020) 29:2441–54. doi: 10.1111/jocn.15260
11. Jansen RCS, Silva KBA, Moura MES. Braden scale in pressure ulcer risk assessment. *Rev Bras Enferm.* (2020) 73:e20190413. doi: 10.1590/0034-7167-2019-0413
12. Cocca AT, Privette A, Leon SM, Crookes BA, Hall G, Lena J, et al. Delayed intracranial hemorrhage in anticoagulated geriatric patients after ground level falls. *J Emerg Med.* (2019) 57:812–6. doi: 10.1016/j.jemermed.2019.09.011
13. Whitney DG, Dutt-Mazumder A, Peterson MD, Krishnan C. Fall risk in stroke survivors: Effects of stroke plus dementia and reduced motor functional capacity. *J Neurol Sci.* (2019) 401:95–100. doi: 10.1016/j.jns.2019.04.035
14. Righi L, Ourahmoune A, Béné N, Rae AC, Courvoisier DS, Chopard P. Effects of a pressure-ulcer audit and feedback regional programme at 1 and 2 years in nursing homes: a prospective longitudinal study. *PLoS ONE.* (2020) 15:e0233471. doi: 10.1371/journal.pone.0233471
15. Huang Y, Wu C, Peng H, Chen Q, Fan X, Xiao L, et al. The correlation between fall prevention knowledge and behavior in stroke outpatients. *J Neurosci Nurs.* (2020) 52:61–5. doi: 10.1097/JNN.0000000000000494
16. Zhang X, Liu T, Xu S, Gao P, Dong W, Liu W, et al. A pro-inflammatory mediator USP11 enhances the stability of p53 and inhibits KLF2 in intracerebral hemorrhage. *Mol Ther Methods Clin Dev.* (2021) 21:681–92. doi: 10.1016/j.omtm.2021.01.015
17. Choi MJ, Kim H, Nah HW, Kang DW. Digital therapeutics: emerging new therapy for neurologic deficits after stroke. *J Stroke.* (2019) 21:242–58. doi: 10.5853/jos.2019.01963
18. Lattanzi S, Brigo F, Trinka E, Cagnetti C, Di Napoli M, Silvestrini M. Neutrophil-to-lymphocyte ratio in acute cerebral hemorrhage: a system review. *Transl Stroke Res.* (2019) 10:137–45. doi: 10.1007/s12975-018-0649-4
19. Uphoff E, Pires M, Barbui C, Barua D, Churchill R, Cristofalo D, et al. Behavioural activation therapy for depression in adults with non-communicable diseases. *Cochrane Database Syst Rev.* (2020) 8:CD013461. doi: 10.1002/14651858.CD013461.pub2
20. Khoshbakht Pishkhani M, Dalvandi A, Ebadi A, Hosseini M. Factors affecting adherence to rehabilitation in Iranian stroke patients: a qualitative study. *J Vasc Nurs.* (2019) 37:264–71. doi: 10.1016/j.jvn.2019.07.001

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang, Liu and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 02 February 2022
doi: 10.3389/fsurg.2022.838879

Uterine Artery Embolization on Serum β-HCG Levels, Fertility Function and Clinical Efficacy in Patients With Cesarean Uterine Scar Pregnancy

Wenyang Zhu[1†], *Xiaofang Zhang*[2†], *Chang Liu*[3], *Yang Liu*[4] *and Wei Xu*[5*]

[1] *Department of Interventional Radiolody, The Affiliated Huaian Hospital of Xuzhou Medical University, Huaian, China,* [2] *Department of Ultrasound, The Huaian Clinical College of Xuzhou Medical University, Huaian Maternity and Children Hospital, Huaian, China,* [3] *Department of Gynaecology, The Affiliated Huaian Hospital of Xuzhou Medical University, Huaian, China,* [4] *Department of Gynecology, The Huaian Clinical College of Xuzhou Medical University, Huaian Maternity and Children Hospital, Huaian, China,* [5] *Department of Interventional Radiolody, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China*

Objective: To analyze the therapeutic effect of uterine artery embolisation (UAE) in patients with cesarean section pregnancy (CSP) delivered by cesarean section and the effect on serum human chorionic gonadotrophin (β-HCG) levels and reproductive function.

Methods: In total 142 patients with CSP, The control group ($n = 71$) received Methotrexate (MTX) with ultrasound monitoring after admission and the research group ($n = 71$) was treated with UAE on basic of the control group. The two groups were compared in terms of treatment outcome, intraoperative bleeding, bed activity, vaginal bleeding and length of hospital stay, and serum follicle stimulating hormone (FSH), oestradiol (E2), luteinising hormone (LH) and β-HCG levels at 1 month postoperatively. The clinical symptoms (normalization of β-HCG and return of menstruation) and clinical outcomes (normal pregnancy, recurrent scar pregnancy) were compared between the two groups, as well as the occurrence of post-operative complications in both groups.

Results: Compared with the control group, the research group had a higher overall near-term effective rate, a lower recurrence rate of CSP in pregnancy, and a lower complication rate ($P < 0.05$); meanwhile, the time to get out of bed, postoperative vaginal bleeding, length of hospital stay, normalization of serum β-HCG, and return to menstruation were shorter in the research group than in the control group ($P < 0.05$); In addition, serum FSH, E2, LH and β-HCG levels improved better in the research group compared with the control group 1 month after surgery ($P < 0.05$).

Conclusion: The treatment of CSP patients with UAE can reduce the amount of intraoperative bleeding and the duration of vaginal bleeding, promote the improvement of patients' clinical symptoms, have less impact on the disruption of patients' sex hormone balance, reduce patients' surgical risks to a greater extent, preserve patients' normal fertility, and have better application.

Keywords: cesarean section, uterine scar pregnancy, uterine artery embolization, serum β-HCG, fertility function

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Lihong Chen,
The First Affiliated Hospital of Fujian Medical University, China
Li Genlin,
University of South China, China

****Correspondence:***
Wei Xu
xuwei02020202@163.com

[†]These authors share first authorship

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *18 December 2021*
Accepted: *05 January 2022*
Published: *02 February 2022*

Citation:
Zhu W, Zhang X, Liu C, Liu Y and Xu W (2022) Uterine Artery Embolization on Serum β-HCG Levels, Fertility Function and Clinical Efficacy in Patients With Cesarean Uterine Scar Pregnancy. Front. Surg. 9:838879. doi: 10.3389/fsurg.2022.838879

INTRODUCTION

Cesarean uterine scar pregnancy (CSP) is defined as a gestational sac lodging with the cesarean scar of the uterus. It is a relatively uncommon but high risk index ectopic pregnancy and is one of the distant complications of cesarean delivery (1). The exact etiology of the condition is not yet fully understood. Some studies (2, 3) have confirmed that in the period following cesarean section, the uterine scar becomes vascularized and rich in blood supply, which may explain the tendency of fertilized eggs to migrate to the vascularized area around the scar for implantation and implantation. It has also been found (4, 5) that more than 70% of CSP after cesarean section occur in those with a history of more than 2 cesarean sections, suggesting that enlarged, fibrotic, poorly formed local blood vessels and poor healing of the uterine scars after multiple cesarean sections are associated with the development of ectopic pregnancy there. In recent years, with the introduction of China's two- and three-child policy and the opening up of the public's ideology, the cesarean section rate of pregnant women has shown a clear upward trend, and the incidence of CSP has gradually increased. As a distant complication of cesarean delivery, CSP can lead to severe bleeding or even haemorrhagic shock in patients, with the possibility of uterine rupture and life-threatening effects of continued pregnancy (6–8).

Currently, there are many treatment options for CSP, including conservative treatment with methotrexate (MTX) alone and curettage, but the drawbacks of these options have gradually emerged with the widespread clinical application (9). The risk of hemorrhage and recurrence of CSP during re-pregnancy with medication alone is high, and is now often used as an adjunctive treatment during surgery; unclear indications for uterine removal can easily lead to intraoperative hemorrhage and even require uterine removal to preserve the patient's life and deprive the patient of fertility (10, 11). Uterine artery embolization (UAE) is a new minimally invasive interventional procedure that can rapidly and effectively control massive vaginal bleeding due to vascular injury. It has the advantage of being minimally invasive, with fewer side effects and fewer postoperative complications than uterine artery ligation, internal iliac artery ligation or hysterectomy, which were previously used to control massive vaginal bleeding (12, 13). In recent years this interventional technique has been widely used in the field of obstetrics and gynecology, especially in the treatment of postpartum hemorrhage (14), uterine fibroids (15) and cervical pregnancy (16), but there are still clinical concerns about whether UAE treatment of CSP will impair patients' reproductive function. In this trial, we treated CSP patients with UAE and analyzed its therapeutic effects as well as its impact on patients' serum Human chorionic gonadotropin (β-HCG) levels and fertility function.

MATERIALS AND METHODS

Materials

Case Collection

A total of 142 patients with CSP requiring surgical treatment were selected and collected from May 2020 to May 2021 in our hospital. The control group received methotrexate (MTX) combined with B ultrasound-monitored clearance after admission, and the research group received MTX+UAE+B ultrasound-monitored clearance after admission. Baseline data on age, pregnancy, delivery, cesarean section, miscarriage, gestational week, gestational typing, gestational sac diameter and preoperative HCG level were collected from the two groups and the results showed no statistically significant differences ($P > 0.05$, **Table 1**) and were comparable.

Diagnostic Criteria

1. Clinical symptoms: history of stop menstruation, positive urine pregnancy test with or without irregular vaginal bleeding and abdominal pain. 2. Ultrasonography was diagnosed (17) as follows: 1. No gestational sac was seen in the normal part of the uterine cavity and cervical canal; 2. Gestational sac or mass was visible in the isthmus incision; 3. Abundant blood flow was seen around the gestational sac and within the mass; 4. Lack of continuity of the myometrium in the cross-section through the gestational sac.

Inclusion Criteria

1. Meeting the above diagnostic criteria; 2. Patients had a clear previous history of cesarean section; 3. No relevant treatment prior to this admission; 4. No embryos in the uterine cavity by ultrasound; 5. Patients voluntarily signed an informed consent form with complete and uncompromised clinical information.

Exclusion Criteria

1. Patients with combined immune system disorders, infections, malignancies, hematological disorders; 2. Patients with ruptured gestational sacs; 3. Patients with severe coagulation abnormalities; 4. Patients with severe cardiac, hepatic, renal and other organ insufficiencies; 5. Patients with other combined pathologies in the uterine region; (6) combined cognitive impairment.

Methods

Treatment Methods

After admission, all patients underwent routine blood routine, blood biochemistry, blood coagulation, electrocardiogram, and chest X-ray examinations, and there were no abnormalities.

Patients in the control group were treated with MTX+B ultrasound-monitored curettage: MTX was given as a single intravenous injection of l00 mg upon admission, and the patient's blood β-HCG level was monitored. When the patient's blood β-HCG decreased to 100 U/L, curettage was performed under B ultrasound-monitored. All operations were performed under transabdominal ultrasound guidance with lidocaine paracervical nerve block anesthesia and the use of an electric suction and scraping spoon to remove the pregnancy, being as careful as possible when scraping the pregnancy residue from the cesarean scar defect to avoid serious complications such as uterine rupture. If active bleeding was seen during clearance, the uterine cavity was filled with iodoform gauze and the gauze was removed after 24 to 48 h. If the above conservative treatment failed, transabdominal gestrectomy or hysterectomy was performed.

TABLE 1 | Comparison of baseline demographic information between the two groups of patients.

Data		Control group ($n = 71$)	Research group ($n = 71$)	t/ χ^2 value	*P* value
Age (years, Mean ± SD)		31.59 ± 5.26	32.41 ± 4.87	0.964	0.337
No. of pregnancies (times, Mean ± SD)		3.08 ± 1.45	3.00 ± 1.26	0.351	0.726
Number of deliveries (times, Mean ± SD)		1.25 ± 0.43	1.17 ± 0.38	1.175	0.242
Number of cesarean sections (times, Mean ± SD)		1.16 ± 0.34	1.17 ± 0.38	0.147	0.884
Number of abortions (times, Mean ± SD)		1.89 ± 1.36	1.92 ± 1.40	0.130	0.897
Pregnancy time (weeks, Mean ± SD)		8.78 ± 3.25	8.46 ± 2.96	0.613	0.541
Gestational sac diameter (cm, Mean ± SD)		4.57 ± 2.24	4.83 ± 2.08	0.717	0.485
Preoperative β-HCG (IU/L, Mean ± SD)		13,158.44 ± 1,302.59	13,136.47 ± 1,289.26	0.101	0.918
Exogenous (*n*, %)	Yes	42 (59.15)	46 (64.79)	0.478	0.489
	No	29 (40.85)	25 (35.21)		
Living embryo (*n*, %)	Yes	25 (35.21)	20 (28.17)	0.813	0.367
	No	46 (64.79)	51 (71.83)		

Patients in the research group were treated with MTX+ UAE+ B ultrasound-monitored for clearance: intraoperative disinfection of the cavity towel and Seldinger femoral artery puncture was performed. The operator searched for a femoral artery puncture site in the patient's right lower limb, followed the course of the femoral artery after routine anesthesia, inserted the needle, placed the cannula into the arterial sheath, withdrew the puncture needle and introduced the ultra-smooth guidewire. Then the arteriogram was performed to determine the status of the uterine artery blood supply according to the display. The embolization of the uterine artery was indicated by the slow injection of diluted MTX 100 mg before embolization, followed by embolization of the uterine artery with gelatin sponge pellets until the signal of blood flow in the uterine artery disappears. Curettage was performed within 48–72 h of UAE (The operation was the same as that of the control group).

Postoperatively, all patients were routinely given antibiotics to prevent infection and urethral tubes were left in place for 1∼2 d. Patients' serum β-HCG levels and vaginal bleeding were closely monitored postoperatively.

Observation Indicators

The operation-related indexes such as operation time, intraoperative bleeding, time of getting out of bed, vaginal bleeding and hospital stay were recorded for both groups; the occurrence of postoperative complications such as fever, lower abdominal pain, vaginal bleeding and uterine adhesions were counted for both groups. Patients were advised to follow up regularly after discharge and were advised to have their serum β-HCG measured weekly as an outpatient until it dropped to a normal value. Serum follicle stimulating hormone (FSH), estradiol (E2), luteinizing hormone (LH) and β-HCG levels were measured preoperatively and at 1 month postoperatively. Ultrasound may be repeated once a month to monitor post-operative uterine recovery, and patients were followed up in clinic or by telephone for menstrual recovery, pregnancy and recurrence of CSP.

Recent efficacy assessment: Cured: blood β-HCG decreased to normal, vaginal bleeding stopped and abdominal pain disappeared; Effective: blood β-HCG decreased and was close to normal, vaginal bleeding decreased and ultrasound showed a smaller pelvic mass; Ineffective: blood β-HCG remained unchanged or even increased, ultrasound indicated that the pelvic mass remained unchanged or increased, or intra-abdominal bleeding occurred and required secondary surgical treatment. Total effective rate = (cured + effective) cases/total number of cases × 100%.

Statistical Methods

The study used SPSS 20.0 to manipulate all figures and Graghpad Prism 8 to create charts for statistics. The mean ± standard deviation (Mean ± SD) was used to represent the econometric information consistent with normal distribution, and the *t*-test was carried out; the caseload and composition ratio were used to represent the count information, and the χ^2 test was carried out. $P < 0.05$ represented a statistically meaningful difference.

RESULTS

Comparison of Recent Outcomes Between the Two Groups

The recent outcomes of both groups were determined and the results were recorded. In the control group, 35 cases were cured, 25 cases were effective and 11 cases were ineffective, with a total effective rate of 84.61% (60/71). In the research group, there were 50 cured cases, 19 effective cases and 2 ineffective cases, with an overall effective rate of 97.18% (69/71). The recent efficacy rate showed significantly higher in the research group when compared against the control group ($P < 0.05$) (**Figure 1**).

Comparison of Surgery-Related Indicators Between the Two Groups

The operation-related indicators of both groups were recorded and statistically analyzed. The outcome revealed that the intraoperative bleeding was less in the research group than in the control group ($P < 0.05$); the postoperative time to bed, postoperative vaginal bleeding time and hospital stay in the research group when compared against the control group ($P < < 0.05$) (**Figure 2**).

Comparison of Reproductive Hormone Levels Between the Two Groups Before and 1 Month After Surgery

The blood samples of the patients were collected before operation and 1 month after operation to test the levels of reproductive hormones and recorded. The results showed that there would be no meaningful statutory variation in the pre-op serum FSH, E2, LH and β-HCG levels in either group ($P > 0.05$). The differences in serum FSH, E2 and LH levels between the control group and the research group at 1 month postoperatively were not statistically significant, and the contrast in plasma FSH, E2 and LH levels of each group at 1 month postoperatively and immediately prior to treatment were not considered of any statistical importance ($P > 0.05$). The serum β-HCG levels in the two groups decreased at 1 month after surgery compared with the preoperative levels, with the research group being lower when compared against the control group($P < 0.05$) (**Figure 3**).

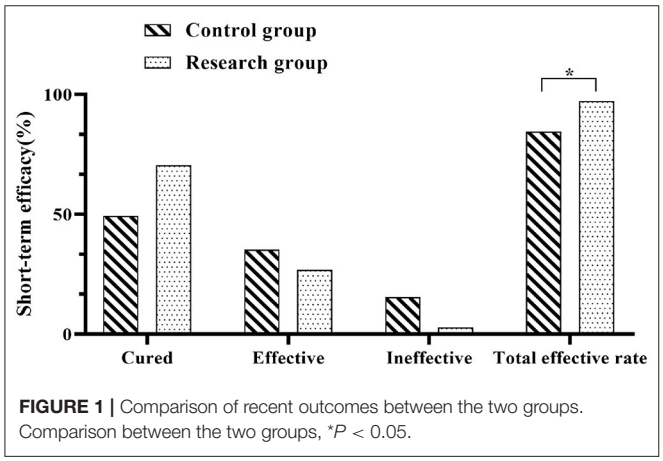


FIGURE 1 | Comparison of recent outcomes between the two groups. Comparison between the two groups, *$P < 0.05$.

Comparison of the Improvement of Clinical Symptoms and Pregnancy Outcome Between the Two Groups

The two groups were followed up regularly, and the improvement of clinical symptoms and pregnancy outcomes during the follow-up period of the two groups were counted. The results showed that the time for serum β-HCG to return to normal and the time for menstruation to return to normal in the research group were shorter when compared against the control group ($P < 0.05$). There were 21 normal pregnancies (29.57%) in the research group and 15 normal pregnancies (21.13%) in the control group.

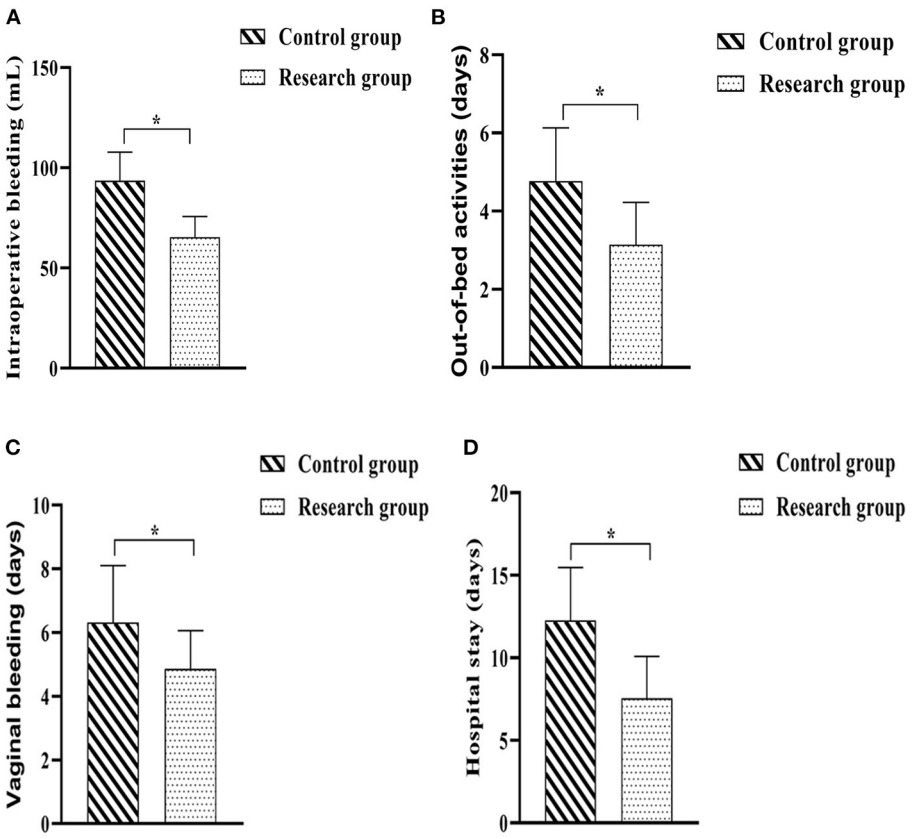


FIGURE 2 | Comparison of surgery-related indicators between the two groups. **(A)** Intraoperative bleeding; **(B)** Out-of-bed activities; **(C)** Time of vaginal bleeding; **(D)** Hospital stay. Comparison between the two groups, *$P < 0.05$.

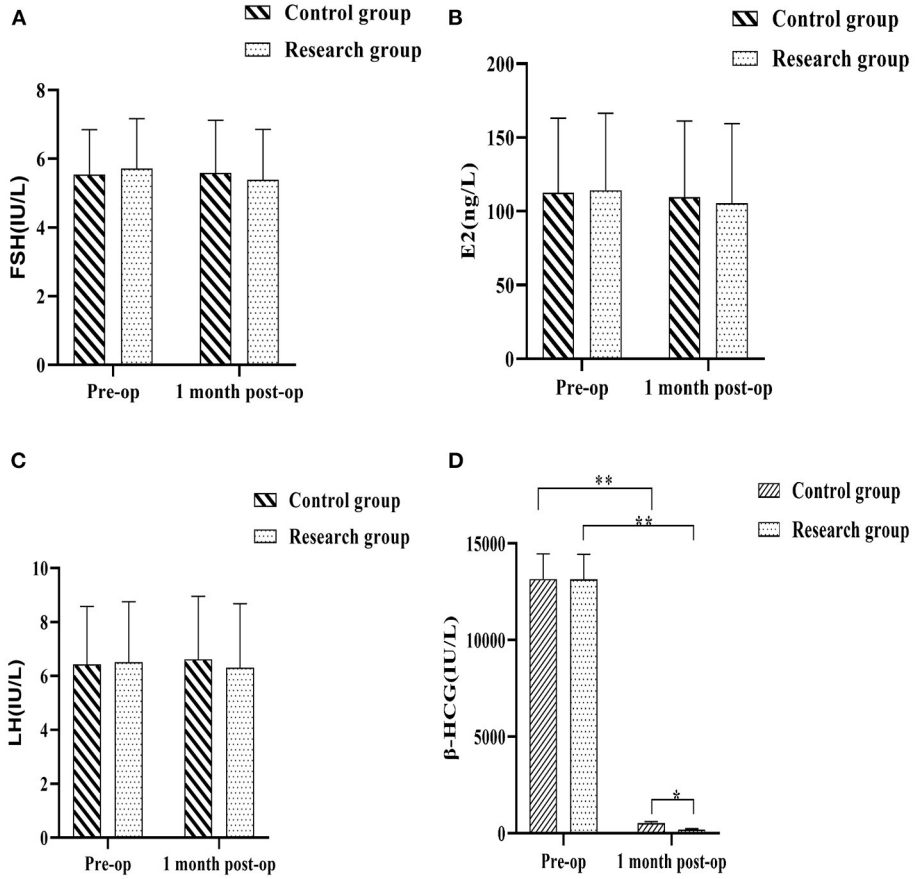


FIGURE 3 | Comparison of reproductive hormone levels between the two groups before and 1 month after surgery. **(A)** follicle stimulating hormone (FSH); **(B)** estradiol (E2); **(C)** luteinizing hormone (LH); **(D)** Human chorionic gonadotropin (β-HCG). Comparison between the two groups over the same period, $^{*}P < 0.05$; compared with the same group pre-op, $^{**}P < 0.05$.

A quick glance at the results of the regular pregnancies carried out among each group showed that there would be no statistically significant difference in the regular pregnancy rates in either group ($P > 0.05$). There were 0 cases (0.00%) of recurrent CSP in the research group and 9 cases (12.68%) of recurrent CSP in the control group, and a comparison of the recurrent CSP in the two groups showed that the rate of recurrent CSP in the research group was lower when compared against the control group ($P < 0.05$) (**Figure 4**).

Comparison of Post-operative Complications Between the Two Groups

Postoperative complications were observed and recorded in both groups. In the control group, there were 12 cases of postoperative vomiting (16.90%), 10 cases of fever (14.08%), 43 cases of lower abdominal pain (60.56%) and 4 cases of uterine adhesions (5.63%); in the research group, there were 3 cases of postoperative vomiting (4.23%), 2 cases of fever (2.82%), 25 cases of lower abdominal pain (35.21%) and 2 cases of uterine adhesions (2.82%). Analysis of the complications in both groups showed that the incidence of vomiting, fever and lower abdominal pain in the research group was lower when compared against the control group ($P < 0.05$) (**Figure 5**).

DISCUSSION

As a long-term complication after cesarean section, CSP can lead to uterine rupture and placental implantation, increasing the incidence of hemorrhage and affecting sexual and reproductive function if not managed correctly (18, 19). The pathogenesis of CSP is not fully understood, but most scholars support the uterine incision defect theory (20, 21), which states that the uterine incision site is not fully healed after lower uterine cesarean section and is defective, thus making it easy for fertilized eggs to implant in the uterine incision scar where the endometrial defect exists. It has also been shown (22, 23) that the development of CSP may be closely related to the low position of the cesarean incision, multiple cesarean sections, defective suturing technique and postoperative incision healing, and wide scars. The currently accepted principles of CSP treatment (24) are early diagnosis, early termination of pregnancy and reduction of complications

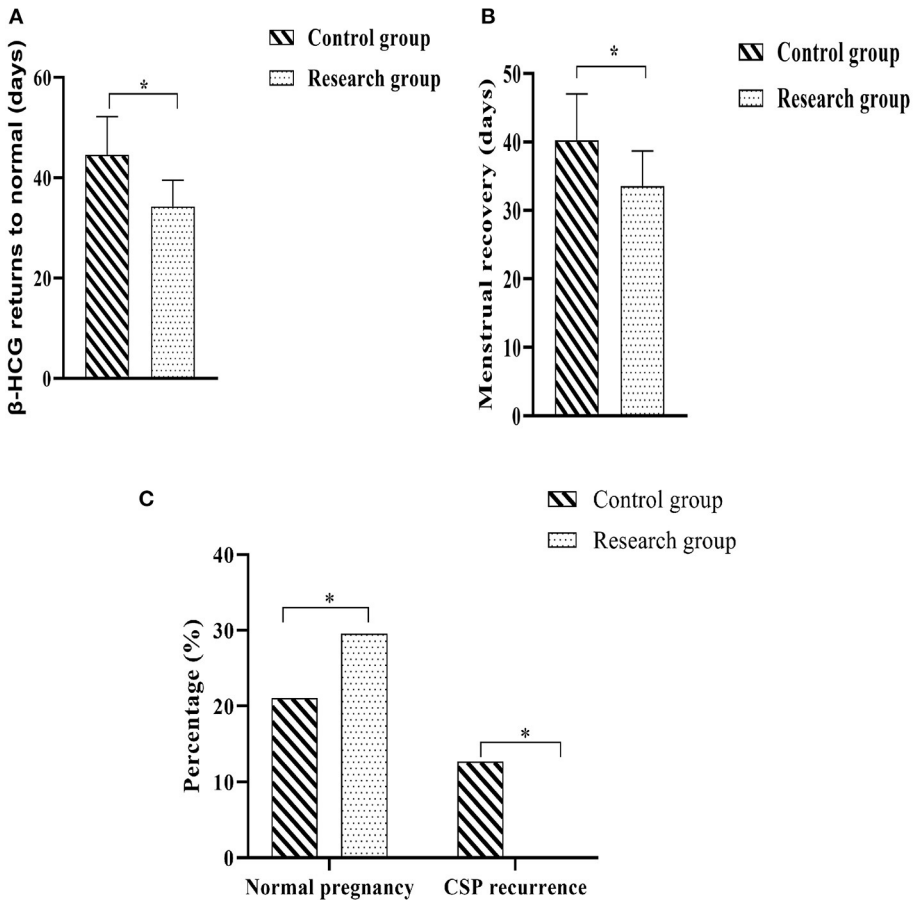


FIGURE 4 | Comparison of the improvement of clinical symptoms and pregnancy outcome between the two groups. **(A)** Time to normalization of β-HCG; **(B)** Time to return to normal menstruation; **(C)** Normal pregnancy rate and CSP recurrence rate. Comparison between the two groups, $^*P < 0.05$.

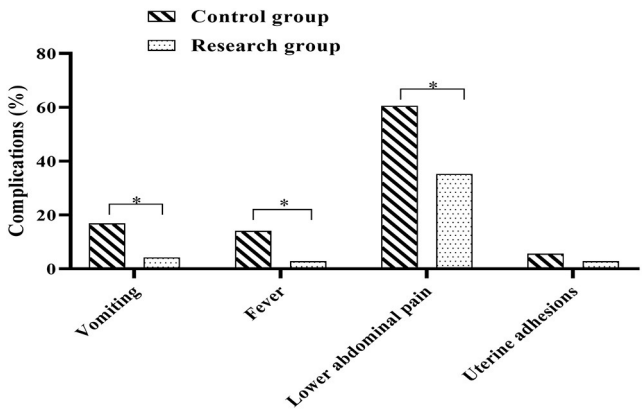


FIGURE 5 | Comparison of post-operative complications between the two groups. Comparison between the two groups, $^*P < 0.05$.

in order to preserve the patient's reproductive function reduce the trauma caused by surgery to the patient and achieve better outcomes.

In the past, hysterectomy was used as the only treatment option for CSP to avoid maternal mortality. In recent years, however, with the widespread use of ultrasound, CSP has been able to be diagnosed clearly at an early stage and conservative treatment has been widely used in clinical practice (25). Currently commonly used programs include systemic drug therapy, surgical therapy, and drug combined surgical therapy. MTX is a conservative drug commonly used in clinical practice, which can effectively preserve fertility by inhibiting trophoblast proliferation and causing necrosis of the villi cells, resulting in embryocidal effects (26, 27). UAE is an interventional procedure in which fresh gelatin sponge particles are introduced into the uterine artery to rapidly cause platelet coagulation and the formation of a thrombus, which can act as an embryocidal agent by blocking the blood supply to the embryo and can also greatly reduce the incidence of hemorrhage and preserve the patient's fertility (28, 29). In this study, the combination of local application of MTX, UAE and curettage for CSP patients showed that the intraoperative bleeding was lower in the research group than in the control group, and the time to get out of bed, postoperative vaginal bleeding, hospital stay, return to normal serum β-HCG and return to normal menstruation were all

significantly shorter in the research group than in the control group; the recent efficacy of the research group was significantly higher than that of the control group ($P < 0.05$). It is possible that the thrombus has formed in the uterine artery and the ischaemic and hypoxic state has developed at the lesion by the time the uterine clearance is performed 48 to 72 h after UAE, which reduces the occurrence of intraoperative hemorrhage to a greater extent, decreases the amount of intraoperative bleeding and also shortens the duration of vaginal bleeding and hospital stay to a certain extent, which facilitates the patient's recovery (30). In this study, the levels of serum FSH, E2, LH and β-HCG and other reproductive hormones were also measured at different times, and the results showed that except for significant changes in serum β-HCG levels, the differences in the levels of other indicators between preoperative and 1 month postoperative were not significant. It is suggested that UAE treatment improves serum β-HCG levels in CSP patients without adversely affecting the secretory function of their ovaries. In addition, there was no difference in the normal pregnancy rate between the two groups during the follow-up period, but the recurrence rate of CSP in the research group was significantly lower than that in the control group, suggesting that UAE treatment is less damaging and more curative, and can preserve the patient's reproductive function to a greater extent, and has a good prognosis for pregnancy outcomes.

The results of this study also showed that the incidence of complications such as vomiting, fever and lower abdominal pain were significantly lower in the study group than in the control group. Analysis of the reasons for this: UAE interventions are able to form embolisms that block the circulation to the uterus, causing necrosis after the lesion is placed in an ischaemic and hypoxic environment (31). The local injection of MTX into the uterus prior to embolisation allows the local concentration of the drug to be at a high level, enabling the trophoblast to atrophy within a relatively short period of time. As the lesions become necrotic and the trophoblast cells are eliminated, the local concentration of MTX in the uterus is significantly reduced and less drug remains, thus reducing to a greater extent the risk of complications such as fever and vomiting associated with the application of MTX to the patient (32).

In conclusion, the use of UAE in CSP patients can reduce intraoperative bleeding and the duration of vaginal bleeding, promote the improvement of patients' clinical symptoms, have less impact on the disruption of patients' sex hormone balance, reduce patients' surgical risks to a greater extent, preserve patients' normal fertility, and have better results.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Affiliated Huaian Hospital of Xuzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WZ and XZ are mainly responsible for data statistics and paper writing. CL and YL are mainly responsible for research design and result testing. WX is mainly responsible for the guidance of the entire research process. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Timor-Tritsch IE, Monteagudo A, Calì G, D'Antonio F, Agten AK. Cesarean scar pregnancy: patient counseling and management. *Obstet Gynecol Clin North Am.* (2019) 46:813–28. doi: 10.1016/j.ogc.2019.07.010
2. Lata K, Davis AA, Panwar A, Kriplani I, Sharma S, Kriplani A. Laparoscopic excision of cesarean scar ectopic pregnancy. *J Obstet Gynaecol India.* (2020) 70:397–401. doi: 10.1007/s13224-020-01325-5
3. Agten AK, Monteagudo A, Timor-Tritsch IE, Thilaganathan B. Cesarean scar pregnancy registry: an international research platform. *Ultrasound Obstet Gynecol.* (2020) 55:438–40. doi: 10.1002/uog.21952
4. Hoffman T, Lin J. Cesarean scar ectopic pregnancy: diagnosis with ultrasound. *Clin Pract Cases Emerg Med.* (2020) 4:65–8. doi: 10.5811/cpcem.2019.10.43988
5. Li X, Sun W, Chen L, Jin M, Zhang Z, Gao J, et al. Cesarean scar pregnancy combined with arteriovenous malformation successfully treated with transvaginal fertility-sparing surgery: a case report and literature review. *Medicine.* (2020) 99:e21432. doi: 10.1097/MD.0000000000021432
6. Qi F, Chai ZY, Liu MM, Zheng LZ, Zhu Y, Chen ZW, et al. Type 2 cesarean scar pregnancy successfully treated via hysteroscopy-assisted laparoscopy. *J Minim Invasive Gynecol.* (2019) 26:1273–81. doi: 10.1016/j.jmig.2018.11.019
7. Xie RH, Guo X, Li M, Liao Y, Gaudet L, Walker M, et al. Risk factors and consequences of undiagnosed cesarean scar pregnancy: a cohort study in China. *BMC Pregnancy Childbirth.* (2019) 19:383. doi: 10.1186/s12884-019-2523-0
8. Fei H, Jiang X, Li T, Pan Y, Guo H, Xu X, et al. Comparison of three different treatment methods for cesarean scar pregnancy. *Ther Clin Risk Manag.* (2019) 15:1377–81. doi: 10.2147/TCRM.S220852
9. Wang LL, Chen JY, Yang HX, Fan LX, Zhang XX, Jing BH, et al. Correlation between uterine scar condition and uterine rupture for pregnancy women after previous cesarean section. *Zhonghua Fu Chan Ke Za Zhi.* (2019) 54:375–80. doi: 10.3760/cma.j.issn.0529-567x
10. Huang L, Zhao L, Shi H. Clinical efficacy of combined hysteroscopic and laparoscopic surgery and reversible ligation of the uterine artery for excision and repair of uterine scar in patients with type II and III cesarean scar pregnancy. *Med Sci Monit.* (2020) 26:e924076. doi: 10.12659/MSM.924076
11. Liu Z, Shi Z, Wei Y, Dai Q. The clinical and ultrasound-based comparison between cesarean scar pregnancy and other lower uterine segment pregnancies with a history of cesarean section. *J Matern Fetal Neonatal Med.* (2021) 34:639–45. doi: 10.1080/14767058.2020.1743669
12. Manyonda I, Belli AM, Lumsden MA, Moss J, McKinnon W, Middleton LJ, et al. Uterine-artery embolization or myomectomy for uterine fibroids. *N Engl J Med.* (2020) 383:440–51. doi: 10.1056/NEJMoa1914735
13. Ochmanek E, Brown MA, Rochon PJ. Fibroid expulsion after uterine artery embolization. *Semin Intervent Radiol.* (2019) 36:126–32. doi: 10.1055/s-0039-1688427
14. Calcott GA, Gaber M, Freedman J, Patni S. An unusual cause of fetomaternal distress at term: uterine vessel rupture in pregnancy. *BMJ Case Rep.* (2015) 30:bcr2014209004. doi: 10.1136/bcr-2014-209004

15. Karlsen K, Hrobjartsson A, Korsholm M, Mogensen O, Humaidan P, Ravn P. Fertility after uterine artery embolization of fibroids: a systematic review. *Arch Gynecol Obstet.* (2018) 297:13–25. doi: 10.1007/s00404-017-4566-7
16. Oleksik TP, Pluta K, Issat T, Jakimiuk A, Wierzba W. The use of super-selective uterine artery branch embolization and methotrexate in cervical pregnancy - case reports and literature review. *Ann Agric Environ Med.* (2021) 28:521–4. doi: 10.26444/aaem/127926
17. Timor-Tritsch IE, Monteagudo A, Calì G, D'Antonio F, Kaelin Agten A. Cesarean scar pregnancy: diagnosis and pathogenesis. *Obstet Gynecol Clin North Am.* (2019) 46:797–811. doi: 10.1016/j.ogc.2019.07.009
18. Birch Petersen K, Hoffmann E, Rifbjerg Larsen C, Svarre Nielsen H. Cesarean scar pregnancy: a systematic review of treatment studies. *Fertil Steril.* (2016) 105:958–67. doi: 10.1016/j.fertnstert.2015.12.130
19. Yoon R, Sasaki K, Miller CE. Laparoscopic excision of cesarean scar pregnancy with scar revision. *J Minim Invasive Gynecol.* (2021) 28:746–7. doi: 10.1016/j.jmig.2020.06.017
20. Di Spiezio Sardo A, Saccone G, McCurdy R, Bujold E, Bifulco G, Berghella V. Risk of Cesarean scar defect following single- vs double-layer uterine closure: systematic review and meta-analysis of randomized controlled trials. *Ultrasound Obstet Gynecol.* (2017) 50:578–83. doi: 10.1002/uog.17401
21. Tekelioglu M, Karataş S, Güralp O, Murat Alinca C, Ender Yumru A, Tug N. Incomplete healing of the uterine incision after elective second cesarean section. *J Matern Fetal Neonatal Med.* (2021) 34:943–7. doi: 10.1080/14767058.2019.1622676
22. Zhang Y, Chen L, Zhou M, Li Y, Luo J, Chen Z. Risk factors of persistent cesarean scar pregnancy after dilation and curettage: a matched case-control study. *Taiwan J Obstet Gynecol.* (2020) 59:237–42. doi: 10.1016/j.tjog.2020.01.011
23. Odeh M, Karwani R, Schnaider O, Wolf M, Bornstein J. Dehiscence of cesarean section scar during pregnancy and delivery - risk factors. *Ginekol Pol.* (2020) 91:539–43. doi: 10.5603/GP.2020.0086
24. Morlando M, Buca D, Timor-Tritsch I, Cali G, Palacios-Jaraquemada J, Monteagudo A, et al. Reproductive outcome after cesarean scar pregnancy: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand.* (2020) 99:1278–89. doi: 10.1111/aogs.13918
25. Xiong X, Gao CY, Ying DM, Yan P, Zhang ZJ, Kuang N, et al. Contrast-enhanced ultrasound evaluation of mifepristone for treatment of low-risk cesarean scar pregnancy. *Contrast Media Mol Imaging.* (2020) 2020:3725353. doi: 10.1155/2020/3725353
26. Maksimovic V, Pavlovic-Popovic Z, Vukmirovic S, Cvejic J, Mooranian A, Al-Salami H, et al. Molecular mechanism of action and pharmacokinetic properties of methotrexate. *Mol Biol Rep.* (2020) 47:4699–708. doi: 10.1007/s11033-020-05481-9
27. Misra DP, Gasparyan AY, Zimba O. Benefits and adverse effects of hydroxychloroquine, methotrexate and colchicine: searching for repurposable drug candidates. *Rheumatol Int.* (2020) 40:1741–51. doi: 10.1007/s00296-020-04694-2
28. Laughlin-Tommaso S, Barnard EP, AbdElmagied AM, Vaughan LE, Weaver AL, Hesley GK, et al. FIRSTT study: randomized controlled trial of uterine artery embolization vs focused ultrasound surgery. *Am J Obstet Gynecol.* (2019) 220:174.e1–174.e13. doi: 10.1016/j.ajog.2018.10.032
29. Li X, Niu H, Li J, Zhang L, Qu Q. Clinical assessment of uterine artery embolization combined with curettage when treating patients with cesarean scar pregnancy: A retrospective study of 169 cases. *J Obstet Gynaecol Res.* (2020) 46:1110–6. doi: 10.1111/jog.14258
30. Ou J, Peng P, Li C, Teng L, Liu X. Assessment of the necessity of uterine artery embolization during suction and curettage for caesarean scar pregnancy: a prospective cohort study. *BMC Pregnancy Childbirth.* (2020) 20:378. doi: 10.1186/s12884-020-03062-z
31. Hofgaard E, Westman K, Brunes M, Bossmar T, Persson J. Cesarean scar pregnancy: Reproductive outcome after robotic laparoscopic removal with simultaneous repair of the uterine defect. *Eur J Obstet Gynecol Reprod Biol.* (2021) 262:40–44. doi: 10.1016/j.ejogrb.2021.05.004
32. Pyra K, Szmygin M, Wozniak S, Jargiello T, Paszkowski T. Recurrent cesarean scar pregnancy treated successfully with uterine artery chemoembolization. *Ginekol Pol.* (2021) 92:394–5. doi: 10.5603/GP.a2021.0048

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhu, Zhang, Liu, Liu and Xu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 03 February 2022
doi: 10.3389/fsurg.2021.826835

Effect of Cluster Nursing Based on Risk Management Strategy on Urinary Tract Infection in Patients With Severe Craniocerebral Injury

Hongbin Qiao[1†], *Jing Yang*[2†] *and Cui Wang*[1*]

[1] *The Hospital Infection Management Department, Chongqing Southeast Hospital, Chongqing, China,* [2] *The Department of Respiratory and Critical Care Medicine, Chongqing People's Hospital, Chongqing, China*

Objective: To observe the effect of cluster nursing based on risk management strategy in the management of urinary tract infection in patients with severe craniocerebral injury.

Methods: A total of 116 patients with severe craniocerebral injury who were admitted to our hospital from March 2019 to March 2021 were included. They were divided into the control group (58 patients) and the observation group (58 patients). The control group received routine nursing care and the observation group received cluster nursing based on risk management strategy. The incidence of catheter-associated urinary tract infection (CAUTI), the results of bacterial culture on the surface of the urinary catheter, the incidence of nursing risk events, the duration of placing the urinary catheter, the length of hospital stay, and hospital costs as well as the patient satisfaction score were compared between the two groups. The knowledge, attitude, and practice scale for prevention of catheter infection and the competence evaluation scale of nurses were used to evaluate the sense-control ability and core competence of the interveners.

Results: The total incidence of CAUTI in the observation group was (6.90%) lower than that in the control group (20.69%) ($p < 0.05$). The bacterial culture results on the catheter surface of patients in the observation group before and after 6 and 12 h of catheter cleaning were better than those of patients in the control group ($p < 0.05$). The duration of indwelling urinary catheter, hospitalization time, and hospitalization expenses of patients in the observation group were lower than those of patients in the control group ($p < 0.05$). The incidence rate of nursing risk events in the observation group was (1.72%) lower than that in the control group (11.86%) ($p < 0.05$). The overall satisfaction score of patients and the control and core ability scores of nursing staff in the observation group were higher than those in the control group ($p < 0.05$).

Conclusion: Cluster nursing based on risk management strategy can effectively reduce the incidence of nursing risk events and the probability of UTI in patients with severe craniocerebral injury, shorten the duration of indwelling urinary catheter and hospitalization.

Keywords: craniocerebral injury, catheter-related urinary tract infection, risk management, cluster nursing, effect

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Qiang Wang,
Guizhou University, China
Li Genlin,
University of South China, China

***Correspondence:**
Cui Wang
WangCui20110706@126.com

[†]*These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *01 December 2021*
Accepted: *14 December 2021*
Published: *03 February 2022*

Citation:
Qiao H, Yang J and Wang C (2022) Effect of Cluster Nursing Based on Risk Management Strategy on Urinary Tract Infection in Patients With Severe Craniocerebral Injury. Front. Surg. 8:826835. doi: 10.3389/fsurg.2021.826835

INTRODUCTION

Severe craniocerebral injury is a common disease in brain surgery, often caused by traffic accidents, falling from high altitude, and other accidents (1). In the recent years, with the increase of space distance and frequent traffic accidents, the incidence of severe craniocerebral injury is increasing year by year. After injury, patients usually have symptoms of different degrees such as dilated pupils, vomiting, nausea, pain, disorder of vital signs, and disturbance of consciousness. In severe cases, serious sequelae such as hemiplegia or even death may even occur, which threaten health and should be paid attention to (2, 3). Patients with severe craniocerebral injury are in critical condition and progressing rapidly. They usually need to have an operation. After the operation, patients need to stay in bed for a long time during hospitalization and leave a catheter to urinate. Indwelling catheter is a commonly used invasive operation method in clinic, especially for some patients with urinary incontinence and coma. It cannot only accurately observe and record the urine volume and the urine proportion of patients with severe craniocerebral injury, but also prevent surgical complications. At the same time, it can also treat dysuria and train the bladder function of patients (4, 5). However, some studies have pointed out that the longer the urinary catheter is used, the higher the probability of catheter-associated urinary tract infection (CAUTI) in patients. In the United States, about 70% of complicated UTIs can be attributed to the use of catheters. CAUTI is associated with an increase in the morbidity and mortality of hospital infection and it is the most common cause of secondary blood-borne infection (6). Improper catheterization will damage the urethra and bladder mucosa and long-term indwelling will weaken the function of detrusor. Urine calcium salt deposition will block the urinary catheter, resulting in urine leakage and damage to the natural defense barrier of the urinary tract, causing bacterial colonization or infection (7). At present, care of clinical nurses for indwelling urinary catheter is still based on Basic Nursing Science, but there are still differences in nursing measures such as selection of urinary catheter of different departments and materials, frequency of urine bag replacement, timing of catheter removal, and evaluation and rehabilitation of bladder function after catheter removal, which have resulted in long time of indwelling urinary catheter in some patients, increased probability of urethral injury and infection, and deepened doctor–patient contradiction (8, 9).

Risk management is a management science that refers to finding, evaluating, and seeking countermeasures for economic loss risks and its purpose is to reduce losses and legal proceedings (10). Medical risks are ubiquitous. Patients with severe craniocerebral diseases are in critical condition and accept various diagnosis and treatment operations including indwelling catheter. The risk of nosocomial infection is several times higher than that of other patients in general wards and most infections are catheter-related infections. Therefore, implementing risk management and controlling CAUTI have become the research focus of medical staff. Cluster nursing was first proposed by the American Health Research Institute and is a set of nursing interventions formulated to address nursing problems that have many clinical influencing factors and are difficult to solve. Since the concept of cluster nursing was put forward, because it is novel, systematic, and more effective, the international community has carried out applied research on clinical nursing of many diseases (11–13). This study has shown that the implementation of cluster nursing strategy can reduce the incidence of CAUTI in patients (14). Cluster nursing based on risk management strategy is not a simple bundle of some clinical nursing measures, but its formulation needs the support of evidence-based theory and clinical evidence. Through formulating an early warning system for the risk of a certain disease or adverse event, we can formulate personalized nursing measures and strengthen early warning and risk management for complications of patients, so as to improve nursing efficiency and reduce nursing risk. In this study, during the management of UTI in patients with severe craniocerebral injury, cluster nursing based on risk management strategy was implemented, which was compared with conventional nursing methods, in order to reduce the incidence of CAUTI in patients and provide reference for clinical indwelling catheter and follow-up nursing.

DATA AND METHODS

General Information

A total of 116 patients with severe craniocerebral injury who were admitted to the hospital from March 2019 to March 2021 were included. Inclusion criteria were as follows: (1) patients who meet the criteria for severe craniocerebral injury and age $\geq$18 years; (2) the catheter needs to be indwelling; (3) the estimated duration of indwelling urinary catheter $\geq$5 days; and (4) families of patients could cooperate with relevant nursing work, research progress, and sign informed consent. Exclusion criteria were as follows: (1) infection occurred within 48 h after admission; (2) there was a history of anti-infection treatment in the last month; (3) the urinary catheter was indwelling before entering the group; (4) complicated with severe organ diseases such as heart, liver, and lung; and (5) patients discharged or transferred to hospital automatically. The patients were divided into the control group (58 patients) and the observation group (58 patients) according to the random number table. The control group received routine nursing care, while the observation group received cluster nursing based on risk management strategy. There were 33 males and 25 females in the control group. Their age ranged from 38 to 68 years, with an average of 49.51 $\pm$ 6.13 years. The Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were 14–26 points, with an average of 18.13 $\pm$ 2.81. There were 34 males and 24 females in the observation group. Their age ranged from 32 to 67 years, with an average of 48.52 $\pm$ 5.91 years. The APACHE II scores ranged from 13 to 27, with an average of 18.05 $\pm$ 2.69. There was no statistically significant difference in general information between the two groups, which was comparable ($p > 0.05$).

Research Methods

Control Group Using Traditional Nursing Methods

Nurses strengthened safety nursing work and carried out comprehensive health knowledge education to patients and their families. Strictly carry out aseptic operation, wash your hands, and wear sterile gloves when inserting a urinary catheter. Select

an appropriate type of catheter and perform a gentle insertion process. After the urinary catheter was placed, the balloon was used for routine fixation and the perineum was rinsed with warm water twice a day. Keep the position of the urine collection bag always lower than the level of the bladder and ensure the patency of the closed drainage. Do a good job of patient restraint, set guardrail beside the bed, and regularly check whether the power supply of medical devices is in good condition to avoid accidents.

Observation Group Using Cluster Nursing Based on Risk Management Strategy

Risk Management Strategy, Cluster Nursing Plan Formulation, and Training

Before the cluster nursing based on risk management strategy was implemented, the infection management department trained the medical staff and an infection control group related to indwelling urinary catheter was established in the department. The group members included the department director, head nurse, and one physician and nurse. Through consulting relevant literature in databases such as Wanfang Database and HowNet Database, intervention measures provided by each guide, expert consensus, and research literature were analyzed. According to the condition, treatment characteristics and susceptible factors of patients with severe craniocerebral injury, risks, and potential risk factors in daily work were analyzed and identified, including gender, age, type of comorbidity (diabetes, etc.), types of antibiotics used, indwelling catheter time, hospitalization time, etc., and then CAUTI was summarized, organized, discussed, and defined one by one. Targeted prevention and control measures for CAUTI were formulated and training was conducted on time of indwelling urinary catheter and time of catheter removal. Department director and head nurse urged team members to strictly implement the CAUTI risk prevention and control measures, irregular supervision and inspection, and continuous improvement of prevention and control measures.

Specific Measures of Cluster Nursing Based on Risk Management Strategy

The responsible nurses performed risk assessment on the patients with indwelling urinary catheter and given antibiotic-coated urinary catheter. (1) Standardizing urethral catheterization method: The maximum sterile barrier was provided and a large sterile towel was laid when the catheter was placed. Hand hygiene was well done. The seven-step washing technique was used before and after nursing the catheter part or operating the urethral catheterization device. The sterile operation was strictly performed and the placing of the catheter was performed gently; (2) Maintaining the tightness of the drainage system and secondary fixation: A three-cavity silica gel urinary catheter with appropriate thickness and a high-capacity reflux-proof mother–child urine collection bag were selected. In addition to balloon fixation, the secondary fixation was performed with a homemade urinary catheter patch. The urinary catheter was uniformly fixed on the penis for men and on the medial thigh for women; (3) Shortening the indwelling time of urinary catheter: A prereporting system was established after the intubation. The CAUTI high-risk "red and blue" logo was placed at the head of the bed of patient and observed every 2 h including urine volume, color, nature, patency of the urinary catheter, and perineal skin condition. Patients with catheter obstruction should be promptly dredged and replaced. Sterile operation should be strictly performed and physiological bladder irrigation should be given priority. Risk assessment was conducted for each shift and it was included as one of the contents of shift change. Everyday, when nurses change shifts, they check urethral catheterization of patients and make CAUTI risk assessment, which was one of the contents of the shifts. The assessment includes whether it is necessary to continue indwelling catheter. If removal is required, the nurse should set a reminder to remove the catheter without indwelling indication as soon as possible; and (4) Improving self-cleaning consciousness of patient: Communication and health education with families of patients were strengthened, so that they could participate in nursing care together. The patients were encouraged to drink about 3 L of water per day, keep the urine volume above 2 L/day, and take urine samples for etiological examination when necessary. For patients with fecal incontinence, disinfection in time after cleaning is essential.

Quality Control of Cluster Nursing Based on Risk Management Strategy

The department director or the head nurse inspects the number of new patients, the total number of hospitalized patients, the number of indwelling catheter, catheter days, and patient-specific information, including gender, age, disease type, catheter time, is expected to pull tube time, etc., truthfully check records, patrol the measures to carry out the situation, and timely guidance to the operation, theory, etc. A special inspection occurs once a week. The existing problems in nursing were analyzed and group members were organized to discuss and propose solutions.

Observation Indicators

(1) The total incidence of CAUTI in patients between the two groups and the incidence of CAUTI in different time periods were compared. The diagnosis of CAUTI was as follows: the patient developed fever, chills, frequent micturition, urgent urination, pain or tenderness above pubic bone, and purulent discharge at urethral meatus 48 h after the indwelling urinary catheter. The laboratory tests showed an increase in blood white cells as well as red and white cells in urine routine test. The colony number in bacteriological culture of middle urine was $\geq$103 colony-forming unit (cfu)/ml (15).

(2) The results of bacterial culture on the surface of urinary catheter were compared between the two groups before and after cleaning of urinary catheter as well as after 6 and 12 h of cleaning. Bacterial culture was performed on the outer end of the urinary catheter. Surface sampling method: The outer end of the urinary catheter was coated with a cotton swab with a length of 12.5 cm (the circumference and length of the urinary catheter were 2 and 12.5 cm, respectively) and the surface area of the outer end of the urinary catheter was close to 5 × 5 cm. The cotton swab was sent for testing in 10 ml of sampling solution and the number of colonies on the surface of the object was detected.

(3) The duration of indwelling urinary catheter, hospitalization, and hospitalization expenses were compared between the two groups.
(4) The incidence rates of nursing risk events such as pipeline falling off and nurse–patient disputes during the treatment were compared between the two groups.
(5) Results of midstream urine culture in patients with CAUTI are performed.
(6) The satisfaction scores of the two groups of patients were compared with the satisfaction questionnaire prepared by the department. At the time of discharge, the head nurse distributed to the patients a nursing satisfaction questionnaire about catheterization, which was divided into four options: very satisfied, satisfied, dissatisfied, and very dissatisfied. The scale adopts a percentage system, with >90 being very satisfied, 76–90 being satisfied, 60–75 being dissatisfied, and <60 being very dissatisfied.
(7) The knowledge, attitude, and practice (KAP) scale for prevention of catheter infection and the evaluation scale of nurses ability were used to evaluate the sense of control ability and core ability of nurses. The KAP scale for prevention of catheter infection included four dimensions including attitude, behavior, indication of catheter placement, and infection prevention strategy and it consisted of 71 items, with 1–5 points for each item. The higher the score was, the better the perception and control ability was. The evaluation scale of nurses ability included three dimensions of emergency ability, health education ability, and communication ability and there were 80 items in total, with 0–4 points for each item. The higher the score was, the better the prompting ability was.

Statistical Methods

The SPSS software version 22.0 (SPSS Incorporation, Chicago, Illinois, USA) was used for processing. The measurement data of the experimental data were expressed as mean ± SD ($\bar{X}\pm$ s) and the *t*-test was used for pairwise comparison. The count data were expressed as (%) and the comparison was performed using the chi-squared test. The test level was $\alpha = 0.05$ and $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of Total CAUTI Incidence Between the Two Groups and CAUTI Incidence in Different Time Periods

The total incidence rate of CAUTI in the control group was 20.69% including two patients with an indwelling urinary catheter for 7–10 days, three patients with an indwelling urinary catheter for 11–15 days, and seven patients with an indwelling urinary catheter above 15 days. The total incidence rate of CAUTI in the observation group was 6.90% including one patient with an indwelling urinary catheter for 7–10 days, one patient with an indwelling urinary catheter for 11–15 days, and two patients with an indwelling urinary catheter above 15 days. The total incidence of CAUTI in the observation group was lower than that in the control group and the difference was statistically significant ($p < 0.05$), as shown in **Figure 1**.

Bacterial Culture Results on Catheter Surface of Patients in the Two Groups

There was no significant difference in the surface bacterial culture results after catheter cleaning between the two groups ($p > 0.05$). The surface bacterial culture results on the catheter surface of patients in the observation group before and after 6 and 12 h of catheter cleaning was better than those of patients in the control group and the differences were statistically significant ($p < 0.05$), as shown in **Figure 2**.

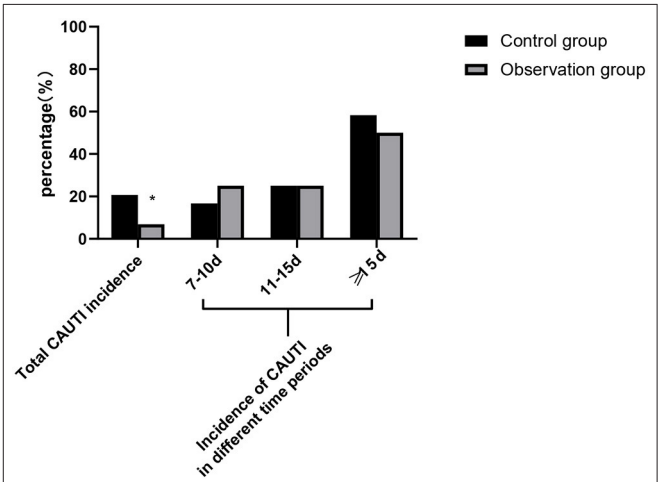


FIGURE 1 | Comparison of total catheter-associated urinary tract infection (CAUTI) incidence between the two groups and CAUTI incidence in different time periods. Compared with the control group, *$p < 0.05$.

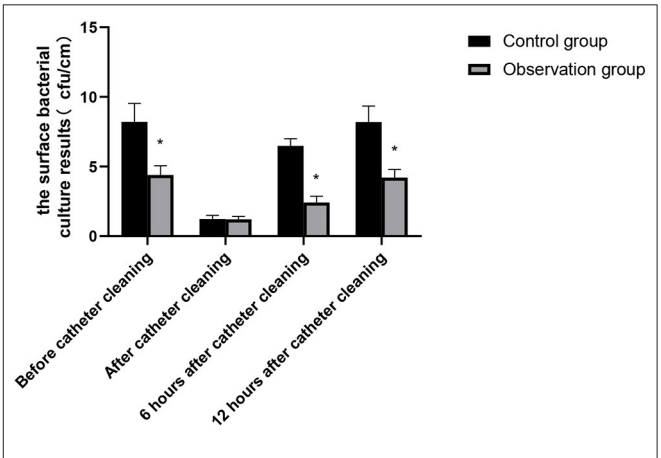


FIGURE 2 | Bacterial culture results on catheter surface of patients in the two groups. Compared with the control group, *$p < 0.05$.

Comparison of Duration of Indwelling Urinary Catheter, Hospitalization Time, and Hospitalization Expenses Between the Two Groups

The duration of indwelling urinary catheter, hospitalization time, and hospitalization expenses of patients in the observation group was lower than those of patients in the control group and the differences were statistically significant ($p < 0.05$), as shown in **Table 1**.

Comparison of the Incidence of Nursing Risk Events During Treatment Between the Two Groups

In the control group, there were one patient of urethral injury, three patients of urinary leakage, two patients of pipeline dropping out, and one patient of nurse–patient dispute during the treatment. The incidence rate of nursing risk events was 11.86%. In the observation group, there were one patient dropped out of the pipeline during the treatment and no nurse–patient dispute occurred. The incidence of nursing risk events was 1.72%. The incidence of nursing risk events in the observation group was lower than that in the control group. The difference was statistically significant ($p < 0.05$), as shown in **Table 2**.

Middle Urine Culture Results of Patients With CAUTI

A total of 16 patients with CAUTI were cultured in clean midstream urine. The cultured bacteria were: *Escherichia coli* (*E. coli*) (62.50%), *Enterococcus faecalis* (25.00%), and *Proteus* (12.50%) in descending order.

TABLE 1 | Comparison of duration of indwelling urinary catheter, hospitalization time, and hospitalization expenses between the two groups.

Group	*n*	Duration of indwelling urinary catheter (d)	Hospitalization time (d)	Hospitalization expenses (yuan)
Control group	58	19.76 ± 3.21	29.71 ± 4.62	33,892.76 ± 672.43
Observation group	58	15.92±3.19	23.95 ± 4.15	31,527.52 ± 567.27
t value		6.462	7.064	20.475
P value		<0.001	<0.001	<0.001

Comparison of Patient Satisfaction Scores Between the Two Groups

The comparison with the self-made satisfaction questionnaire showed that the overall satisfaction score of the observation group was higher than that of the control group and the difference was statistically significant ($p < 0.05$), as shown in **Figure 3**.

Nursing Staff Sense Control Ability and Core Ability Comparison Between the Two Groups

The scores of core competencies such as attitude, behavior, indication of catheter indwelling and infection prevention measures, emergency response ability, health education ability, and communication ability of the nursing staff in the observation group were higher than those of the nursing staff in the control group and the differences were statistically significant ($p < 0.05$), as shown in **Figures 4**, **5**.

DISCUSSION

Operation is the main treatment method for patients with severe craniocerebral injury. Although it can reduce the pain of patients, the catheter needs to be indwelling for a long time after surgery. Naturally, bacteria will grow after 1 week of indwelling urethral catheter in patients. With the extension of the indwelling time, the occurrence rate of bacterial biofilm is higher and higher

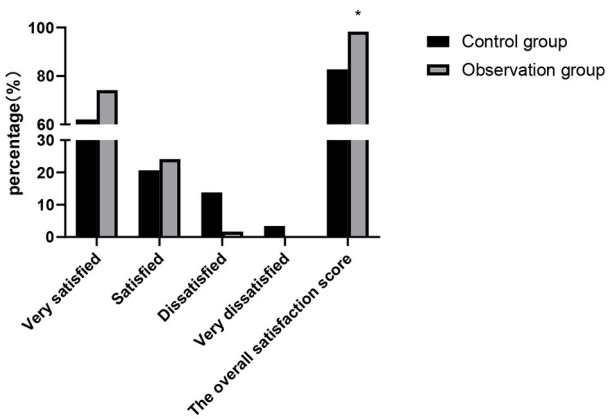


FIGURE 3 | Comparison of patient satisfaction scores between the two groups. Compared with the control group, *$p < 0.05$.

TABLE 2 | Comparison of the incidence of nursing risk events during treatment between the two groups.

Group	*n*	Urethral injury	Urine leakage	Pipeline dropping out	Nurse-patient dispute	Incidence of nursing risk events
Control group	58	1 (1.72%)	3 (5.18%)	2 (3.45%)	1 (1.72%)	12.07%
Observation group	58	0 (0.00%)	0 (0.00%)	1 (1.72%)	0 (0.00%)	1.72%
χ^2 value						4.721
P value						0.030

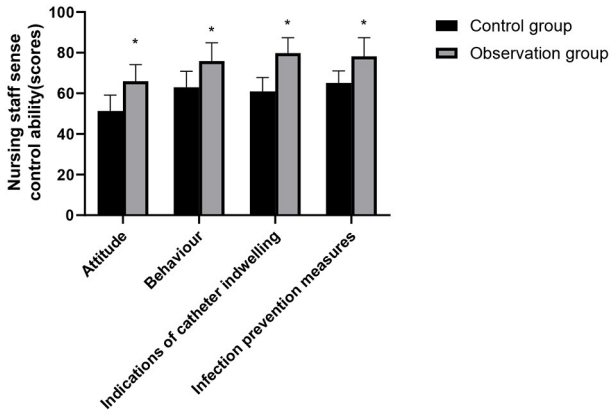


FIGURE 4 | Nursing staff sense control ability comparison between the two groups. Compared with the control group, $^*p < 0.05$.

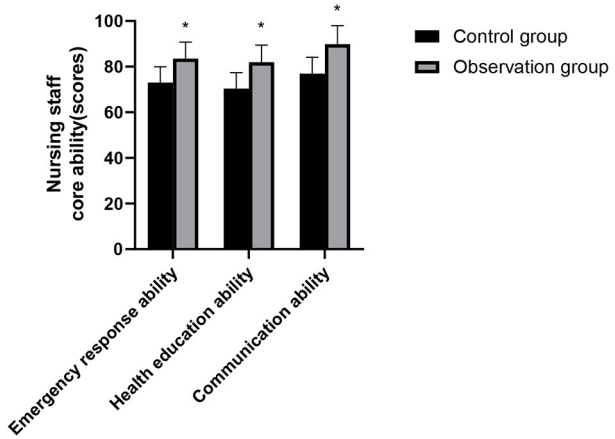


FIGURE 5 | Nursing staff core ability comparison between the two groups. Compared with the control group, $^*p < 0.05$.

and the formed biofilm gradually diffuses inside and outside the catheter surface through the lumen. This, in turn, leads to UTI, catheter blockage, and other conditions, seriously affecting the surgical effect and the recovery process of the postoperative patients (16–18).

In the recent years, cluster nursing has developed into a new concept of clinical nursing. Compared with the traditional nursing mode, it has the systematic characteristics and can carryout comprehensive intervention on the disease, which is more effective than performing a single nursing measure alone (19). Cluster nursing based on risk management strategy includes risk identification and evaluation, implementation of specific nursing measures, and nursing quality control. Risk identification and risk assessment are the first step, which can identify the objective existence and potential risk factors of CAUTI, comprehensively and quantitatively assess the risk of patients with CAUTI, and provide reference for the subsequent formulation and implementation of specific nursing measures. Nurse quality control is that last link of nursing intervention and also the key step to avoid adverse event and improve nursing quality.

In this study, the total incidence of CAUTI in the observation group was significantly lower than that in the control group and the incidence of CAUTI in both the groups increased gradually with the prolongation of indwelling urinary catheter. It is suggested that cluster nursing based on risk management strategy could reduce the incidence of CAUTI in patients with severe craniocerebral injury. Through consulting relevant literature and analyzing the interventions provided by various guidelines, expert consensus, and research articles, we found that the main risk factors of CAUTI were as follows: (1) Patient factors: Severe craniocerebral patients were in a coma, incontinent, the normal physiological environment of the urethral meatus and mucosa was imbalanced, the antibacterial function of neutrophils was weakened and destroyed, and the body resistance was decreased. In addition, the catheter indwelling time was long, which was more likely to lead to infection. However, own factors of patient, such as old age, basic diseases, and the severity of the disease, could not be interfered; (2) Personnel factors: The concept of sterility of medical staff is not strong, disinfection and isolation measures are not in place, and the compliance of hand hygiene is poor. Catheter placement technology is not skilled, the operation is not standardized, catheter care is not in place, etc.; and (3) Environmental factors: Family members of patients paid more visits, which easily brought pathogenic bacteria into the ward; pathogens can also be transmitted, if the daily environment is not cleaned properly (20–22). In view of the above risk factors, targeted prevention and control measures of CAUTI were formulated and strictly controlled for implementation to ensure the quality of care.

Based on the risk management strategy of cluster nursing, the specific implementation measures include: (1) Specification catheterization method, do a good job in hand hygiene, and strict aseptic operation; (2) Suitable urinary catheter was selected and self-made urinary catheter paste was used for secondary fixation; (3) To solve the problem of the long indwelling catheter in patients, setup risk assessment and reminder for indwelling catheter, so as to remove it as soon as possible; (4) Strengthen communication with families of patients and health education of cleaning and disinfection. Clustering consisting of four elements is feasible for every nursing measure in clinic. The results of this study showed that the bacterial culture results on the surface of urinary catheter of patients in the observation group in different time periods were better than those of patients in the control group. At the same time, the time of indwelling urinary catheter, hospital stay, and hospital expenses of patients in the observation group were lower than those of patients in the control group. Moreover, the incidence of nursing risk events was also significantly reduced. A study by Mitchell showed that the incidence of CAUTI was positively correlated with the catheter indwelling time and the longer the catheter indwelling time, the more bacteria colonization outside the catheter (23). The time of indwelling urinary catheter for patients in the observation group was shortened. By setting the reminder mechanism, the doctors were prompted to stop

pulling out the urinary catheter according to the advice of doctor in time, so as to improve the effectiveness of nursing implementation. In this study, we performed secondary fixation of the urinary catheter to avoid the change in the position of the urinary catheter and ensure that no mechanical damage was caused to the urethra and bladder mucosa during the period of indwelling urinary catheter, thereby reducing the occurrence of CAUTI.

A total of 16 patients with CAUTI were cultured in clean midstream urine and the cultured strains were in the order of *E. coli* > *Enterococcus faecalis* > *Proteus* from high to low. *E. coli* in the Gram-negative Enterobacteriaceae family is a common pathogen isolated from the urinary tract. A study covering 38 centers in 11 countries in the Asia-Pacific region showed that the constituent ratio of *E. coli* in Gram-negative bacterial isolates causing UTI was 56.8% (24).

With the increasing awareness of hospital infection monitoring and demand of people for medical services, the incidence of medical disputes has been increasing year by year. It is an inevitable trend of the management development of medical institutions in the future to reduce the infection factors from the root, reduce the incidence of infection, ensure the safety of patients, and improve the effect of care details and medical quality (25). In this study, the overall satisfaction score of patients and the control and core ability scores of nursing staff in the observation group were higher than those in the control group. It proved the high-quality application effect of cluster nursing based on risk management strategy in the process of nursing risk management for patients with severe craniocerebral injury. Nursing can assess the risk of nursing by mastering the characteristics of condition of patients and summarize the high-risk factors and the advantages and disadvantages of intervention measures, which will help to improve the quality of clinical nursing and reduce the incidence of nursing risk events. At the same time, it can improve the subjective ability of nursing staff to resist risks, the quality of nursing care, and the degree of patient care satisfaction (26).

In summary, cluster nursing based on risk management strategy can effectively reduce the incidence of nursing risk events and the probability of UTI in the management of UTI in patients with severe craniocerebral injury, shorten the duration of indwelling urinary catheter and hospitalization, and improve the nursing satisfaction and the sense of control and nursing ability of nursing staff.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Chongqing Southeast Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HQ, JY, and CW: collect datas. HQ: write the paper. CW: revise the paper. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Wang Z, Zhang R, Han Z, Wang J, Wu R, Zhao W, et al. [Application of continuous monitoring of intracranial pressure and brain oxygen partial pressure in the treatment of patients with severe craniocerebral injury]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* (2021) 33:449–54. doi: 10.3760/cma.j.cn121430-20201106-00700
2. McCafferty RR, Neal CJ, Marshall SA, Pamplin JC, Rivet D, Hood BJ, et al. Neurosurgery and medical management of severe head injury. *Mil Med.* (2018) 183:67–72. doi: 10.1093/milmed/usy071
3. Maegele M, Lefering R, Sakowitz O, Kopp MA, Schwab JM, Steudel WI, et al. The incidence and management of moderate to severe head injury. *Dtsch Arztebl Int.* (2019) 116:167–73. doi: 10.3238/arztebl.2019.0167
4. Clayton JL. Indwelling urinary catheters: a pathway to health care-associated infections. *AORN J.* (2017) 105:446–52. doi: 10.1016/j.aorn.2017.02.013
5. Giles M, Graham L, Ball J, King J, Watts W, Harris A, et al. Implementation of a multifaceted nurse-led intervention to reduce indwelling urinary catheter use in four Australian hospitals: a pre- and postintervention study. *J Clin Nurs.* (2020) 29:872–86. doi: 10.1111/jocn.15142
6. Lo E, Nicolle LE, Coffin SE, Gould C, Maragakis LL, Meddings J, et al. Strategies to prevent catheter-associated urinary tract infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol.* (2014) 35:464–79. doi: 10.1086/675718
7. Yu S, Marshall AP, Li J, Lin F. Interventions and strategies to prevent catheter-associated urinary tract infections with short-term indwelling urinary catheters in hospitalized patients: an integrative review. *Int J Nurs Pract.* (2020) 26:12834. doi: 10.1111/ijn.12834
8. Milo S, Nzakizwanayo J, Hathaway HJ, Jones BV, Jenkins ATA. Emerging medical and engineering strategies for the prevention of long-term indwelling catheter blockage. *Proc Inst Mech Eng H.* (2019) 233:68–83. doi: 10.1177/0954411918776691
9. Niederhauser A, Züllig S, Marschall J, Schwappach DL. Nurses' and physicians' perceptions of indwelling urinary catheter practices and culture in their institutions. *J Patient Saf.* (2020) 16:82–9. doi: 10.1097/PTS.0000000000000502
10. Silva RP, Valente GSC, Camacho ACLF. Risk management in the scope of nursing professionals in the hospital setting. *Rev Bras Enferm.* (2020) 73:303. doi: 10.1590/0034-7167-2019-0303
11. Wang W, Tang C, Ji QL, Xiu H, Shao H, Yu XM. Use of multiple nursing interventions (cluster nursing) in ABO hemolytic disease of neonates and evaluation of its effect. *J Int Med Res.* (2020) 48:300. doi: 10.1177/0300060519887630
12. Wang L, Li X, Yang Z, Tang X, Yuan Q, Deng L, et al. Semi-recumbent position versus supine position for the prevention of ventilator-associated pneumonia in adults requiring mechanical ventilation. *Cochrane Database Syst Rev.* (2016) 2016:9946. doi: 10.1002/14651858.CD009946.pub2
13. Faria DA, da Silva EM, Atallah ÁN, Vital FM. Noninvasive positive pressure ventilation for acute respiratory failure following upper abdominal surgery. *Cochrane Database Syst Rev.* (2015) 2015:9134. doi: 10.1002/14651858.CD009134.pub2

14. Pham TB, Srinivas S, Martin JR, Brandel MG, Wali AR, Rennert RC, et al. Risk factors for urinary tract infection or pneumonia after admission for traumatic subdural hematoma at a level I trauma center: large single-institution series. *World Neurosurg.* (2020) 134:754–60. doi: 10.1016/j.wneu.2019.10.192
15. Rebmann T, Greene LR. Preventing catheter-associated urinary tract infections: an executive summary of the association for professionals in infection control and epidemiology, Inc, elimination guide. *Am J Infect Control.* (2010) 38:644–6. doi: 10.1016/j.ajic.2010.08.003
16. Ho CH, Liang FW, Wang JJ, Chio CC, Kuo JR. Impact of grouping complications on mortality in traumatic brain injury: a nationwide population-based study. *PLoS ONE.* (2018) 13:190683. doi: 10.1371/journal.pone.0190683
17. Tsitsopoulos PP, Iosifidis E, Antachopoulos C, Anestis DM, Karantani E, Karyoti A, et al. Nosocomial bloodstream infections in neurosurgery: a 10-year analysis in a center with high antimicrobial drug-resistance prevalence. *Acta Neurochir.* (2016) 158:1647–54. doi: 10.1007/s00701-016-2890-5
18. Davis C. Catheter-associated urinary tract infection: signs, diagnosis, prevention. *Br J Nurs.* (2019) 28:96–100. doi: 10.12968/bjon.2019.28.2.96
19. Durant DJ. Nurse-driven protocols and the prevention of catheter-associated urinary tract infections: a systematic review. *Am J Infect Control.* (2017) 45:1331–41. doi: 10.1016/j.ajic.2017.07.020
20. Neugent ML, Hulyalkar NV, Nguyen VH, Zimmern PE, De Nisco NJ. Advances in understanding the human urinary microbiome and its potential role in urinary tract infection. *MBio.* (2020) 11:218–20. doi: 10.1128/mBio.00218-20
21. Holroyd S. The importance of indwelling urinary catheter securement. *Br J Nurs.* (2019) 28:976–7. doi: 10.12968/bjon.2019.28.15.976
22. Shum A, Wong KS, Sankaran K, Goh ML. Securement of the indwelling urinary catheter for adult patients: a best practice implementation. *Int J Evid Based Healthc.* (2017) 15:3–12. doi: 10.1097/XEB.0000000000000084
23. Mitchell BG, Fasugba O, Gardner A, Koerner J, Collignon P, Cheng AC, et al. Reducing catheter-associated urinary tract infections in hospitals: study protocol for a multi-site randomised controlled study. *BMJ Open.* (2017) 7:18871. doi: 10.1136/bmjopen-2017-018871
24. Jean SS, Coombs G, Ling T, Balaji V, Rodrigues C, Mikamo H, et al. Epidemiology and antimicrobial susceptibility profiles of pathogens causing urinary tract infections in the Asia-Pacific region: results from the Study for Monitoring Antimicrobial Resistance Trends (SMART), 2010-2013. *Int J Antimicrob Agents.* (2016) 47:328–34. doi: 10.1016/j.ijantimicag.2016.01.008
25. Poortaghi S, Salsali M, Ebadi A, Pourgholamamiji N. Accreditation of nursing clinical services: development of an appraisal tool. *Nurs Open.* (2020) 7:1338–45. doi: 10.1002/nop2.505
26. Watanabe N, Morikawa G, Kubota K, Okazawa K, Tanaka C, Horiuchi M. [A clinical pathway based on medical and nursing teamwork in drug management facilitates integrated community care for elderly patients with chronic heart failure]. *Yakugaku Zasshi.* (2018) 138:797–806. doi: 10.1248/yakushi.17-00209-4

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Qiao, Yang and Wang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 08 February 2022
doi: 10.3389/fsurg.2022.842716

Application of the Six-Step Standard Communication Process in the Communication Training for Newly Recruited Nurses in Cancer Specialist Hospitals

Jingzhi Geng[1†], *Miao Liu*[1†], *Huanhuan Zhang*[2], *Jian Gao*[3], *Li Wang*[4], *Yu Zhang*[4], *Fengyan Ma*[2] *and Yan Liu*[2*]

[1] *Department of Gynecologic Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences Peking Union Medical College, Beijing, China,* [2] *Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences Peking Union Medical College, Beijing, China,* [3] *Department of Radiation Therapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences Peking Union Medical College, Beijing, China,* [4] *Department of VIP Medical Services, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences Peking Union Medical College, Beijing, China*

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Guilu Tao,
The Second Affiliated Hospital of Dalian Medical University, China
Fang Wei,
Central South University, China

***Correspondence:**
Yan Liu
15201119199@139.com

[†] *These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *24 December 2021*
Accepted: *11 January 2022*
Published: *08 February 2022*

Citation:
Geng J, Liu M, Zhang H, Gao J, Wang L, Zhang Y, Ma F and Liu Y (2022) Application of the Six-Step Standard Communication Process in the Communication Training for Newly Recruited Nurses in Cancer Specialist Hospitals. Front. Surg. 9:842716. doi: 10.3389/fsurg.2022.842716

Purpose: Discuss the application effect of the six-step standard communication process in the communication ability training of newly recruited nurses.

Methods: This is a before and after control study. The control group included 45 newly recruited nurses in our hospital in 2019, and the observation group included 40 newly recruited nurses in our hospital in 2020. The control group completed the training according to the existing communication training program, and the observation group implemented a training program based on the "six-step standard communication process" on the basis of the existing communication training. The training period was 12 months. The training effect of the two groups of new nurses was compared.

Results: After training, the total scores of clinical communication skills of the new nurses in the control group and observation group were 252.56 ± 24.950 and 268.05 ± 19.335 points, respectively; the total scores of communication behavior were 39.00 ± 4.676 and 48.08 ± 2.515 points, respectively; the total scores of general self-efficacy were 26.89 ± 3.017 and 31.25 ± 5.027 points, respectively; the satisfaction scores of communication training were 17.56 ± 2.018 and 19.45 ± 0.986 points, respectively, and the differences were statistically significant ($P < 0.05$).

Conclusion: The implementation of a training program based on the "six-step standard communication process" can effectively improve the clinical communication skills and self-efficacy of newly recruited nurses, and can be promoted and applied to the communication training of newly recruited nurses.

Keywords: six-step standard communication process, cancer specialist hospital, new nurses, clinical communication skills, self-efficacy

INTRODUCTION

A specialized tumor hospital is a technically sophisticated and specialized hospital with the prevention and treatment of tumor diseases as its main business scope. Most of the patients it receives are special groups who are facing death threats and bear huge psychological pressure, so the oncology specialist hospital needs to show more humanistic care while providing them with superb medical technology. Nursing-patient communication is a key link in expressing humanistic care in the operation of tumor specialized hospitals. It plays a very important role in increasing patient satisfaction and improving clinical services, and most of the complaints of patients are related to poor doctor-patient or nurse-patient communication (1, 2). It has been reported that the problem of insufficient communication skills among newly recruited nurses is particularly prominent, and the nurse-patient communication skills they have mastered cannot meet their job needs (3, 4). And in the existing training, the communication training of newly recruited nurses is more inclined to theoretical learning and experience introduction, and there are problems such as low practicability and insignificant effect, so it cannot meet the special nursing needs of tumor hospitals for tumor diseases (5). In 2016, my country required communication ability training for new nurses in the "Training Outline for Newly Enrolled Nurses (Trial)" (6). The six-step standard communication process is formed by domestic scholars through the Chineseization and revision of the CICARE communication model, namely "connect-introduce-communicate-ask-respond-exit," it streamlines and standardizes every communication between nurses and patients, which helps to rapidly improve the professionalism and communication skills of nurses, thereby providing better nursing support for patients. It is an effective communication method to build nurse-patient trust and promote nurse-patient harmony (7). This study intends to combine the nursing characteristics and clinical needs of cancer patients to construct a communication skills training program for newly recruited nurses based on the "six-step standard communication process," and to explore its application effects. The report is as follows.

MATERIALS AND METHODS

Research Object

Nurses who had been employed in our hospital for <1 year in 2019 and 2020. The new nurses were divided into a control group and an observation group according to their entry time. The control group included 45 newly recruited nurses in our hospital in 2019, and the observation group included 40 newly recruited nurses in our hospital in 2020. Inclusion criteria: ① Those who had not received the six-step standard communication process training; ② Those who had passed the nurse qualification examination; ③ Those who had a college degree or above. Exclusion criteria: ① Those who could not participate in the whole training; ② Those who had work experience; ③ Those who worked in the operating room, ICU, and auxiliary examination departments after entering the job.

Training Program

Nurses in the control group received communication training according to the existing program. This included theoretical lectures on communication-related knowledge, simulation training on communication, communication case analysis and discussion, communication practice under the supervision of a specialist during clinical work, participation in clinical department work, ward rounds and business learning, learning the communication style and skills of teaching teachers, and timely guidance from teaching teachers on communication problems arising from new nurses.

The observation team implemented a training program based on the "six-step standard communication process" on the basis of the control group. Specifically, this includes: ① Establishing a training team. The team leader was the associate director for teaching in the nursing department, and the team consisted of six members. They included head nurses, teaching teachers, quality control nurses, the titles were all nurses in charge and above. ② Developing a six-step standard communication flow chart and publicity posters and posting them in the departments and wards where the observation group nurses were located. The main contents included: connect (polite contact: using the preferred term of address when approaching patients and families), introduce (enthusiastic introduction: introducing yourself and explaining duties), communicate (explain in detail: what would be done to communicate with the patient, how long it would take, and how it would affect the patient), ask (careful inquiry: obtaining consent before performing the procedure and asking the patient's needs), respond (patiently answer: patiently answering questions from patients or families), exit (leave politely: politely explaining what needed to be done next, saying goodbye politely). ③ Production of training materials. The aforementioned flowchart would be made into a manual and distributed to new nurses; a video of scenario-based communication simulation would be filmed for new nurses to learn. ④ Establishing a "communication typical case library." Each department summarizing clinical nursing scenarios according to the characteristics of diseases, and the training team selecting typical cases and using the "six-step standard communication process" to create a "communication typical case library," which was divided into common nursing situations such as receiving consultation, intravenous infusion, health education and psychological guidance. ⑤ Training implementation. Divided into 3 phases. Phase 1 was the theoretical lecture phase. Conducting lectures on related knowledge of the "six-step standard communication process," mainly training its connotation, definition, communication skills knowledge and specific applications. At the same time, citing cases and watching scenario simulation videos, inspiring members to ask questions, and solve difficulties and doubts in communication in time. Phase 2 was the scenario training stage. Using standardized patients, new nurses can experience different scenarios and feel the communication skills in special situations, so that theory and practice can be integrated to strengthen in-depth understanding of the communication process. Phase 3 was the clinical practice and consolidation stage. Implementing the "six-step standard communication process" in clinical work, and

TABLE 1 | General information of new nurses.

Items	Control group ($n = 45$)	Observation group ($n = 40$)	t/χ^2 value	*P*-value
Gender				
Male	0 (0.00%)	0 (0.00%)		
Female	45 (100.00%)	40 (100.00%)		
Average age	23.31 ± 1.08	22.80 ± 0.97	2.279	0.025
Only child or not				
Yes	19 (42.22%)	11 (27.50%)	2.010	0.156
No	26 (57.78%)	29 (72.50%)		
Residence				
Urban	18 (40.00%)	21 (52.50%)	1.333	0.248
Rural	27 (60.00%)	19 (47.50%)		
Education level				
College	20 (44.44%)	16 (40.00%)	0.171	0.679
Bachelor or above	25 (55.56%)	24 (60.00%)		
Personality type				
Outgoing	31 (68.9%)	25 (62.50%)	0.385	0.535
Introverted	14 (31.1%)	15 (37.50%)		
Have received communication training before entering the job				
Yes	37 (82.22%)	8 (17.78%)	0.455	0.500
No	35 (87.50%)	5 (12.50%)		

making a nursing summary of the problems encountered in the actual operation, and the nurses shared actual work cases and exchanged discussions with each other.

Research Tools

General information questionnaire: It was designed by the researchers themselves, including the gender, age, marital status, education background of the research object, whether it was an only child, the attitude of choosing a nursing major, and whether they had participated in communication skills training, etc.

Nurses' clinic communication competence scale (NCCCS): Including 6 dimensions, a total of 58 items. The KMO of the scale was 0.972, the overall Cronbach's α coefficient was 0.978, and the Cronbach's α coefficient of each dimension was between 0.873 and 0.954. Using the Likert 5-level scoring method, each item was assigned a value of 1 to 5 points from "very poor" to "very good," and the score ranged from 58 to 290 points. All items were scored positively, the higher the score, the better the communication skills.

Clinical communication behavior scale: The content included 10 entries. A Likert 5-point scale (1=very poor, 5=very good) was used. each item was assigned a score of 1 to 5 from very poor to very good, with a total score of 10 to 50. The higher the score, the better the communication ability.

General self-efficacy scale (GSES): The total Cronbach's α coefficient of the scale was 0.87, and the test-retest reliability was 0.83 (8). The Chinese version of GSES had a total of 10 entries, all of which were forward entries. The Likert 4-level scoring method was used to score 1–4 points from "completely incorrect" to "completely correct," with a total score of 10–40 points. The higher the score, the stronger the nurse's sense of self-efficacy. The self-efficacy score of the international norm was (28.6 ± 4.0) points.

Nurse communication training satisfaction questionnaire: The questionnaire consisted of 5 items and was scored on a 4-point scale from 1 to 4, ranging from "strongly disagree" to "strongly agree," with higher scores indicating higher satisfaction. The questionnaire was reviewed by experts and had good reliability and validity, with a Cronbach's S coefficient of 0.85 and a retest reliability of 0.95.

Evaluation Method

After 12 months of new nurses' training, a questionnaire was distributed by the research team to investigate the new nurses' clinical communication ability, self-efficacy and satisfaction with communication training in 2019 and 2020, respectively, while the new nurses' communication behaviors in clinical nursing were rated by a dedicated person.

Statistical Analysis

Count data were expressed as number of cases and composition ratio (%), and the chi-square test was used for comparison between groups; normally distributed measures were expressed as mean ± standard deviation, and the independent samples *t*-test was used for comparison between groups. Differences were indicated as statistically significant at $P < 0.05$.

RESULTS

General Information of New Nurses

The differences in general information between the new nurses in the control and observation groups were not statistically significant ($P > 0.05$) and were comparable. As seen in **Table 1**.

NCCCS Score of New Nurses

The total NCCCS scores of new nurses in the control and observation groups were 252.56 ± 24.95 and 268.05 ± 19.34 points, respectively ($P < 0.05$), and the scores of each dimension are shown in **Table 2** and **Figure 1**.

Clinical Communication Behavior Score of New Nurses

The total clinical communication behavior scores of new nurses in the control and observation groups were 39.00 ± 4.68 and 48.08 ± 2.52 points, respectively ($P < 0.05$), and the scores of each dimension are shown in **Table 3** and **Figure 2**.

GSES Score of New Nurses

The total GSES scores of new nurses in the control and observation groups were 26.89 ± 3.02 and 31.25 ± 5.03 points, respectively ($P < 0.05$), and the scores of each items are shown in **Table 4** and **Figure 3**.

Communication Training Satisfaction Score of New Nurses

The total communication training satisfaction scores of new nurses in the control and observation groups were 17.56 ± 2.02 and 19.45 ± 0.99 points, respectively ($P < 0.05$), and the scores of each item are shown in **Table 5** and **Figure 4**.

DISCUSSION

New nurses lack communication skills and experience, and often do not know how to communicate properly when in contact with patients. And in view of the particularity of tumor diseases, patients and their families have shown more nursing needs for medical staff, which puts forward stricter nursing communication requirements for newly recruited nurses in cancer hospitals. This study applied the "six-step standard

TABLE 2 | NCCCS scale of new nurses.

Serial number	Number of entries	Dimension
①	11	Basic verbal communication skills
②	6	Team communication skills
③	7	Basic non-verbal communication skills
④	6	Emotional support capabilities
⑤	19	Communication skills in difficult situations
⑥	9	Emotional perception ability
⑦	58	Communication total items

TABLE 3 | Clinical communication behavior scale of new nurses.

Serial number	Item
①	Knock before entering the door
②	Introduce yourself before communicating
③	Inform and explain when communicating
④	Gaze when communicating
⑤	Pay attention to the patient's reaction when communicating
⑥	Ask for patients' opinions when communicating
⑦	Answer questions from patients during communication
⑧	Leave politely
⑨	Put the stool away when leaving and close the door gently
⑩	Overall evaluation
⑪	Total score

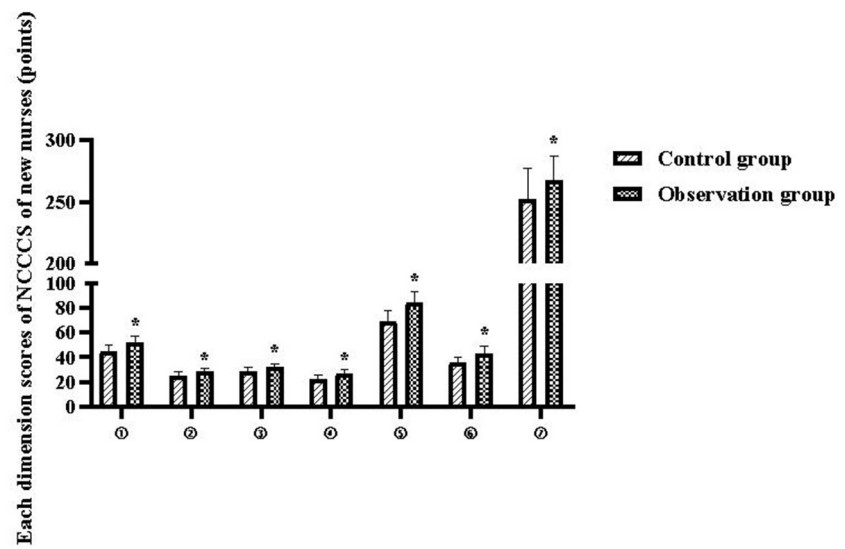


FIGURE 1 | Each dimension scores of NCCCS of new nurses. Compared with the control group, *$P < 0.05$.

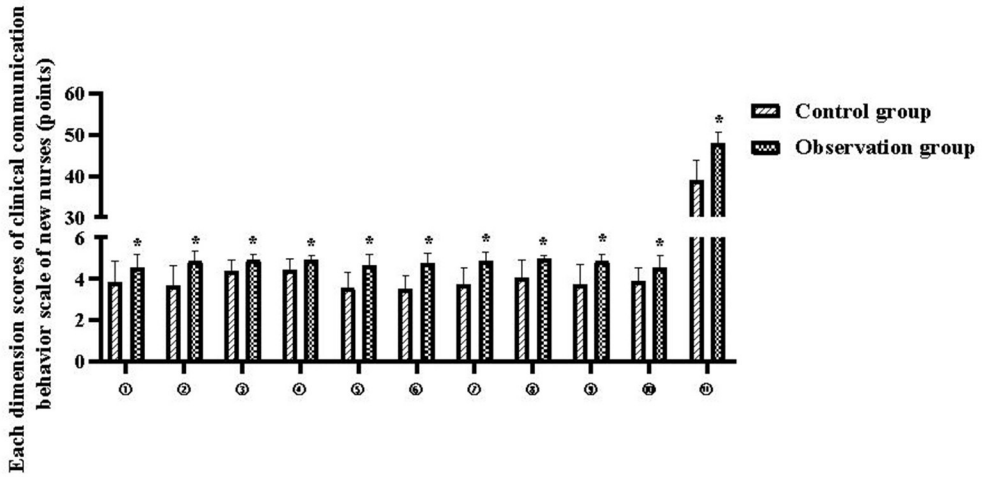


FIGURE 2 | Each dimension scores of clinical communication behavior scale of new nurses. Compared with the control group, $^*P < 0.05$.

TABLE 4 | GSES scale of new nurses.

Serial number	Item
①	If I do my best, I can always solve the problem
②	Even if others oppose me, I still have the means to get what I want
③	It is easy for me to stick to my ideals and reach my goals
④	I am confident that I can deal effectively with anything that comes up unexpectedly
⑤	With my talent, I'm sure I can handle the unexpected
⑥	If I put in the necessary effort, I will be able to solve most of the puzzles
⑦	I can face difficulties calmly because I trust my ability to deal with problems
⑧	When faced with a difficult problem, I can usually find several solutions
⑨	When there is trouble, I can usually think of some ways to deal with it
⑩	No matter what happens to me, I can handle it
⑪	Total score

communication process" to the training of newly recruited nurses' communication skills, and the results showed that:

After training, in clinical communication ability and communication behavior, the total score and each item score of the observation group were significantly higher than those of the control group ($P < 0.05$). This suggests that training based on the "six-step standard communication process" can effectively improve the clinical communication skills of newly recruited nurses in cancer specialist hospitals and promote the norms of communication behavior. The cultivation of nurse-patient communication skills of newly recruited nurses is an important part of nursing human resource management, and it is also a necessary measure to meet the needs of patients and ensure the quality of clinical care. The "six-step standard communication process" is a training method proposed by the University of California, Los Angeles General Hospital, which is divided into six processes of "connect-introduce-communicate-ask-respond-exit." Its content covers standard phrases and procedures for communication with patients, and its core contains communication details such as respect, courtesy, communication, civility, listening and smiling, which can provide a practical template for new nurses' clinical communication and can better transition communication skills from theory to practice. And in the form of communication, it goes from shallow to deep, from polite conversation to declarative communication, and up to emotional communication, so that the theory of nursing communication becomes easy to understand and operable from complicated, which is convenient to correct irrational understanding, improve communication ability and solve patients' practical problems. The application of the six-step standard communication process in this study, through theoretical lectures, posters, the production of training materials, and the filming of scenario-based communication videos, can enable new nurses to quickly grasp the specific definition, connotation and application of the six-step standard communication process, and actively create an atmosphere of nurse-patient communication using the six-step standard communication process; At the same time, each department summarizes clinical nursing scenarios according to disease characteristics, and the training team selects typical cases and uses the "six-step standard communication process" to create a "communication typical case library," which can provide new nurses with rich, typical and realistic learning cases. The above nursing training process is interlocked and step-by-step, which can guide new nurses to have friendly contact with patients and strengthen communication, so that nurses can know the specific communication methods and contents each time they serve patients, which is an important way to realize the rapid transformation of humanistic theoretical knowledge into practical application, rapidly improve the clinical

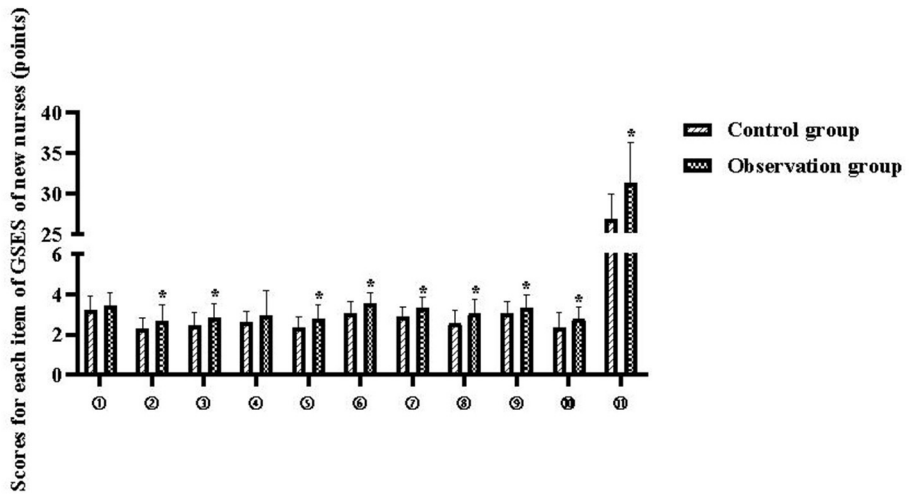


FIGURE 3 | Each item scores of GSES of new nurses. Compared with the control group, *$P < 0.05$.

TABLE 5 | Communication training satisfaction scale of new nurses.

Serial number	Item
①	I was generally very satisfied with the way the communication course was conducted
②	I think the course content is presented in an easy-to-understand way, easy to imitate and remember
③	I have put the communication skills I have learned to good use in my daily work
④	I am more confident in my work and daily communication
⑤	The use of communication skills has made my interpersonal relationships more harmonious
⑥	Total score

communication ability of new nurses, create a harmonious treatment environment, and promote the standardization and homogenization of nursing services (9).

After training, the total score of general self-efficacy and communication training satisfaction scores of the observation group were higher than those of the control group, and the total score of self-efficacy of the observation group was higher than the international norm value (28.6 ± 4.0) points ($P < 0.05$). This suggests that training based on the "six-step standard communication process" can enhance the self-efficacy and job confidence of newly recruited nurses in cancer specialist hospitals, and increase satisfaction with communication training. Self-efficacy is a concept proposed by the American psychologist Bandura in 1977. It refers to people's confidence or belief in their ability to achieve behavioral goals in a specific field (10). Nurses' self-efficacy is positively correlated with their nursing behaviors (11–13). Nurses with a high sense of self-efficacy can effectively exercise self-control, regulate their own behaviors, and promote professional behaviors in nursing practice. By improving their sense of self-efficacy, they can promote nurses to increase their work rate and work quality, and reduce their tendency to leave, and ultimately increase quality of nursing service. In addition, nurses with stronger communication skills can also positively influence the overall sense of experience and nursing satisfaction of cancer patients and have the effect of improving the overall health status of patients, however, new oncology nurses rarely receive formal nursing communication instruction during clinical learning, and with insufficient theoretical knowledge and lack of practical experience, they often fall into a flustered and passive situation when communicating with patients, and therefore have a low sense of self-efficacy, which is not conducive to the cultivation of work confidence and the establishment of a harmonious nurse-patient relationship (14–16). This study implements a six-step standard communication process that integrates theory and practice. Compared with the previous communication training process, the content is not only easier to understand and easy for new nurses to imitate and remember, but also helps to cultivate new nurses' critical thinking and exercise their ability to analyze and solve practical problems. For example, the application of standardized patient scenarios during training allows new nurses to experience different scenarios and perceive nursing communication skills in special situations, which helps them to have a deeper understanding of communication processes and skills and be able to apply them flexibly in conjunction with actual clinical needs.

As a result, the new nurses' overall clinical competence improved significantly, and their self-efficacy and satisfaction with the communication training increased accordingly.

The results of this study also showed that in GSES, the scores of entries ① and ④ were higher in the observation group than in the control group, but there was no statistical difference ($P > 0.05$). The reason may be that the training subjects in this study were new nurses in oncology hospitals, and although a "communication typical case library" was established and training on "communication in difficult scenarios" was conducted, oncology nursing is faced with more complex diseases and patients, which has higher demands on nursing staff (17, 18).

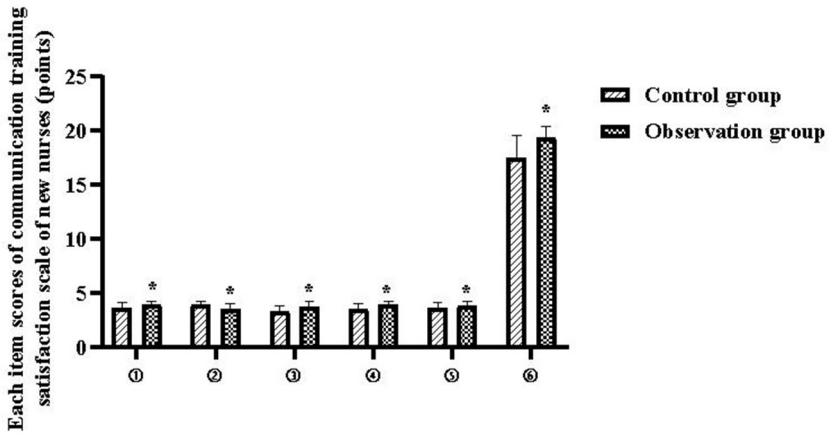


FIGURE 4 | Each item scores of communication training satisfaction scale of new nurses. Compared with the control group, $^*P < 0.05$.

Therefore, new nurses still do not feel confident that they can "always solve problems" and "deal effectively with anything that comes up" due to their lack of oncology nursing knowledge and clinical experience.

Cancer treatment is a long and complicated process. In this process, patients and their families suffer from multiple burdens from mental, physical and economic aspects, and nurses are faced with various demands from patients, so they must treat each patient with "love, patience, care, compassion and responsibility," continuously improve service quality and service attitude, and really make our nursing work to the heart of patients (19, 20). The six-step standard communication process of this study practiced the "people-oriented" nursing concept throughout the entire process. It focuses on the needs of patients, pays attention to evaluating and meeting the needs of patients, fully embodies the nursing philosophy of humanistic care, and helps new nurses to win the satisfaction of patients. The increase in positive reviews received by new nurses in nursing work also contributes to the improvement of self-efficacy and job satisfaction (21, 22).

CONCLUSION

Training based on the "six-step standard communication process" can improve the communication skills and self-efficacy of new nurses in cancer specialist hospitals, enhance the confidence of new nurses in communication, and enable them to quickly master nurse-patient communication skills, and effectively apply them in clinical nursing work. It is worth promoting and applying in the communication training of newly recruited nurses. However, due to the short tracking time of this study, the long-term maintenance effect of this training model in the clinical communication of newly recruited nurses needs to be further tracked and refined.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Chinese Academy of Medical Sciences Peking Union Medical College. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JGe and ML are mainly responsible for the writing of the manuscript. HZ and JGa are mainly responsible for the design of the research. LW and YZ are mainly responsible for the evaluation and collection of the results. FM is responsible for the statistics of the data. YL is responsible for the guidance of the entire study. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Special Fund for Hospital Management Research (LC2020D02).

REFERENCES

1. Liaw SY, Ooi SW, Rusli KDB, Lau TC, Tam WWS, Chua WL. Nurse-physician communication team training in virtual reality versus live simulations: randomized controlled trial on team communication and teamwork attitudes. *J Med Internet Res.* (2020) 22:e17279. doi: 10.2196/17279
2. Iwanoff C, Giannopoulos M, Salamon C. Follow-up postoperative calls to reduce common postoperative complaints among urogynecology

patients. *Int Urogynecol J.* (2019) 30:1667–72. doi: 10.1007/s00192-018-3809-x
3. Li J, Li X, Gu L, Zhang R, Zhao R, Cai Q, et al. Effects of simulation-based deliberate practice on nursing students' communication, empathy, and self-efficacy. *J Nurs Educ.* (2019) 58:681–9. doi: 10.3928/01484834-20191120-02
4. Lee J, Mast M, Humbert J, Bagnardi M, Richards S. Teaching handoff communication to nursing students: a teaching intervention and lessons learned. *Nurse Educ.* (2016) 41:189–93. doi: 10.1097/NNE.0000000000000249
5. Curtis JR, Back AL, Ford DW, Downey L, Shannon SE, Doorenbos AZ, et al. Effect of communication skills training for residents and nurse practitioners on quality of communication with patients with serious illness: a randomized trial. *JAMA.* (2013) 310:2271–81. doi: 10.1001/jama.2013.282081
6. National Health and Family Planning Commission. *Training Syllabus For Newly Recruited Nurses (for trial implementation) [EB/OL].* Available online at: http://www.nhfpc.gov.cn/yzygj/s3593/201602/91b5a8fa3c9a45859b036558a5073875.shtml (accessed January 22, 2016).
7. Wang T, Shao XF, Chen SZ. Study on application of CICARE communication mode in ICU nurse-patient communication. *Hosp Manag Forum.* (2019) 36:23–5. doi: 10.3969/j.issn.1671-9069.2019.03.007
8. Schwarzer R, Bassler J, Kwiatek P, Schröder K, Zhan JX. The assessment of optimistic self-beliefs: comparison of the German, Spanish, and Chinese versions of the general serf-efficacy scale. *ApplPsychol-Int-Rev-PsycholAppl-Rev Int.* (1997) 46:69–88. doi: 10.1111/j.1464-0597.1997.tb01096.x
9. Chang YY, Chao LF, Xiao X, Chien NH. Effects of a simulation-based nursing process educational program: a mixed-methods study. *Nurse Educ Pract.* (2021) 56:103188. doi: 10.1016/j.nepr.2021.103188
10. Alimohammadi L, Zarei F, Mirghafourvand M. The effect of counseling based on Bandura's self-efficacy theory on sexual self-efficacy and quality of sexual life. *Women Health.* (2020) 60:473–86. doi: 10.1080/03630242.2019.1662871
11. Lee TW, Ko YK. Effects of self-efficacy, affectivity and collective efficacy on nursing performance of hospital nurses. *J Adv Nurs.* (2010) 66:839–48. doi: 10.1111/j.1365-2648.2009.05244.x
12. Karabacak Ü, Serbest S, Kan Öntürk Z, Eti Aslan F, Olgun N. Relationship between student nurses' self-efficacy and psychomotor skills competence. *Int J Nurs Pract.* (2013) 19:124–30. doi: 10.1111/ijn.12051
13. Zengin N, Pinar R, Akinci AC, Yildiz H. Psychometric properties of the self-efficacy for clinical evaluation scale in Turkish nursing students. *J Clin Nurs.* (2014) 23:976–84. 10.1111/jocn.12257. doi: 10.1111/jocn.12257
14. Coats H, Downey L, Sharma RK, Curtis JR, Engelberg RA. Quality of communication and trust in patients with serious illness: an exploratory study of the relationships of race/ethnicity, socioeconomic status, and religiosity. *J Pain Symptom Manage.* (2018) 56:530–40. doi: 10.1016/j.jpainsymman.2018.07.005
15. Hunter JJ, Maunder RG, Sui D, Esplen MJ, Chaoul A, Fisch MJ, et al. A randomized trial of nurse-administered behavioral interventions to manage anticipatory nausea and vomiting in chemotherapy. *Cancer Med.* (2020) 9:1733–40. doi: 10.1002/cam4.2863
16. Baer L, Weinstein E. Improving oncology nurses'communication skills for difficult conversations. *Clin J Oncol Nurs.* (2013) 17:E45-51. doi: 10.1188/13.CJON.E45-E51
17. Lu Z, Fang Y, Liu C, Zhang X, Xin X, He Y, et al. Early interdisciplinary supportive care in patients with previously untreated metastatic esophagogastric cancer: a phase III randomized Controlled trial. *J Clin Oncol.* (2021) 39:748–56. doi: 10.1200/JCO.20.01254
18. Banerjee SC, Manna R, Coyle N, Penn S, Gallegos TE, Zaider T, et al. The implementation and evaluation of a communication skills training program for oncology nurses. *Transl Behav Med.* (2017) 7:615–23. doi: 10.1007/s13142-017-0473-5
19. Franciosi V, Maglietta G, Degli Esposti C, Caruso G, Cavanna L, Bertè R, et al. Early palliative care and quality of life of advanced cancer patients-a multicenter randomized clinical trial. *Ann Palliat Med.* (2019) 8:381–9. doi: 10.21037/apm.2019.02.07
20. Casillas JN, Schwartz LF, Crespi CM, Ganz PA, Kahn KL, Stuber ML, et al. The use of mobile technology and peer navigation to promote adolescent and young adult (AYA) cancer survivorship care: results of a randomized controlled trial. *J Cancer Surviv.* (2019) 13:580–92. doi: 10.1007/s11764-019-00777-7
21. Van Spall HGC, Lee SF, Xie F, Oz UE, Perez R, Mitoff PR, et al. Effect of patient-centered transitional care services on clinical outcomes in patients hospitalized for heart failure: the PACT-HF randomized clinical trial. *JAMA.* (2019) 321:753–61. doi: 10.1001/jama.2019.0710
22. Chhatre S, Jefferson A, Cook R, Meeker CR, Kim JH, Hartz KM, et al. Patient-centered recruitment and retention for a randomized controlled study. *Trials.* (2018) 19:205 doi: 10.1186/s13063-018-2578-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Geng, Liu, Zhang, Gao, Wang, Zhang, Ma and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 09 February 2022
doi: 10.3389/fsurg.2022.845653

Correlation and Influencing Factors Between Laryngopharyngeal Reflux Disease and Sleep Status in Patients

*Yue Liu†, Jian Wu†, Feng Xiao, Xiaofeng Gu and Li Ji**

Department of Otolaryngology, The Second People's Hospital of Changzhou, Changzhou, China

Objective: To observe the correlation between laryngopharyngeal reflux disease (LPRD) and patients' sleep status, and to explore the related factors of LPRD.

Methods: Four hundred and sixteen patients who visited the otorhinolaryngology clinic in our hospital from June 2019 to June 2021 were selected as the research subjects. According to the scale of reflux symptom index, the subjects were divided into a patients group (120 patients) with an the reflux symptom index (RSI) $>$ 13 and a control group (296 patients) with an RSI $\leq$ 13 according to the RSI scale score. General patient information was collected. The sleep state and emotional state of patients in the two groups were evaluated, and the related influencing factors for LPRD were also evaluated. The correlation between sleep state and depression in LPRD patients was analyzed.

Results: Four hundred and sixteen patients were divided into patients group and control group according to RSI score, the ratio of the two groups was 1:2.47. In the patients group, the common symptoms of RSI score and the top three of the total score were as follows: Foreign body sensation in throat in 112 patients, 438 points; Keep voice clear in 108 patients, 381 points; Excessive phlegm or nasal discharge reflux in 101 patients, 348 points. The PSQI and HADS scores in the patients group were higher than those in the control group ($t = 19.990$, 13.007, 14.690, P all <0.001). Logistic regression analysis showed that high-fat diet and high PSQI score were the risk factors for the development of LPRD ($P = 0.012$, $P = 0.007$). According to the PSQI score, the patients in the patients group were divided into 35 patients with abnormal PSQI score, 85 patients with normal PSQI score, and the HADS scores of those with abnormal PSQI score were all lower than those with normal PSQI score ($P > 0.05$). The PSQI score of the patients in the patients group was positively correlated with the HADS score ($r = 0.714$, $P = 0.013$).

Conclusion: Sleep disorder may lead to the occurrence or aggravation of anxiety and depression in patients with LPRD, and it is an independent risk factor for the development of LPRD. Clinical attention to the treatment of sleep disorders in patients with LPRD may be conducive to improving the efficacy of LPRD.

Keywords: laryngopharyngeal reflux disease, sleep disorders, reflux symptom index, influencing factor, depressive mood

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Feng Qin,
Shanghai Jiao Tong University School of Medicine, China
Jiangang Liu,
The Second Affiliated Hospital of Shandong First Medical University, China

***Correspondence:**
Li Ji
Ji1983li@163.com

†These authors share first authorship

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *30 December 2021*
Accepted: *17 January 2022*
Published: *09 February 2022*

Citation:
Liu Y, Wu J, Xiao F, Gu X and Ji L (2022) Correlation and Influencing Factors Between Laryngopharyngeal Reflux Disease and Sleep Status in Patients. Front. Surg. 9:845653. doi: 10.3389/fsurg.2022.845653

INTRODUCTION

Reflux diseases include gastroesophageal reflux disease and laryngopharyngeal reflux disease (LPRD), in which LPRD is a clinical syndrome caused by reflux of stomach contents to the upper esophageal sphincter. Clinical manifestations include foreign body sensation in the throat, pain, persistent throat clearing, hoarseness, chronic cough, asthma, and so on. If it is not effectively controlled in time, it can cause serious problems such as laryngeal disappearance, granuloma, subglottic stenosis, and so on, which will seriously affecting the daily life and work quality of patients (1–3). Reflux diseases such as LPRD disease are caused by various pathophysiological abnormalities, such as dynamic changes, increased visceral sensitivity, and disturbance of brain-gut axis regulation. Some psychological factors, such as life stress, social stress, and psychological state, are caused by the interaction of the central nervous system and intestinal nervous system of the brain (4, 5).

The earliest objective reflection of human body's response to stress events is sleep behavior disorder. Studies have pointed out that sleep disorders is closely related to the occurrence of intestinal symptoms, and patients with reflux disease are often accompanied by sleep quality decline or sleep disorders (6). Previous reports paid more attention to the effects of smoking and drinking on the LPRD, but there was little research on the sleep state of this group. In recent years, with the change of modern lifestyle, people's circadian rhythm has been disrupted, and sleep deprivation has become an increasingly common problem. The proportion of normal people, especially young people, with unhealthy living habits such as sleep disorder and high-fat diet has increased significantly. At the same time, studies have confirmed that patients with LPRD disease are usually accompanied by psychological disorders, and anxiety and depression are more common in people with sleep disorders (7). In this study, we conducted a comprehensive analysis of the clinical symptoms, sleep, and diet of the patients seeking treatment, aiming to explore the correlation between LPRD and the sleep status of patients and the influencing factors of their onset, so as to provide more data reference for the clinical prevention and treatment of LPRD.

DATA AND METHODS

General Information

Total of 416 patients who visited the otorhinolaryngology outpatient department from June 2019 to June 2021 were selected as the research subjects. Inclusion criteria of patients: age $\geq$ 18 years; Patients cooperated with the research and signed informed consent form; Clinical data are complete. Patient exclusion criteria: malignant tumor; Heart disease; Hypertension; Diabetes; Take anti-acid drugs for nearly 2 weeks. The subjects were divided into a patients group (120 patients) with $>$ 13 points and a control group (296 patients) with $\leq$ 13 points according to reflux symptom index (RSI) scale score. This study was approved by the Medical Ethics Committee of our hospital, with the informed consent of the patients.

Research Methods

General patient information was collected, including gender, age, height, weight, and medical history. The medical history mainly includes whether there are stomach diseases such as gastric ulcer and chronic gastritis. Have a history of catching cold; Whether there is too much work and study pressure; Anxiety and depression, etc. Patients were evaluated for smoking, alcohol consumption, constipation, and dietary habits including a high-fat diet. The smoking criterion is to smoke more than one cigarette every day for 6 months continuously or cumulatively. The criterion of drinking is drinking for 3 days or more per week, 25 grams or more for men, and 15 grams or more for women. The criterion of constipation is difficulty and hard defecation 3 months before admission; There is defecation but can't be discharged, defecation frequency is reduced or defecation is not complete, defecation is less than 3 times a week, defecation weight is less than 35 g/d, and defecation is laborious more than 25% of the time. The judging standard of high-fat diet is that fat $>$ 50 g/d and fish protein $>$ 225 g/d are carried out three or more days a week.

The Pittsburgh sleep quality index (PSQI) scale was used to assess the sleep status of the two groups. PSQI $>$ 7 points indicated the existence of sleep disorders, and PSQI $\leq$ 7 points indicated normal. The hospital anxiety and depression scale (HADS) was used to assess the emotional state of the two groups. PSQI $>$ 7 points indicated that there might be depression and anxiety, and HADS $\leq$ 7 indicated that there was no depression and anxiety problem.

In order to analyze the correlation between sleep status and depression in patients with LPRD, and then to analyze the related influencing factors of LPRD, the differences of PSQI and HADS scores between the two groups were compared.

Statistical Methods

SPSS22.0 software was used for processing. The measurement data of the experimental data were expressed as mean standard deviation ($x \pm s$), and t-test was used for pairwise comparison. The enumeration data were expressed as (%) and the comparison was conducted by χ^2 test. Multivariate Logistic regression analysis was used for multivariate analysis. Pearson correlation was used for correlation analysis between scores. The test level was $\alpha = 0.05$, and $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Study Subject Composition and RSI Score

Among the 416 patients, there were 244 males and 172 were females, with the ratio of male to female being 1.42:1, RSI 0–6 score of 83 patients, 7–13 score of 37 patients and $>$13 score of 296 patients. According to RSI score, the patients were divided into two groups: the patients group ($n = 120$) and control group ($n = 296$), with the ratio of 120:296 = 1:2.47. In the patients group, the common symptoms of RSI score and the top three of the total score were as follows: Foreign body sensation in throat in 112 patients, 438 points; Keep voice clear in 108 patients, 381

TABLE 1 | Patients and scores of reflux symptom index scale in patients group.

Clinical symptoms	Number of patients	Percentage (%)	Scoring (score)
Foreign body sensation in throat	112	93.33	438
Keep voice clear	108	90.00	381
Excessive phlegm or nasal discharge reflux	101	84.17	348
Cough	87	72.50	270
Hoarseness or dysphonia	82	68.33	233
Cough after eating or after lying down	79	65.83	217
Dyspnea or recurrent episodes of suffocation	77	64.17	185
Burning sensation in the stomach, chest pain, indigestion or stomach pain	63	52.50	160
Difficulty in swallowing food, liquids, tablets	59	49.17	157

TABLE 2 | Comparison of general data between the two groups (*n*, %).

Variable		Control group ($n = 296$)	Patients group ($n = 120$)	χ^2 *value*	*P-value*
Gender	Male	171 (57.77)	73 (60.83)	0.330	0.565
	Female	125 (42.23)	47 (39.17)		
Age (years)	>50	53 (17.91)	23 (19.17)	0.105	0.949
	31–50	127 (42.91)	50 (41.67)		
	18–30	116 (39.19)	47 (39.17)		
BMI (kg/m^2)	≤24	180 (60.81)	76 (63.33)	0.230	0.632
	>24	116 (39.19)	44 (36.67)		
Occupation	Brainpower	47 (15.88)	18 (15.00)	1.260	0.533
	Physical strength	121 (40.88)	43 (35.83)		
	Freelance	128 (43.24)	59 (49.17)		
Smoke	Yes	68 (22.97)	33 (27.50)	0.952	0.329
	No	228 (77.03)	87 (72.50)		
Alcohol	Yes	51 (17.23)	37 (30.83)	9.474	0.002
	No	245 (82.77)	83 (69.17)		
Constipation	Yes	29 (9.80)	13 (10.83)	0.101	0.751
	No	267 (90.20)	107 (89.17)		
High-fat diet	Yes	91 (30.74)	49 (40.83)	3.893	0.048
	No	205 (69.26)	71 (59.17)		
Catch cold	Yes	82 (27.70)	37 (30.83)	0.410	0.522
	No	214 (72.30)	83 (69.17)		
Pressure	Yes	56 (18.92)	24 (20.00)	0.064	0.800
	No	240 (81.08)	96 (80.00)		
Gastric disease history	Yes	92 (31.08)	74 (61.67)	33.308	<0.001
	No	204 (68.92)	46 (38.33)		

points; Excessive phlegm or nasal discharge reflux in 101 patients, 348 points. See **Table 1** for details.

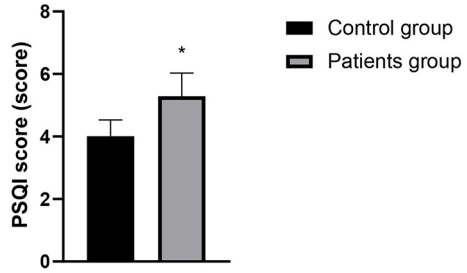


FIGURE 1 | Comparison of PSQI scores between the two groups. Compared with the control group, *$P < 0.05$.

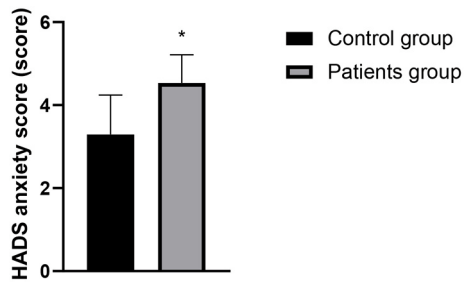


FIGURE 2 | Comparison of HADS anxiety scores between the two groups. Compared with the control group, *$P < 0.05$.

Comparison of General Data Between the Two Groups

The differences in alcohol, high-fat diet, and gastric disease history between the two groups were statistically significant ($P < 0.05$). There was no significant difference in gender, age, BMI, occupation, smoking, constipation, catching cold and stress between the two groups ($P > 0.05$). See **Table 2** for details.

Comparison of PSQI and HADS Scores Between the Two Groups

The PSQI score, HADS anxiety score and HADS depression score of the patients in the case group were higher than those in the control group, and the differences were statistically significant ($P < 0.05$). See **Figures 1**–**3** in detail.

Analysis of Multiple Factors Affecting the Onset of LPRD

Logistic regression analysis showed that high-fat diet and high PSQI score were the risk factors for the development of LPRD ($P < 0.05$). See **Tables 3**, **4** for details.

Analysis of the Correlation Between Sleep State and Depression and Anxiety in Patients of Patients Group

The patients in the patients group were divided into two groups according to PSQI scores, including 35 patients with abnormal PSQI scores, 85 patients with normal PSQI scores, and the HADS anxiety score (5.19 ± 0.36) and HADS depression score (5.86 ±

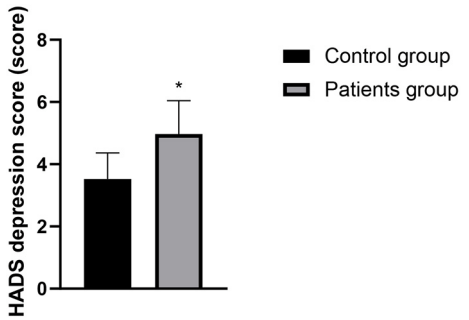


FIGURE 3 | Comparison of HADS depression scores between the two groups. Compared with the control group, *$P < 0.05$.

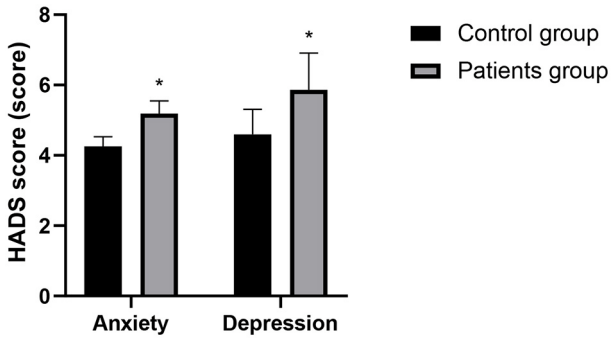


FIGURE 4 | Comparison of HADS scores between the abnormal PSQI and normal PSQI. Compared with the control group, *$P < 0.05$.

TABLE 3 | Assignment for multivariate analysis of factors.

Factors	Variables	Assignment
Alcohol	X1	No = 0, Yes = 1
High-fat diet	X2	No = 0, Yes = 1
Gastric disease history	X3	No = 0, Yes = 1
PSQI score	X4	Continuous variable
HADS score	X5	Continuous variable

TABLE 4 | Analysis of multiple factors affecting the onset of LPRD.

Factors	*B*	*S.E*	*Walds*	*P*	*OR*	*95% CI*
Alcohol	0.463	0.294	2.480	0.113	1.589	0.893–2.827
High-fat diet	0.791	0.224	12.469	0.012	2.206	1.422–3.421
Gastric disease history	0.511	0.296	2.980	0.059	1.667	0.933–2.978
PSQI score	1.095	0.309	12.558	0.007	2.989	1.631–5.477
HADS score	0.416	0.307	1.273	0.127	1.397	0.782–2.495

1.05) of those with abnormal PSQI scores were all higher than those with normal PSQI scores (4.26 ± 0.27, 4.60 ± 0.71), with statistically significant difference ($P < 0.05$). The PSQI score of the patients in the patients group was positively correlated with the HADS score ($r = 0.714$, $P = 0.013$). See **Figure 4** for details.

DISCUSSION

A recent multi-center epidemiological survey in China shows that the incidence of LPRD among outpatients in otolaryngology in China was about 10%, and there are regional, gender and age differences (8). LPRD can cause adult asthma, idiopathic pulmonary fibrosis and sinusitis, otitis media, tumors, and other otorhinolaryngology diseases. Therefore, it has been paid more and more attention in the clinical field, hoping to deepen the understanding of the pathophysiology of LPRD, and to find new targets for the diagnosis, prevention, and treatment of diseases (9).

Studies have found that patients with LPRD have decreased vagal tone and dysfunction, suggesting that vagal disorders are involved in the occurrence and development of LPRD (10). The vagus nerve is widely distributed in the throat, esophagus, gastrointestinal tract, lung, heart and other organs, among which throat is the most sensitive part. The abnormal vagus nerve function will cause chronic cough, foreign body sensation in the throat, frequent throat cleaning and so on (11). The results of this study showed that the top three common symptoms of RSI score and comprehensive scores in the patients group were pharyngeal foreign body sensation, continuous throat clearing, excessive sputum or nasal discharge. Reflux stimulates the cough receptors in the larynx and C fiber in the tracheal wall. The stimulation is introduced by the vagus nerve. It may interact with each other at the afferent nerves or nerves and cause cross-sensitization of esophagus and bronchi. That is to say, reflux increases the sensitivity of cough or directly leads to cough onset. However, cough once again increases the relaxation reaction of esophageal sphincter, which leads to LPRD disease (12).

There is a two-way regulatory effect between digestive function and brain in human body, that is, through the brain-gut axis and the sympathetic/parasympathetic nervous system, the central nervous system and the digestive system are closely linked to form a complete dynamic feedback loop to regulate biological rhythm and sleep state, so there is a correlation between sleep disorders and changes in digestive function (13). Changes of modern lifestyle disrupts the circadian rhythms, and sleep disorders has become an increasingly common problem. Sleep disorders include difficulty falling asleep, frequent awakening, abnormal sleep structure, short deep sleep period, fast eye movement sleep period, short total sleep time in a day, etc. The research by Pandey and Kar (14) confirmed that more than 25% of patients with gastroesophageal reflux disease have sleep disorders, and sleep disorders can also affect the development of gastroesophageal reflux disease through multiple pathways. However, there are relatively few reports on whether LPRD is related to sleep disorders. The results of this study showed that the PSQI and HADS scores of patients in the patients group were higher than those in the control group. It indicated that sleep disorder, depression, and anxiety might be closely related to the occurrence of LPRD. The clinical research by Teklu et al. (15) has confirmed that the relationship between sleep state and reflux

diseases may be two way, and reflux may cause uncomfortable symptoms and may also disturb sleep state. Heartburn is also a representative symptom at night, which often causes GERD patients to wake up for a short time, and affects the overall sleep quality. Anxiety, depression and excessive pressure can cause gastric peristalsis slowdown in patients, which should be related to LPRD in theory. According to reports by Caparroz et al. (13), most patients with LPRD disease have poor autonomic nerve regulation function and increased sympathetic activity, so they often suffer from anxiety and/or depression.

The study also shown that patients in the patients group had a higher drinking history, high fat diet history and stomach diseases than those in the control group. Since the mid-1980s, there has been frequent reports of pharyngeal reflux among throat cancer patients with a history of alcohol and tobacco abuse. The incidence of gastroesophageal reflux in smoking and drinking patients is high, and it is speculated that tobacco, alcohol and gastroesophageal reflux have a synergistic effect on the etiology of pharyngeal cancer. Further logistic regression analysis showed that high-fat diet and sleep disorder were the independent risk factors for LPRD. It is pointed out that fat intake, especially cholesterol and saturated fatty acid intake, is positively correlated with the occurrence of gastroesophageal reflux disease (16). It is speculated that the pathogenesis may be related to the fact that a high-fat diet can delay gastric emptying and reduce lower esophageal sphincter pressure, making reflux more likely to occur, thus inducing cough and other LPRD symptoms.

At present, it is considered that the interactions between sleep disorders and LPRD mostly includes the following possible mechanisms: (1) Sleep disorders reduce the secretion of melatonin, promote the secretion of gastric acid/pepsin, increase the incidence of transient relaxation of lower esophageal sphincter, and causes corresponding gastrointestinal motility disorders and reflux diseases aymptoms by disrupting circadian rhythm; (2) Sleep disorders cause gastrointestinal motility disorders, thus increasing the incidence of reflux; (3) Sleep disorders stimulates the formation of excessive free radicals, inhibits the antioxidant capacity of cells, leading to or aggravates pathological damage of multiple systems, and finally induces various inflammation-related diseases; (4) Sleep disorder may also affect the reproduction of intestinal flora. The intestinal flora can regulate brain development by itself or metabolites, thus affecting physiological activities. The regulation of intestinal microecology may provide a new direction for the treatment of LPRD. (5) Sleep disorder is also associated with mental and psychological disorders (17). Lechien et al. (18) recognized that the risk of GERD was significantly and positively correlated with the severity of negative emotions, and a considerable part of the negative emotional effects were achieved through sleep disorders. This study showed that the HADS scores of patients with abnormal PSQI scores are lower than those of patients with normal PSQI scores, and there is a positive correlation between PSQI score and HADS scores. It is further confirmed that sleep disorder may be related to the occurrence of negative emotions in patients with LPRD patients. Improving sleep state is beneficial to reducing the patients' bad emotional state and improving the overall curative efficacy of LPRD.

In summary, sleep disorder may result in the appearance or aggravation of anxiety and depression in patients with LPRD, and sleep disorder is an independent risk factor for the development of LPRD. Clinical attention to the treatment of sleep disorders in patients with LPRD may be conducive to improving the efficacy of LPRD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Second People's Hospital of Changzhou. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL was responsible for the writing and revision of the manuscript. JW was responsible for the design of the study. FX was responsible for the inclusion of cases. XG was responsible for the statistics of the results. LJ was the instructor of the entire study. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Salihefendic N, Zildzic M, Cabric E. Laryngopharyngeal reflux disease - LPRD. *Med Arch.* (2017) 71:215–8. doi: 10.5455/medarh.2017.71.215-218
2. Chen XM Li Y, Guo WL, Wang WT, Lu M. [Prevalence of laryngopharyngeal reflux disease in Fuzhou region of China]. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* (2016) 51:909–13. doi: 10.3760/cma.j.issn.1673-0860.2016.12.006
3. Sikavi DR, Cai JX, Carroll TL, Chan WW. Prevalence and clinical significance of esophageal motility disorders in patients with laryngopharyngeal reflux symptoms. *J Gastroenterol Hepatol.* (2021) 36:2076–82. doi: 10.1111/jgh.15391
4. Li J, Wang J, Wu M, Zhao J, Guo H. The role of nonacid reflux in laryngopharyngeal reflux diseases. *Eur Arch Otorhinolaryngol.* (2020) 277:2813–9. doi: 10.1007/s00405-020-06015-6
5. An X, Acquah I, Liu H, Li W, Tan S. A critical review on saline wastewater treatment by membrane bioreactor (MBR) from a microbial perspective. *Chemosphere.* (2019) 220:1150–62. doi: 10.1016/j.chemosphere.2019.01.027
6. Lim KG, Morgenthaler TI, Katzka DA. Sleep and Nocturnal Gastroesophageal reflux: an update. *Chest.* (2018) 154:963–71. doi: 10.1016/j.chest.2018.05.030
7. Zhang Y, Jiang X, Chen H, Li H, Wang Z, Chen Y, et al. Chronic REM-sleep deprivation induced laryngopharyngeal reflux in rats: a preliminary study. *Auris Nasus Larynx.* (2021) 48:683–9. doi: 10.1016/j.anl.2020.10.011
8. Xiao S, Li J, Zheng H, Yan Y, Li X. Zhang L, et al. An epidemiological survey of laryngopharyngeal reflux disease at the otorhinolaryngology-head and neck

surgery clinics in China. *Eur Arch Otorhinolaryngol.* (2020) 277:2829–38. doi: 10.1007/s00405-020-06045-0
9. Lechien JR, Saussez S, Karkos PD. Laryngopharyngeal reflux disease: clinical presentation, diagnosis and therapeutic challenges in 2018. *Curr Opin Otolaryngol Head Neck Surg.* (2018) 26:392–402. doi: 10.1097/MOO.0000000000000486
10. Lechien JR, Nandhan Sampath Kumar R, Chiesa-Estomba CM. Laryngopharyngeal reflux and autonomic nerve dysfunction: what about stress? *Eur Arch Otorhinolaryngol.* (2020) 277:2937–8. doi: 10.1007/s00405-019-05567-6
11. Wang AM, Wang G, Huang N, Zheng YY, Yang F, Qiu X, et al. Association between laryngopharyngeal reflux disease and autonomic nerve dysfunction. *Eur Arch Otorhinolaryngol.* (2019) 276:2283–7. doi: 10.1007/s00405-019-05482-w
12. Benninger MS, Campagnolo A. Chronic laryngopharyngeal vagal neuropathy. *Braz J Otorhinolaryngol.* (2018) 84:401–3. doi: 10.1016/j.bjorl.2018.04.001
13. Caparroz FA, Campanholo MAT, Regina CG, Park SW, Haddad L, Gregório LC, et al. Clinical and polysomnographic predictors of laryngopharyngeal reflux in obstructive sleep apnea syndrome. *Braz J Otorhinolaryngol.* (2019) 85:408–15. doi: 10.1016/j.bjorl.2018.03.007
14. Pandey A, Kar SK. Rapid eye movement sleep deprivation of rat generates ROS in the hepatocytes and makes them more susceptible to oxidative stress. *Sleep Sci.* (2018) 11:245–53. doi: 10.5935/1984-0063.20180039
15. Teklu M, Gouveia CJ, Yalamanchili A, Ghadersohi S, Price CPE, Bove M, et al. Predicting obstructive sleep apnea status with the reflux symptom index in a sleep study population. *Laryngoscope.* (2020) 130:952–7. doi: 10.1002/lary.28592
16. Lechien JR, Bobin F, Muls V, Horoi M, Thill MP, Dequanter D, et al. Patients with acid, high-fat and low-protein diet have higher laryngopharyngeal reflux episodes at the impedance-pH monitoring. *Eur Arch Otorhinolaryngol.* (2020) 277:511–20. doi: 10.1007/s00405-019-05711-2
17. Li CF, Zhang LH, Wang WL, Cao J, Wang YG, Zhao YX. The prevalence and relationship between laryngopharyngeal reflux disease, anxiety and depression in otolaryngology outpatients. *Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi.* (2020) 55:241–8. doi: 10.3760/cma.j.issn.1673-0860.2020.03.010
18. Lechien JR, Schindler A, Robotti C, Lejeune L, Finck C. Laryngopharyngeal reflux disease in singers: pathophysiology, clinical findings and perspectives of a new patient-reported outcome instrument. *Eur Ann Otorhinolaryngol Head Neck Dis.* (2019) 136:39–43. doi: 10.1016/j.anorl.2018.08.008

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Liu, Wu, Xiao, Gu and Ji. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 09 February 2022
doi: 10.3389/fsurg.2022.839157

Analysis of the Guiding Role of CYP2C19 Gene Combined With Platelet Function Detection in Antiplatelet Therapy in Patients With Complex Coronary Artery Disease After PCI

Jiancai Yu[1,2], *Yongxing Liu*[2], *Wanzhong Peng*[2], *Juan Liu*[2], *Ya Li*[2], *Junyan Liu*[2], *Yang Jiang*[2], *Demin Liu*[2] *and Zesheng Xu*[1,2*]

[1] Department of Cardiology, Teaching Hospital of Cangzhou Central Hospital of Tianjin Medical University, Tianjin Medical University, Tianjin, China, [2] Department of Cardiology, Cangzhou Central Hospital, Cangzhou, China

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Xuefeng Yang,
University of South China, China
Wenjun Gu,
Shanghai Jiaotong University School of Medicine, China

***Correspondence:**
Zesheng Xu
xuzesheng112021@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: 19 December 2021
Accepted: 06 January 2022
Published: 09 February 2022

Citation:
Yu J, Liu Y, Peng W, Liu J, Li Y, Liu J, Jiang Y, Liu D and Xu Z (2022) Analysis of the Guiding Role of CYP2C19 Gene Combined With Platelet Function Detection in Antiplatelet Therapy in Patients With Complex Coronary Artery Disease After PCI. Front. Surg. 9:839157. doi: 10.3389/fsurg.2022.839157

Objective: To explore the influence of CYP2C19 gene combined with platelet function test on clinical prognosis of patients with complex coronary artery disease receiving antiplatelet therapy after PCI.

Methods: A total of 200 patients undergoing PCI in our hospital due to complex coronary artery disease from February 2019 to February 2021 were selected and divided into the control group and the observation group according to whether CYP2C19 gene detection was performed. The control group was treated with dual antiplatelet therapy of classical aspirin combined with clopidogrel, and the observation group was treated with individual antiplatelet therapy. The patients in the two groups were followed up for 1 year after PCI, and their quality of life was assessed using the Seattle Angina Questionnaire (SAQ score). The occurrence of major adverse cardiovascular events (MACE) during the follow-up period was also recorded.

Results: The incidence of total MACE events in the observation group was slightly less than that in the control group, and the difference was statistically significant ($P = 0.040$). In particular, the observation group was superior to the control group in reducing the readmission rate of recurrent unstable angina pectoris, and the difference was statistically significant ($P = 0.023$). The location of coronary culprit lesions with recurrent ischemic events was commonly seen in non-interventional target lesions (interventional/non-interventional target sites: 12.9%: 77.1%). The SAQ score in the observation group was larger than that in the control group, and the difference was statistically significant ($P = 0.012$). There was no statistical difference in the incidence of major bleeding between the two groups ($P = 0.352$).

Conclusion: Using CYP2C19 genotype combined with platelet function test to guide individualized antiplatelet therapy after complex coronary artery PCI is beneficial to reducing ischemic events in a short period (1 year), mainly due to reducing the risk of

readmission for recurrent unstable angina pectoris, and improving the quality of daily life of patients without increasing the risk of massive hemorrhage, which can improve clinical prognosis.

Keywords: CYP2C19, platelet function test, complex coronary artery lesions, PCI, antiplatelet therapy

INTRODUCTION

Dual anti-platelet therapy (DAPT) composed of aspirin combined with a P2Y12 receptor inhibitor is the cornerstone for the prevention of cardiac and systemic ischemic events in patients with coronary heart disease (1, 2). It is recommended by a large number of clinical studies and domestic and foreign guidelines that DAPT should be accepted after coronary artery percutaneous coronary intervention (PCI). With the recent iterations of drug-eluting stents, the promotion of potent P2Y12 receptor inhibitors, and the continuous updating of other combined drug strategies, DAPT has many new options compared with classical regimens in terms of drug selection, timing, and optimal duration (3, 4). Antiplatelet drug therapy differs among individuals based on genetic differences and individual factors, which are significantly associated with the occurrence of adverse events such as ischemia or hemorrhage. Clinicians expect an appropriate approach to guide antiplatelet therapy after PCI to improve the clinical outcome of coronary heart disease. With the development of clinical trials in recent years, CYP2C19 gene and platelet function testing have become a hot topic to guide DAPT treatment after PCI, and more clinical evidence has been accumulated (5, 6). Although the recently released Chinese Experts Consensus on Dual-antiplatelet Therapy for Coronary Heart Disease points out that routine platelet function and genotyping tests are not supported based on current evidence to guide the selection of antiplatelet strategies, they can be applied in specific cases. For example, patients with high ischemic risk factors can receive DAPT escalation therapy with gene detection and platelet function guidance, and patients with high bleeding risk can receive DAPT escalation therapy (7, 8). The enrolled populations in this study were patients with complex coronary artery lesions (including CTO lesions, calcified lesions, left main artery lesion, bifurcated lesions, three-vessel lesion, lesions with the total stent length >60 mm and more than three stents implanted in a single time), which were high risk factors for ischemia and had high risk of ischemic adverse cardiovascular events. According to the statistics of previous studies, the incidence of MACE events in patients with complex coronary lesions within 1 year after PCI is as high as 10.4–19.7%, which seriously affects the clinical outcome (9, 10). Therefore, in this study, CYP2C19 gene combined with platelet function testing was intended to guide individualized antiplatelet therapy for patients with complex coronary artery lesions after PCI, and to explore its impact on clinical prognosis.

MATERIALS AND METHODS

Patients

A total of 200 patients who were confirmed with complex coronary artery lesions by coronary angiography and successfully completed PCI in Cangzhou Central Hospital from February 2019 to February 2021 were selected as the research subjects. This study was approved by the Ethics Committee of our hospital and has completed the national clinical study registration. It was conducted with the informed consent of the patients and met the following inclusion criteria: Meet the diagnostic criteria for coronary heart disease and meet the criteria for PCI confirmed by coronary angiography and/or intravascular ultrasound (IVUS) (11, 12); Patients with complex coronary artery lesions, including coronary CTO lesions, calcified lesions, left main artery lesion, bifurcated lesion, three-vessel lesion, lesions with the total stent length >60 mm, and lesions requiring more than three stents implantation at a time. Exclusion criteria: Patients who used P2Y12 receptor antagonist within 30 days before operation; Patients who had hemorrhagic stroke in the past, ischemic stroke or cerebrovascular event within 6 months, and rational bleeding due to active diseases (such as peptic ulcer or upper gastrointestinal bleeding); Patients with contraindications to use tigrew or clopidogrel or drug allergy; Patients with malignant tumor and expected survival time of not more than 1 year; Patients with moderate to severe liver and kidney damage and coagulation dysfunction; Patients who are going to undergo CABG in the near future; Patients who failed to cooperate with the completion of the experiment.

Research Methods

Method of Administration

The patient was given a load of 300 mg of clopidogrel (75 mg*7 tablets/box, Sanofi, France) and aspirin (100 mg*30 tablets/box, Bayern Chemie) 30 min before PCI, and a maintenance dose of clopidogrel 75 mg/d + aspirin 100 mg/d from the next day. Patients with elective interventional therapy were given clopidogrel 75 mg/d + aspirin 100 mg/d for at least 4 days.

Surgical Methods

The operation was completed using Siemens cardiovascular imaging machine. The operator had mature experience in PCI of complicated coronary arteries, and more than half of the cases were completed under the guidance of intravascular ultrasound.

Grouping and Administration

Fasting blood was collected in the morning of the first day after PCI for CYP2C19 gene polymorphism detection, and sent to our central laboratory. The results were reported within 6 h. They were divided into the control group ($n = 100$) and the observation group ($n = 100$) according to whether or not CYP2C19 gene testing was performed. Patients in the control group after PCI continued to take aspirin combined with clopidogrel antiplatelet regimen (aspirin 100 mg, once a day; Clopidogrel 75 mg, once a day). The observation group according to the CYP2C19 genotype will be divided into three groups

of patients with rapid metabolism (ultra-fast metabolism and fast metabolism), intermediate metabolism and slow metabolism. Patients with rapid metabolism continued to take aspirin and clopidogrel orally; Patients with slow metabolism were adjusted for aspirin in combination with tigroid DAPT regimen (aspirin 100 mg, once a day; ticagrelor 90 mg, twice a day); Platelet function of patients in the intermediate metabolic group was tested 5 days after surgery, and patients in this group were subdivided into clopidogrel normal response group (NCR; Maximal platelet aggregation rate <46) and clopidogrel low response type group (LCR; Maximum platelet aggregation rate ≥46). Patients in the NCR group continued to take aspirin in combination with clopidogrel. Patients in the LCR group were adjusted to aspirin combined with ticagrelor antiplatelet therapy.

Observation Index

Major adverse cardiovascular events (MACE) include unstable angina, recurrent non-fatal acute myocardial infarction, stent thrombosis, unexpected revascularization of rake vessels, cardiac death, ischemic stroke, and massive hemorrhage. Cardiac death is defined as death from any definite cardiovascular cause. Stent thrombosis is defined as the formation of thrombus at the original stent implantation caused by any cause after PCI, which leads to complete or incomplete coronary artery obstruction. Ischemic stroke is defined as transient ischemic attack, cerebral infarction, etc. Massive hemorrhage was defined as BRAC standard type 3 (13). Quality of life was evaluated based on Seattle Angina Questionnaire (SAQ) (14): It was divided into five items and 19 items, including: degree of physical activity limitation (Question 1), stable angina pectoris (Question 2), attack of angina pectoris (Questions 3–4), treatment satisfaction (Questions 5–8), and disease cognition (Questions 9–11). The 19 items in the five items were scored item by item as well as the SAQ total score, which was then converted into a standard score according to the formula. The standard score = (actual score—the lowest score in this aspect)/(the highest score in this aspect—the lowest score in this recipe) ×100. The higher the score was, the better the quality of life and body functional status would be.

Clinical Data Collection

Detailed clinical data of the patients were collected: (1) General data: gender, age, weight, BMI, smoking history and drinking history. (2) Previous medical history: hypertension, diabetes, cerebral infarction and coronary heart disease. (3) Blood tests: white blood cell count (WBC), hemoglobin (HGB), platelet count (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (CR), uric acid (UA), glycated hemoglobin, triglycerides (TG), total cholesterol (TC), high density lipoprotein (HDL-L), low density lipoprotein (LDL-C). (4) Cardiac function: left ventricular diastolic diameter and EF value. (5) Clinical medication: angiotensin converting enzyme inhibitor (ACEI)/angiotension receptor blocker (ARB), β -receptor blockers, statins, calcium-channel antagonist (CCB), proton pump inhibitor (PPI). (6) Surgical conditions: IVUS utilization rate and immediate success rate of surgery (residual stenosis of the lesion < 10% and TIMI blood flow grade 3).

Follow-Up

All patients included in the present study were followed up for 9∼12 months after PCI through the department follow-up system, telephone, readmission tracking, and so on. If the patients were not contacted for more than three times through the appeal method, they were considered lost to follow-up (9). A total of 200 patients were included in this study. A total of 195 cases were successfully followed up, including 97 cases in the control group and 98 cases in the observation group.

Statistical Methods

The results of this experiment were statistically analyzed by SPSS 20.0 (SPSS Co., Ltd., Chicago, USA). Count data were expressed by (rate), and chi-square test was used for their comparison between groups. Measurement data were expressed by (mean ± standard deviation), and *t*-test was used for their comparison between groups. $P < 0.05$ indicates that the difference is statistically significant.

RESULTS

Comparison of Baseline Information

There was no statistically significant difference between the two groups in gender, age and other baseline data ($P > 0.05$). As shown in **Table 1**.

Grouping and Distribution of CYP2C19 Genotype in the Observation Group

A CYP2C19 genotype subgroup (98 cases) involving only observation group patients was conducted and the subgroup met the 2013 CPIC guidelines. The fast metabolism group included 33 patients (33.68%) with fast metabolism progressive CYP2C19*1/*1 and ultrafast metabolism progressive CYP2C19*1/*17. The intermediate metabolic group included patients with CYP2C19*1/*3, CYP2C19*1/*2, CYP2C19*2/*17, and CYP2C19*3/*17 (36 cases, or 36.73%); The slow metabolic group included patients with CYP2C19*2/*2, CYP2C19*3/*3, and CYP2C19*2/*3 (29 cases, or 29.59%). As shown in **Table 2**.

Comparison of Incidence of MACE Events

Comparison of MACE event results between the two groups showed that although the individualized antiplatelet treatment group (observation group) did not show statistical difference in ischemic adverse events such as re-admission of non-fatal acute myocardial infarction, stent thrombosis, unexpected revascularization of rake vessels, cardiac death, and ischemic stroke ($P > 0.05$), it benefited from reducing the risk of re-admission for recurrent unstable angina pectoris ($P = 0.040$). The total incidence of MACE events in the observation group was less than that in the control group, and the difference was statistically significant ($P = 0.046$). Moreover, the incidence of massive hemorrhage did not increase ($P = 0.352$). As shown in **Figure 1**.

TABLE 1 | Comparison of baseline data between the two groups.

Baseline information	Control group ($n = 97$)	Observation group ($n = 98$)	t/χ^2	P
Age (years)	68.40 ± 9.10	67.38 ± 8.50	0.808	0.417
Gender [male (%)]	54 (55.67)	46 (46.94)	1.487	0.253
Body weight (kg)	70.23 ± 9.28	68.12 ± 9.45	1.573	0.118
BMI (kg/m^2)	24.99 ± 1.97	24.84 ± 2.17	0.505	0.614
Smoking history [*n* (%)]	32 (32.99)	31 (31.63)	0.041	0.879
Drinking history [*n* (%)]	22 (22.68)	19 (19.39)	0.318	0.602
Past medical history [*n* (%)]				
Hypertension	24 (24.74)	29 (29.59)	0.579	0.520
Type 2 diabetes	26 (26.80)	24 (24.49)	0.137	0.745
Cerebral Infarction	14 (14.43)	17 (17.35)	0.309	0.696
Coronary heart disease	26 (26.80)	28 (28.57)	0.046	0.873
Blood examination				
WBC ($10\hat{9}$ L)	7.45 ± 1.61	7.34 ± 1.53	0.489	0.623
HGB ($10\hat{9}$ L)	129.82 ± 10.54	131.15 ± 13.88	0.753	0.453
PLT ($10\hat{9}$ L)	206.56 ± 62.92	212.55 ± 63.13	0.664	0.508
ALT (U/L)	31.64 ± 6.74	32.44 ± 9.24	0.690	0.491
AST (U/L)	32.73 ± 8.46	30.96 ± 8.37	1.469	0.143
CR (μmol/L)	91.32 ± 15.73	87.21 ± 16.70	1.769	0.079
UA (μmol/L)	355.55 ± 70.74	368.94 ± 88.33	1.168	0.244
HbA1c (%)	5.75 ± 0.79	5.77 ± 0.68	0.189	0.843
TC (μmol/L)	4.68 ± 0.55	4.81 ± 0.44	1.854	0.056
TG (μmol/L)	1.78 ± 0.43	1.80 ± 0.27	0.538	0.550
HDL-L (μmol/L)	1.27 ± 0.39	1.17 ± 0.23	2.709	0.027
LDL-C (μmol/L)	3.58 ± 0.31	3.65 ± 0.43	1.303	0.202
Cardiac function				
Left ventricular diastolic diameter (mm)	48.26 ± 4.61	49.08 ± 4.74	1.224	0.220
EF (%)	54.46 ± 4.80	53.87 ± 4.03	0.929	0.354
Clinical medication [*n* (%)]				
ACEI/ARB	87 (89.69)	89 (90.82)	0.071	0.814
Statin	88 (90.72)	91 (92.86)	0.295	0.624
β-blocker	87 (89.69)	90 (91.84)	0.268	0.630
CCB	10 (10.31)	7 (7.14)	0.614	0.459
PPI	95 (97.94)	92 (93.88)	2.043	0.153
Surgery [*n* (%)]				
IVUS use	46 (47.42)	43 (43.88)	0.658	0.248
PCI immediate success	92 (94.85)	94 (95.92)	0.128	0.721

Comparison of SAQ Scores Between the Two Groups

In view of the fact that the observation group could reduce the readmission risk of recurrent unstable angina pectoris, the Seattle Angina Survey Scale was used in this experiment to analyze the quality of life of patients in two groups. Among them, the observation group was significantly superior to the control group in the aspects of limited physical activity, stable state of angina, onset of angina and treatment satisfaction, with a statistical difference ($P < 0.05$). The difference was basically the same in the disease cognition, with no statistical difference ($P = 0.062$). As shown in **Figure 2**.

Analysis of the Location of Offenders With Recurrent Ischemic Events in the MACE Event

Further, we wanted to determine the lesion location of criminals who excluded stent thrombosis and died from cardiac causes in the MACE event and experienced another ischemic event. As a result, CAG was reexamined in a total of 31 patients who were readmitted for recurrent unstable angina pectoris and non-fatal acute myocardial infarction and who underwent unexpected revascularization of target vessels. Among them, 4 cases (12.90%) were located at interventional target lesion, and 27 cases (87.10%) were located at non-interventional target lesion. Hence, non-interventional target lesion sites were more common.

TABLE 2 | Grouping and distribution of CYP2C19 genotype in the observation group.

Metabolic type	Genotype	Cases (*n*)	Percentage (%)
Fast metabolism type ($n = 32$)	*1/*1	19	19.39
	*1/*17	14	14.29
Intermediate metabolic ($n = 30$)	*1/*3	9	9.18
	*1/*2	10	10.21
	*2/*17	9	9.18
	*3/*17	8	8.16
Slow metabolism type ($n = 36$)	*2/*2	11	11.22
	*3/*3	10	10.21
	*2/*3	8	8.16

*According to gene distribution, the gene frequencies at *2, *3, and *17 loci, the actual genotype frequency and the theoretical genotype frequency were counted, and the analysis of variance test was used to test the actual genotype frequency and the theoretical genotype frequency at *2, *3, and *17 loci. The results showed that there was no significant difference between the actual genotype frequency and the theoretical genotype frequency ($P > 0.05$), which was in line with the Hardy–Weinberg genetic balance test, indicating that the gene frequency of the sample population was in line with the genetic balance rule and was representative.*

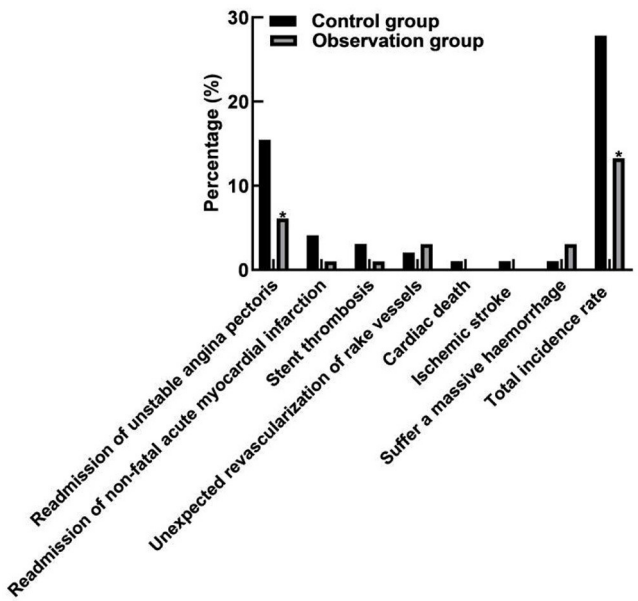


FIGURE 1 | Comparison of MACE event incidence between two groups. Compared with the control group, *$P < 0.05$.

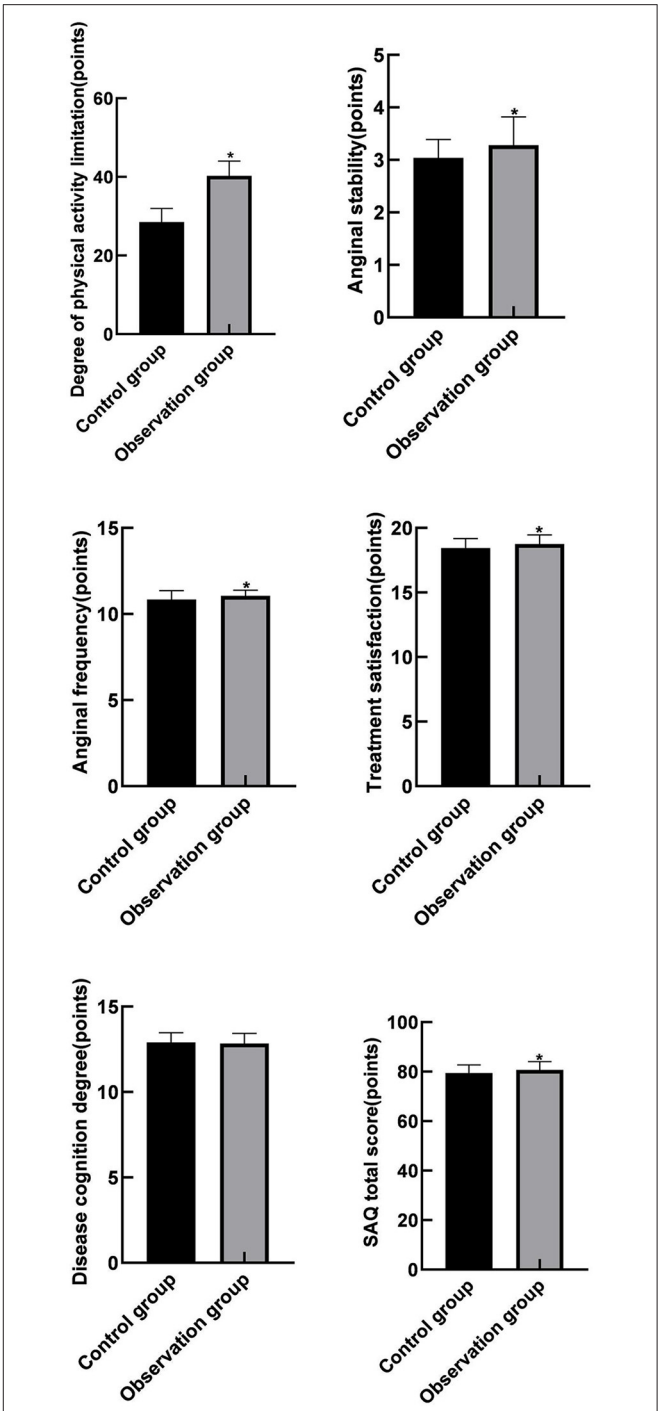


FIGURE 2 | Comparison of SAQ scores between the two groups. Compared with the control group, *$P < 0.05$.

DISCUSSION

Aspirin combined with P2Y12 receptor inhibitors is the basis of antiplatelet therapy after PCI. However, individual platelet drug therapy shows diversity differences, which are significantly associated with the occurrence of adverse events such as recurrent thrombosis or hemorrhage (15, 16). It has been found in clinical practice that patients after complicated coronary artery PCI are more likely to suffer from such adverse cardiovascular events as angina pectoris, revascularization of target vessels, readmission for non-fatal myocardial infarction, and cardiogenic death. Even after standardized DAPT treatment, the probability of such adverse cardiovascular events is still significantly higher than that of common lesions (17, 18). The reason was related to clopidogrel resistance and low clopidogrel response in addition to surgical

factors. Clopyrrole resistance is related to a variety of factors, of which genetic factors play a significant role (19, 20). Previous studies have found that Asian patients have a greater risk of adverse cardiovascular events than western populations, which may be related to the high proportion of CYP2C19 gene variation in Asian (21). However, the application of clopidogrel gene detection alone to distinguish the population with clopidogrel metabolism cannot independently predict the occurrence of cardiovascular ischemic events. It was also found in the clinical practice that ischemic adverse events after PCI were associated with platelet reactivity (22). Because studies have found that even after the application of CYP2C19 gene testing guidance and the administration of standard DAPT drug dose treatment, 20–30% of patients with coronary heart disease still have high platelet reactivity (HPR), and about 5–6% of patients after stent implantation have DAPT resistance, which is more likely to occur in patients in East Asia (23, 24). Based on this, clinicians expect to find an appropriate method to guide antiplatelet therapy after PCI, so as to capture the pros and cons of the triggered endpoint events and make them become the method to optimize and guide antiplatelet therapy after PCI, so as to improve the clinical outcome of coronary heart disease. Unfortunately, no consensus has been reached in the worldwide regarding the optimal guidance of antiplatelet drug therapy after PCI.

The purpose of this experiment is to initially explore whether CYP2C19 gene combined with platelet function testing can improve the clinical prognosis of individualized antiplatelet therapy after PCI, as compared with the classical aspirin combined with clopidogrel DAPT regimen. Therefore, our subgroup design was not complex, and although the observation group involved multiple subgroups, we were only concerned with the overall clinical outcome. As a result, the individualized antiplatelet therapy group (observation group) showed no statistical difference in ischemic adverse events such as readmission of non-fatal acute myocardial infarction, stent thrombosis, unexpected revascularization rake vessels, cardiac death, and ischemic stroke. The possible reason is that the ischemic events in this part may be more related to the surgical factors or to the stability of the interventional target lesion. In recent years, with the innovation of interventional instruments, endovascular examination methods and the improvement surgical techniques, ischemic events (especially in-stent thrombosis and restenosis) after PCI have been significantly reduced, so there is not enough room to change the clinical outcome through antiplatelet drug therapy. In this study, about half of the PCI operations were conducted under the guidance of IVUS. Moreover, the surgeons had rich experience in complex coronary intervention, and the immediate success rates of the operations were above 90%, which could basically eliminate the surgical bias.

Different from other similar studies, the results of this experiment showed that the individualized antiplatelet therapy could reduce the readmission risk of recurrent unstable angina pectoris and improve the quality of daily life of patients, which might be related to the promotion of tigroid therapy, which could more effectively inhibit platelet aggregation, improve endothelial function, reduce plaque erosion and rupture, and provide better blood flow reserve. This part of the effect might be more on non-interventional target locations, reducing ischemic events caused by plaques outside of the interventional target locations. Therefore, we further analyzed the location of the lesions in the MACE events that excluded patients with stent thrombosis and cardiogenic death, and recurred ischemic events The results confirmed that the lesion sites of recurrent ischemic events were mainly located in non-intervention target lesions, and the promotion to tigroid therapy improved the stability of non-intervention target lesions and reduced the ischemic events caused by the location of non-intervention target lesions.

CONCLUSION

Using CYP2C19 genotype combined with platelet function test to guide individualized antiplatelet therapy after complex coronary artery PCI is beneficial to reducing ischemic events in a short period (1 year), mainly due to reducing the risk of readmission for recurrent unstable angina pectoris, and improving the quality of daily life of patients without increasing the risk of massive hemorrhage, which can improve clinical prognosis. Of course, when choosing antiplatelet drugs in clinical practice, patients' risk of ischemia and hemorrhage should be considered comprehensively, which is sometimes difficult to grasp. At this time, gene and platelet detection are considered as optional tools to guide treatment.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Cangzhou Central Hospital (2019002). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JY is mainly responsible for the writing of the paper. YoL and WP are mainly responsible for the design of the research. JuaL and YaL are mainly responsible for the detection and evaluation of the results. JunL is mainly responsible for the recording of the research results. DL is mainly responsible for the statistics of the result data. ZX is mainly responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the Medical Science Research Project of Hebei Province (20200176).

REFERENCES

1. Hahn JY, Song YB, Oh JH, Chun WJ, Park YH, Jang WJ, et al. Effect of P2Y12 inhibitor monotherapy vs dual antiplatelet therapy on cardiovascular events in patients undergoing percutaneous coronary intervention: the SMART-CHOICE randomized clinical trial. *JAMA*. (2019) 321:2428–37. doi: 10.1001/jama.2019.8146
2. Giacoppo D, Matsuda Y, Fovino LN, D'Amico G, Gargiulo G, Byrne RA, et al. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. *Eur Heart J*. (2021) 42:308–19. doi: 10.1093/eurheartj/ehaa739
3. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, et al. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. (2017) 389:1025–34. doi: 10.1016/S0140-6736(17)30397-5
4. Grines CL, Marshall JJ. Short DAPT after DES: P2Y12 monotherapy is in, aspirin is out!. *Eur Heart J*. (2019) 40:2605–6. doi: 10.1093/eurheartj/ehz519
5. Kuno T, Ueyama H, Takagi H, Bangalore S. Choosing between aspirin or P2Y12 monotherapy after short course of DAPT. *Am Heart J*. (2020) 230:100. doi: 10.1016/j.ahj.2020.09.003
6. Malik AH, Yandrapalli S, Shetty SS, Aronow WS, Cooper HA, Panza JA. Meta-analysis of dual antiplatelet therapy versus monotherapy with P2Y12 inhibitors in patients after percutaneous coronary intervention. *Am J Cardiol*. (2020) 127:25–9. doi: 10.1016/j.amjcard.2020.04.027
7. Gallus A. After PCI and 3 mo of DAPT, P2Y12-inhibitor monotherapy was noninferior to DAPT at 12 mo. *Ann Intern Med*. (2019) 171:C53. doi: 10.7326/ACPJ201911190-053
8. Yerasi C, Case BC, Forrestal BJ, Torguson R, Weintraub WS, Garcia-Garcia HM, et al. Optimizing monotherapy selection, aspirin versus P2Y12 inhibitors, following percutaneous coronary intervention. *Am J Cardiol*. (2020) 135:154–65. doi: 10.1016/j.amjcard.2020.07.061
9. Wernly B, Rezar R, Gurbel P, Jung C. Short-term dual antiplatelet therapy (DAPT) followed by P2Y12 monotherapy versus traditional DAPT in patients undergoing percutaneous coronary intervention: meta-analysis and viewpoint. *J Thromb Thrombolysis*. (2020) 49:173–6. doi: 10.1007/s11239-019-01985-9
10. Kim W, Kim JS, Rha SW, Choi BG, Jang WY, Kang DO, et al. Cilostazol-based triple versus potent P2Y12 inhibitor-based dual antiplatelet therapy in patients with acute myocardial infarction undergoing percutaneous coronary intervention. *Heart Vessels*. (2020) 35:1181–92. doi: 10.1007/s00380-020-01598-w
11. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. (2016) 68:1082–115. doi: 10.1016/j.jacc.2016.03.513
12. Raber L, Mintz GS, Koskinas KC, Johnson TW, Holm NR, Onuma Y, et al. Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. *Eur Heart J*. (2018) 39:3281–300. doi: 10.1093/eurheartj/ehy285
13. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. (2011) 123:2736–47. doi: 10.1161/CIRCULATIONAHA.110.009449
14. Duruoz MT, Sanal TC, Ulutatar F, Suhaimi A, Agirbasli M. The validity and reliability of the Turkish version of the Seattle Angina Questionnaire. *Turk Kardiyol Dern Ars*. (2020) 48:731–8. doi: 10.5543/tkda.2020.24583
15. Ohman EM, Roe MT, Steg PG, James SK, Povsic TJ, White J, et al. Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial. *Lancet*. (2017) 389:1799–808. doi: 10.1016/S0140-6736(17)30751-1
16. Tan S, Jiang T, Ebrahimi A, Langrish T. Effect of spray-drying temperature on the formation of flower-like lactose for griseofulvin loading. *Eur J Pharm Sci*. (2018) 111:534–9. doi: 10.1016/j.ejps.2017.10.040
17. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: The STOPDAPT-2 randomized clinical trial. *JAMA*. (2019) 321:2414–27. doi: 10.1001/jama.2019.8145
18. Alvarado F, Borzak S. After PCI and short-term DAPT, P2Y12 inhibitors alone vs. ongoing DAPT reduce major bleeding; CV events do not differ. *Ann Intern Med*. (2020) 173:C42. doi: 10.7326/ACPJ202010200-042
19. Valgimigli M, Cao D, Makkar RR, Bangalore S, Bhatt DL, Angiolillo DJ, et al. Design and rationale of the XIENCE short DAPT clinical program: an assessment of the safety of 3-month and 1-month DAPT in patients at high bleeding risk undergoing PCI with an everolimus-eluting stent. *Am Heart J*. (2021) 231:147–56. doi: 10.1016/j.ahj.2020.09.019
20. Chichareon P, Modolo R, Kawashima H, Takahashi K, Kogame N, Chang CC, et al. DAPT score and the impact of ticagrelor monotherapy during the second year after PCI. *JACC Cardiovasc Interv*. (2020) 13:634–46. doi: 10.1016/j.jcin.2019.12.018
21. El RN, Lima JJ, Johnson JA. Proton pump inhibitors: from CYP2C19 pharmacogenetics to precision medicine. *Expert Opin Drug Metab Toxicol*. (2018) 14:447–60. doi: 10.1080/17425255.2018.1461835
22. Hicks JK, Bishop JR, Sangkuhl K, Muller DJ, Ji Y, Leckband SG, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. *Clin Pharmacol Ther*. (2015) 98:127–34. doi: 10.1002/cpt.147
23. Sienkiewicz-Oleszkiewicz B, Wiela-Hojenska A. CYP2C19 polymorphism in relation to the pharmacotherapy optimization of commonly used drugs. *Pharmazie*. (2018) 73:619–24. doi: 10.1691/ph.2018.8689
24. Ellithi M, Baye J, Wilke RA. CYP2C19 genotype-guided antiplatelet therapy: promises and pitfalls. *Pharmacogenomics*. (2020) 21:889–97. doi: 10.2217/pgs-2020-0046

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Yu, Liu, Peng, Liu, Li, Liu, Jiang, Liu and Xu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 14 February 2022
doi: 10.3389/fsurg.2022.847135

A Preliminary Cadaveric MRI Study of Fetal Hip Development

*Zhenqing Liu[1], Huixian Li[2], Shuai Wang[1], Qianqian Wu[1] and Hongsheng Liu[1]**

[1] Department of Radiology, Guangzhou Woman and Children's Medical Center, Guangzhou Medical University, Guangzhou, China, [2] Institute of Pediatrics, Guangzhou Woman and Children's Medical Center, Guangzhou Medical University, Guangzhou, China

Purpose: The earlier the detection of the hip joint is discovered, the better the final result. The purpose of this study aimed to investigate the fetal hip development using magnetic resonance imaging (MRI), so as to alert clinicians to possible abnormal development during intrauterine life.

Method: Measurements of 34 cadaver fetuses (68 hips) were obtained regarding acetabular width and depth, anterior bony acetabular index (ABAI), anterior cartilaginous acetabular index (ACAI), posterior bony acetabular index (PBAI), and posterior cartilaginous acetabular index (PCAI). The standard values of each acetabular measurement index were obtained, and the gestational age-measurement index change trend chart was drawn to comprehensively analyze the normal development law of the fetal hip joint.

Results: With the development of fetuses, the width and depth of acetabular increase linearly, and the slope of acetabular width was larger than that of depth. In addition, two change points during the 24th and 34th weeks of gestation were detected with regard to width. ABAI and PBAI also decreased. ABAI demonstrated an approximately linear trend, while PBAI shows a non-linear trend. During the 36th week, the change point in PBAI was observed. ACAI and PCAI exhibited slow increases, indicating a non-linear trend. During the 21st and 36th weeks of gestation, the change points regarding ACAI were observed. During the 22nd week of gestation, the change point for PCAI was observed.

Conclusion: Plots of the parameters obtained *via* MRI examinations of cadaver fetuses across gestational age comprehensively illustrated the fetal hip development. This developmental information about the hip joint has the potential to guide clinicians in the early detection of abnormal hip joint development during intrauterine life.

Keywords: acetabular index, development, fetal hip, MRI, MULTTEST

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Guilu Tao,
The Second Affiliated Hospital of Dalian Medical University, China
Fenglong Sun,
Capital University of Medical Sciences, China

****Correspondence:***
Hongsheng Liu
liuhs72@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *01 January 2022*
Accepted: *24 January 2022*
Published: *14 February 2022*

Citation:
Liu Z, Li H, Wang S, Wu Q and Liu H (2022) A Preliminary Cadaveric MRI Study of Fetal Hip Development. Front. Surg. 9:847135. doi: 10.3389/fsurg.2022.847135

INTRODUCTION

Developmental dysplasia of the hip (DDH) is a common teratogenesis disease in children. The risk factors for DDH are breech presentation, family history, and oligohydramnios (1). Previous studies have shown that late DDH usually leads to more complicated treatments and increased long-term complications (2). The earlier DDH is discovered, the better the final result will be (3). Although high-risk DDH infants are usually formally examined at birth, it is not possible to find dislocation of hip joint until the children are obviously limping. This is because clinical symptoms are not obvious

in the early childhood (2). There is evidence that abnormal mechanical forces acting on the hip joint in uterus is related to the occurrence of DDH disease (1, 4). Investigators pay more attention to indicate the prenatal hip development (5). Published research shows that this information is usually gained from post-mortem examinations or ultrasonic imaging (6–8).

And the shape of acetabulum and femoral head have only been monitored in anatomical studies (6, 7). Also, various indicators have been used in ultrasonographic studies to assess the fetal hip development (8). Graf described the most extensive method, which is implemented by measuring the acetabular obliquity (the α angle) and the acetabular cartilage apex angle (the β angle) (9). Baróti et al. concluded that the hip joint was less stable during perinatal life, as the α angle decreased (8). In DDH, the left hip is more common, because it is adducted against the mother's lumbosacral spine in the most common intrauterine position (10). However, the left hip was a poor show on ultrasound in the case of breech presentation (11).

In 2007, Whitby et al. indicated magnetic resonance imaging (MRI) as a valid method for assessing fetal hip development owing to its high resolution and satisfactory soft tissue contrast (12). Measure the width and depth of acetabulum, the radius and diameter of femoral head, volume and area, and fully reflect the shape of femoral head. However, insufficient coverage of the femoral head is a significant precursor of a hip dysplasia (13, 14).

According to the literature (15, 16) and the accumulated experience, specific parameters were measured in this study using MRI obtained from 34 cadaver fetuses (68 hips) ranging in age from 18 to 42 weeks of gestation, so as to comprehensively evaluate coverage of the femoral head of fetal hip joint. Acetabular width and depth were measured to indicate the morphology of the acetabulum, and the anterior bony acetabular index (ABAI), anterior cartilaginous acetabular index (ACAI), posterior bony acetabular index (PBAI), and posterior cartilaginous ace-tabular index (PCAI) were measured to indicate the anterior or posterior acetabular coverage of the femoral head.

The parameters obtained using MRI of cadaveric fetuses of different gestational ages were plotted to investigate the development of fetal hip, and to remind clinicians to find abnormal hip development early during intrauterine life, so as to assess pathological severity and make emergency interventions.

MATERIALS AND METHODS

Fetal Specimens

The study was approved by the hospital ethics committee. Informed consent was obtained from the individuals concerned for the storage and use of the fetus for study purposes. The 68 hip joints of 34 cadaver fetuses (aged 18–42 weeks of gestation; nine females and 25 males) were included from 2012 through 2016 to investigate the development of fetal hip. Fetuses older than 18 weeks were required because the ossification of the acetabulum started by that time (8). The all fetuses were spontaneous miscarriages in the hospital with the exception of congenital malformations affecting fetal hip development, validated by ultrasound, absence of maternal drug use, breech position, twin fetuses, and family history of DDH. And the fetuses were excluded when gestational age was inconformity with the actual assessing both last menstruation date and ultrasonography. None of the fetuses were from a vulnerable population and all donors or next of kin provided written informed consent that was freely given.

Experimental Grouping

All the subjects were divided into five groups according to different gestational ages: 18–22 weeks, eight cases, 16 hips in total; 23–27 weeks, five cases, 10 hips in total; 28 to 32 weeks, seven cases, 14 hips in total; 33 to 37 weeks, seven cases, 14 hips in total; 38–42 weeks, seven cases, a total of 14 hips.

Imaging Methods

The hips were scanned using 1.5T MRI (Philips, Achieva, The Netherlands) within 24 h of death. Take the fetus in supine position, straighten the lower limbs together, moderately press the calf and bilateral hip joints with sandbags, and place the midpoint of the connecting line of bilateral hip joints at the center of the coil. T2-weighted images (T2WIs) were obtained using eight-channel SENCE cardiac coils in T2-weighted fast spin-echo (repetition time 2,137 ms; echo time 92 ms; time of acquisition 2 min 36 s; seam thickness 2 mm; matrix 110 × 110) in the transverse plane. The remaining imaging parameters varied slightly based on the size of the fetus. The scanning methods are mentioned in Whitby's study (12). The scan took approximately 20 min.

Measurements

The measurements of acetabular width and depth, ABAI, ACAI, PBAI, and PCAI were completed using Picture Archiving and Communication System (PACS; YLZ, Fujian, China). The acetabular width was considered as the length of the line drawn from the anterior cartilaginous vertex to the posterior. The acetabular depth was considered as the perpendicular distance from the line to the maximum distance of the acetabulum (**Figure 1**). A line was drawn from the common center of the acetabulum and femoral head (point E) to the thinnest point of the acetabular cartilage (point O), which was regarded as the baseline. The baseline definition was similar to the method described by Harnroongroj et al. using computed tomography (16). The angles formed by the baseline and the line from the anterior or posterior osteal vertex of the acetabulum to point O represented ABAI and PBAI, respectively (**Figure 2**). The angles formed by the baseline and the line from the anterior or posterior cartilaginous vertex of the acetabulum to point O represented ACAI and PCAI, respectively (**Figure 3**). These angles were measured to represent the anterior or posterior acetabular coverage of the femoral head. Larger angles denoted less acetabular coverage of the femoral head. The obtained MR images of the hip joint were independently analyzed and measured by two senior radiologists who were in charge of imaging diagnosis, and each measurement was repeated three times. In the case of inconsistent measurement results, a third senior radiologists participated in the discussion and an agreement was finally reached.

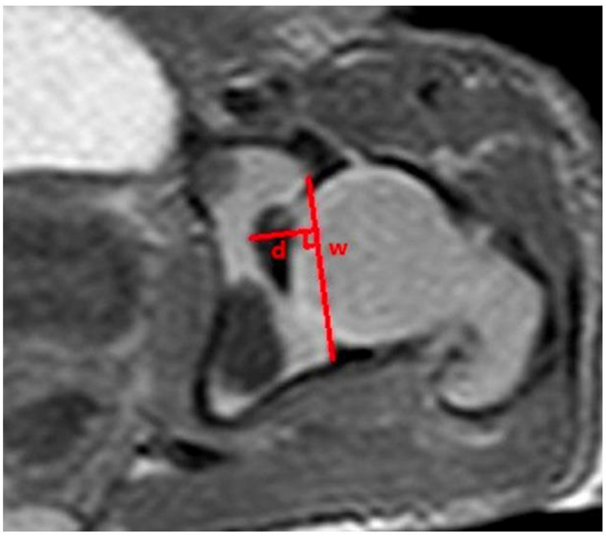


FIGURE 1 | Distance w is the width of the acetabulum, and distance d is the depth of the acetabulum.

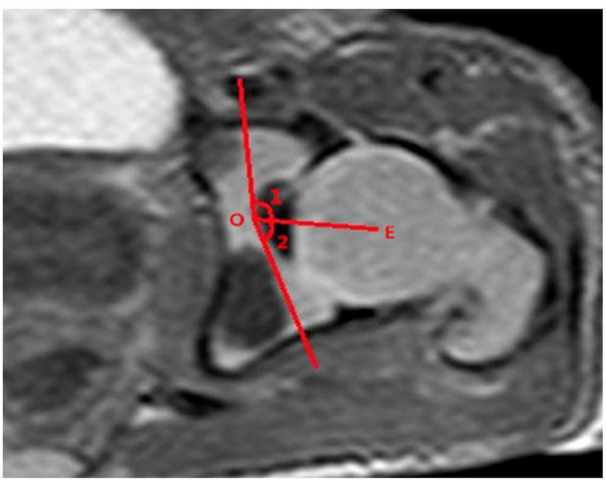


FIGURE 2 | Line OE is the baseline. Angle 1 is the ABAI, and angle 2 is the PBAI.

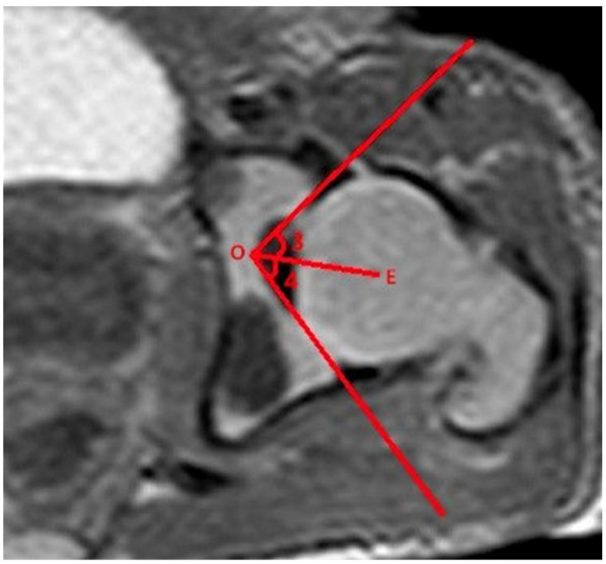


FIGURE 3 | Line OE is the baseline. Angle 3 is the ACAI and angle 4 is the PCAI.

Statistical Methods

SPSS13.0 statistical software was used to establish the database and make statistical analysis. The sample ($n = 68$), which was used to collect data to draw the growth curve of the measurement, was divided into five age classes of comparable size according to the statistical standards. Moreover, comparisons were performed between the two sides and sexes. For each group, the means and the reference range of measurements were calculated. The fetal hip development was assessed in three steps. First, the MULTTEST procedure (SAS PROC MULTTEST) was performed to address multiple analyses and determine the trends for the six indicators. To correct for multiple comparisons, the *P*-value of each contrast was adjusted to a family-wise corrected α of 0.05 using Bootstrap permutation testing implemented in SAS 9.4 PROC MULTTEST (SAS Institute Inc., USA). Second, the normative trends of all parameters were plotted against gestational age to evaluate the relationships among the different age groups with regard to the indicators. Furthermore, linear or non-linear regression analyses were performed simultaneously with the corresponding $R2 \geq 0.60$. Third, a change-point analysis (CPA) was used to detect the time point at which the statistical properties of a sequence of observations changed over time. Moreover, the CPA method was used to detect the changes in variability using the cpt.var function in R (version 3.2.5) (17). The detected change point(s) illustrated that the datasets could be divided into different segments with different variations, suggesting that the indicators changed across gestational age and at different rates. These change points are indicated in the corresponding regression graphs.

RESULTS

Analysis of Consistency of Fetal Hip Joint Measurement Indexes in Different Gestational Age Groups

Six parameters were measured with regard to the 68 cadaver fetal hips ranging in age from 18 to 42 weeks of gestation to indicate the growth of the femoral head coverage during the fetal stage. All the inter-block correlation coefficients were close to 1, and the intra-class correlation coefficients were between 0.708 and 0.933 (P all < 0.05). No significant differences were observed between the two sides of the hip or between sexes (P all > 0.05). The means, reference ranges, and trends of the different groups are indicated in **Table 1**.

TABLE 1 | Six indicators of femoral head coverage grouped by gestational age.

GA	Num	Width (cm)	Depth (cm)	ABAI (°)	PBAI (°)	ACAI (°)	PCAI (°)
18∼	16	0.67 (0.40, 0.94)	0.30 (0.27, 0.34)	121.13 (110.39, 131.86)	73.99 (65.13, 82.85)	44.77 (38.60, 50.94)	43.76 (34.12, 53.40)
23∼	10	0.91 (0.58, 1.24)	0.35 (0.23, 0.47)	105.22 (98.55, 111.88)	71.72 (67.07, 76.36)	50.30 (46.60, 54.00)	49.37 (44.35, 54.38)
28∼	14	1.03 (0.82, 1.23)	0.39 (0.28, 0.50)	100.95 (82.18, 119.72)	70.76 (63.22, 78.30)	50.61 (45.88, 55.35)	51.26 (48.96, 53.57)
33∼	14	1.34 (0.88, 1.79)	0.47 (0.31, 0.62)	94.55 (77.12, 111.97)	67.52 (53.98, 81.07)	51.05 (47.38, 54.72)	51.63 (49.69, 53.57)
38∼	14	1.57 (1.39, 1.74)	0.56 (0.46, 0.66)	87.48 (81.43, 93.52)	56.48 (46.77, 66.18)	53.94 (46.97, 60.91)	52.43 (49.96, 54.89)
Pe[*]		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Characteristics are reported as means (95% confidence intervals). ABAI, anterior bony acetabular index; ACAI, anterior cartilaginous acetabular index; GA, gestational age; PBAI, posterior bony acetabular index; PCAI, posterior cartilaginous acetabular index. A total of 68 cases were divided into five groups of comparable size, and trends were observed with regard to all six indicators; [*]P-values were adjusted to a family-wise corrected α of 0.05 using Bootstrap permutation testing implemented in SAS 9.4 PROC MULTTEST (SAS Institute Inc.).

The Hip Joint Measurement Index and Change Trend of Gestational Age

The indicators changed at different gestational ages and at different rates. As the gestational age increased, the acetabular width and depth increased linearly. The slope of gestational age against acetabular width was 0.05 (adjusted R2 = 0.86). Two change points in width were detected in the 24th and 34th weeks of gestation. These data represented three segments, and the middle segment decreased at a slower rate compared with the first and third segments (**Figure 4**). The slope of gestational age against acetabular depth was 0.01 (adjusted R2 = 0.73; **Figure 5**). Decreases in the ABAI and PBAI were noted during fetal hip development. The ABAI demonstrated an approximate linear trend. The slope of gestational age against the ABAI was −1.69 (adjusted R2 = 0.75; **Figure 6**). However, a non-linear trend was noted with regard to the PBAI (adjusted R2 = 0.66), and a change point was detected in the 36th week of gestation. These data represented two segments, and the former decreased more slowly compared with the latter (**Figure 7**). The ACAI and PCAI both exhibited a slow increase, indicating a non-linear trend, and the change points in the ACAI were observed at the 21st and 36th weeks of gestation. The ACAI changed slowly from the 21st to the 36th week of gestation, and then increased rapidly (**Figure 8**). The change point in the PCAI was observed in the 22nd week of gestation. Then, the PCAI increased relatively slowly (**Figure 9**).

DISCUSSION

MRI has greater advantages in studying the morphological changes of fetal acetabular cartilage and the development of femoral head epiphysis by virtue of the characteristics of no radiation, good spatial resolution and good imaging of cartilaginous structures, which can provide a large amount of information about the development of hip joints in the fetal period. To clarify the normal incidence of fetal hip joint is the theoretical basis for the early diagnosis and treatment of fetal DDH, and it is conducive to taking effective interventions to reduce the incidence of DDH during pregnancy. The trends between the indicators and gestational age comprehensively illustrated the development of the fetal hip. With the ossification of the acetabulum, the bone segment of the anterior and posterior acetabular coverage of the femoral head increases, but the cartilage segment of the anterior and posterior acetabular coverage of the femoral head decreases to a minimum value at term.

The anatomical details of the fetal hip were clear on T2WI MRI for all of the fetuses included in the present study (12). The parameters obtained in cross section are selected for the fetal presentation instead of the ace-tabular index in the coronal section, so it is difficult to obtain standard coronal section to fetal hip joint. In Buckley's study, a line through the anterior aspect of the triradiate cartilage was seen as the baseline; and the deficiency of anterior and posterior acetabulum was proved by DDH (15). The aforementioned baseline required that the bilateral hip joint was revealed in a transverse plane. However, the standard transverse plane was difficult to obtain for the fetal presentation. Generally, the acetabulum and femoral head are round and had the same point (16). Therefore, a line was drawn along the cross section from the thinnest point of the acetabular wall to the center of the femoral head. This line is considered to be the baseline to avoid using the contralateral acetabulum as a reference of calculation. In order to determine the baseline, the influence of the passive fetal position on the measurement parameters of nuclear MRI was avoided, and thus the evaluation of the fetal hip circumference of pregnant fetus was provided. The data represented three segments. Compared with the first and third segments, the middle segment decreased at a slower rate. These data indicated that the coverage of the acetabulum of the femoral head decreases between the 21st and 36th weeks of gestation, and this values decreases rapidly before 21 weeks or after 36 weeks of pregnancy. Based on an ultrasonographic study of the prenatal hip joints by Baróti et al., the most intensive growth of the head occurs at 24 weeks of gestation (8). Whitby et al. demonstrated an exponential increase in acetabular width until 24 weeks of gestation (12). Rális showed that at the 11th week of pregnancy, the spherical femoral head was almost completely surrounded by the deepest acetabulum. Then, the acetabulum became shallower, and the femoral head rapidly increased in size. At birth, the acetabular coverage rate of femoral head before delivery was the lowest (18). As far as PCAI is concerned, the change points was observed in the 22nd week of gestation, and then the value slowly increased. Therefore, after 22 weeks of development, the posterior cartilaginous acetabulum remained

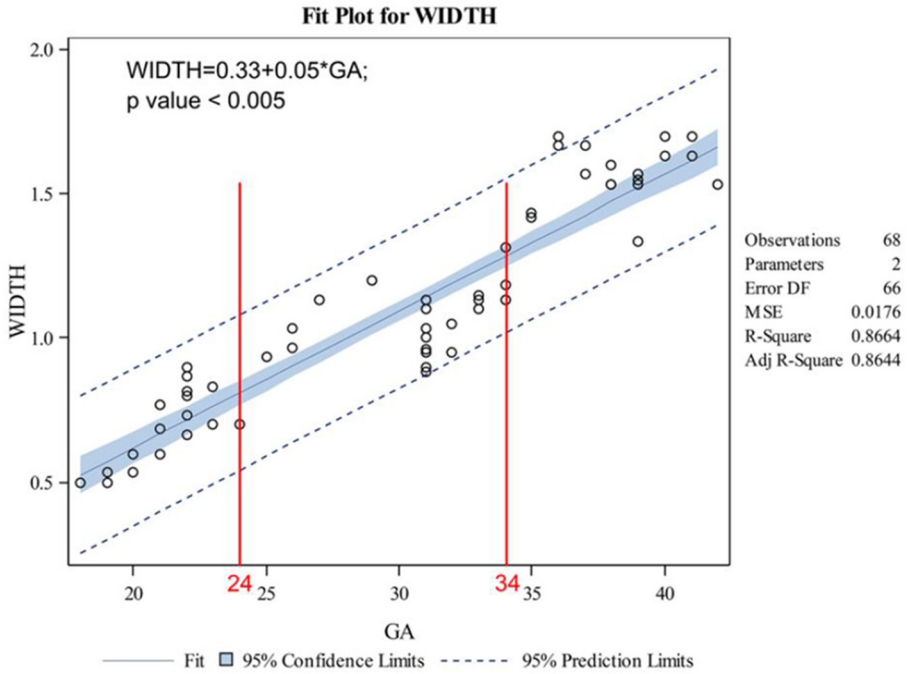


FIGURE 4 | Correlation between gestational age and acetabular width.

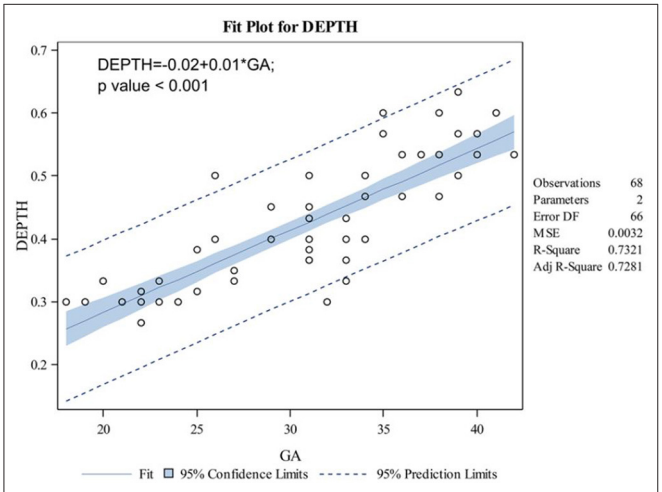


FIGURE 5 | Correlation between gestational age and acetabular depth.

relatively stable. Harnroongroj et al. described this baseline on computed tomography and it has been demonstrated to be a reliable method (16).

As a fetus develops, the ACAI and PCAI exhibit a slow increase, indicating a decrease in the anterior and posterior femoral head coverage of the cartilaginous acetabulum. This conclusion is consistent with previous research studies (1, 8, 12, 18). As far as ACAI is concerned, the change were observed in the 21st and 36th pregnancy. In perinatal period, insufficient anterior coverage and relatively stable posterior coverage of acetabulum might explain why the unstable hip is prone to anteroposterior dislocations at birth (19).

In addition, the changes of width and depth of acetabulum during the development of fetal hip joint were analyzed, and these values increased linearly with the development of the acetabulum. Based on the variation of the acetabular width and depth, the former increased more rapidly compared with the latter, and the acetabulum became shallower as gestational age increased. A previous anatomical study have shown that the acetabular depth was the slowest variable of growing hip, and it has increased < 4 fold during the period studied. This study also showed that in the 18th semester, shallow nest (18). In addition, two change in width were detected at the 24th and 34th weeks of pregnancy. These data could be separated into three segments, and the middle segment decreased slowly compared with the first and third segments. These data demonstrate the slower growth of the acetabulum during the second trimester, and the acetabulum developed rapidly after 34 weeks of pregnancy. The rapid growth of the acetabular width and the slower growth of the depth led to a less stable hip during perinatal life (20). Early diagnosis and good prognosis of DDH disease need to pay more attention to the development of fetal hip joints in perinatal period.

The ABAI and PBAI decreased, which indicated that the acetabular coverage of anterior and posterior femoral head increased with acetabulum ossification. However, an ultrasound study found that with the development of fetus, the α angle gradually decreased (18). The positive correlation between

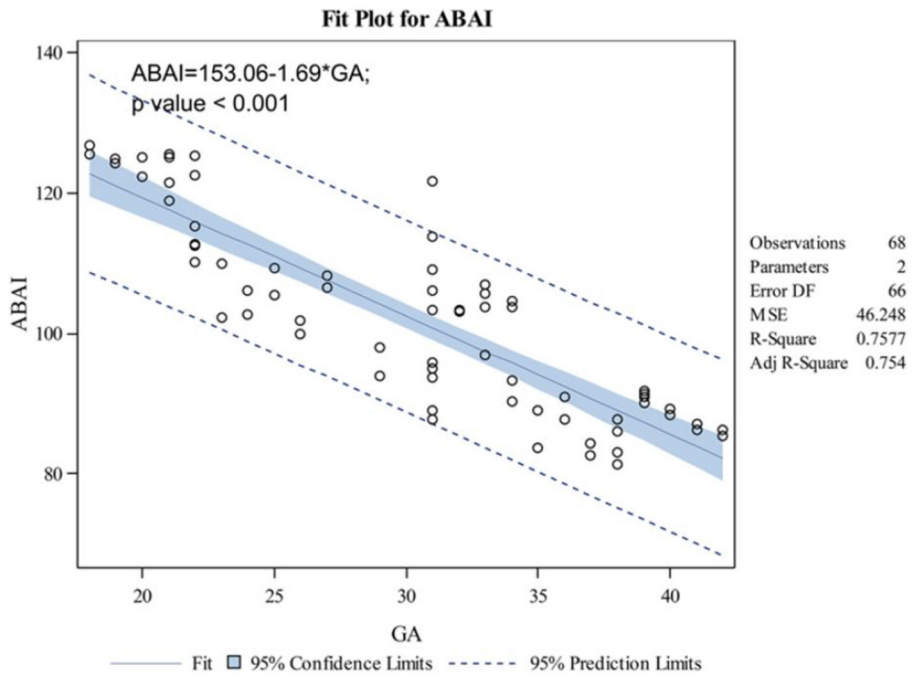


FIGURE 6 | Correlation between gestational age and anterior bony acetabular index.

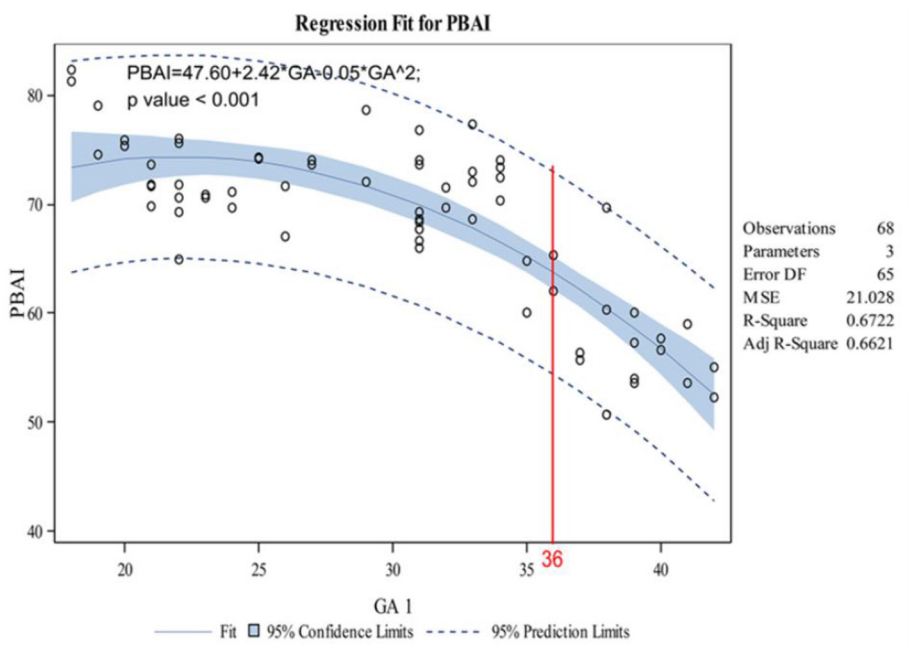


FIGURE 7 | Correlation between gestational age and posterior bony acetabular index.

femoral head coverage and the α angle was confirmed (21). The conclusions of this study are different from those of these ultrasonography. This difference was likely because of the disparate indicators measured. The acetabular coverage of the femoral head was divided into four parts: anterior, posterior, medial and lateral (22). The ultrasound revealed the α angle formed between the baseline (parallel to the lateral iliac border) and the crest line (tangential to the

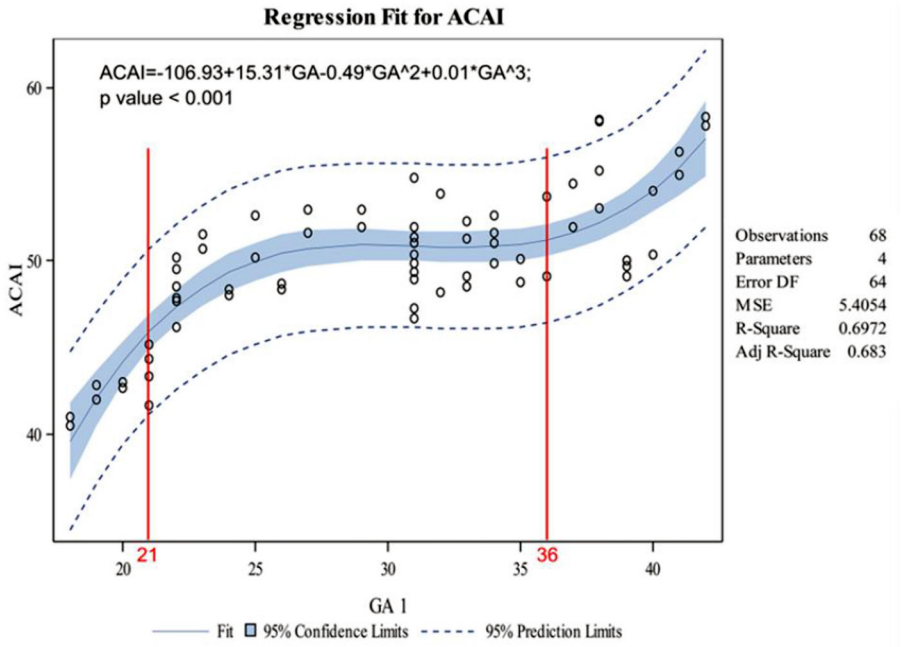


FIGURE 8 | Correlation between gestational age and anterior cartilaginous acetabular index.

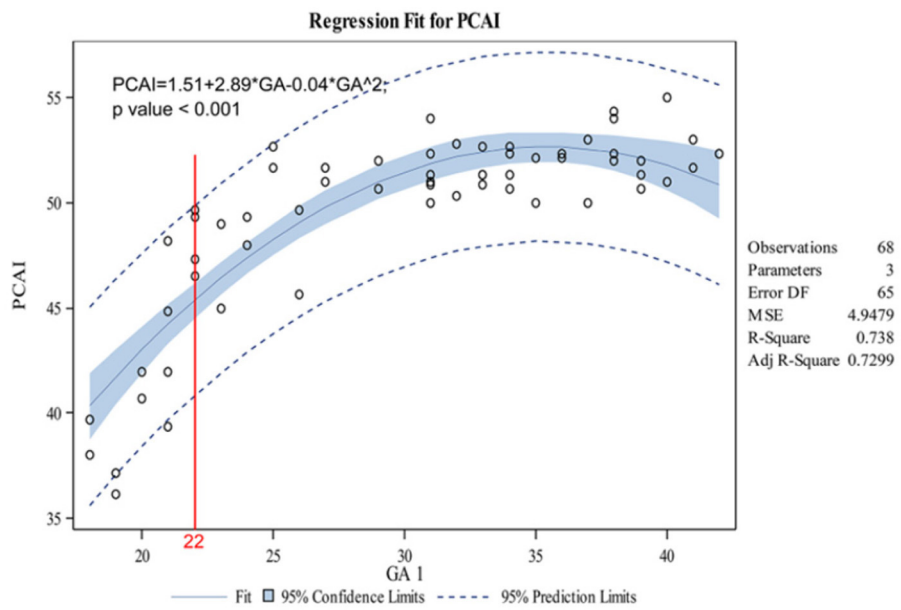


FIGURE 9 | Correlation between gestational age and posterior cartilaginous acetabular index.

bony acetabular roof) along the coronal plane of hip joint (8). The α angle represented the superior bony acetabular coverage of the femur head. In this study, these parameters were measured along the transverse plane, indicating the anterior or posterior coverage of acetabulum of femoral head. Moreover, the baseline used in the present study is likely to influence the angles. This issue needs further discussion. The change point of PBAI was observed in the 36th week of gestation, and the changed was slow before 36 weeks of pregnancy. These data indicated that before the 36th week of pregnancy, the ossification of posterior acetabulum is relatively slow.

Although this study intended to alert clinicians to the early detection of abnormal prenatal hip development by providing normative femoral head coverage parameters, the relatively small sample sizes limited the generalizability of these values. The sample sizes of the different age classes were small, and the reference values of normative femoral head coverage were restricted. More patients need to be further studied to provide an accurate database for measuring development of the hip joint. In addition, there may be some differences between the fetal ages of cadaveric fetuses and the actual fetal age. This study used cadaver fetus data to draw the normative curve. The conclusion of this study should be inferred carefully. A study on *in vivo* fetal imaging is needed to confirm these data before introducing fetal hip MRI in the clinical practice. Moreover, the measurement described in this study avoids the influence of the passive fetal position, and can evaluate the coverage of femoral head of the fetal hip joint in uterus. However, the MRI data of the intrauterine fetal hip were not included in this study. Therefore, the MRI data of the fetal hip joints during intrauterine life should be used to verify the sensitivity and specificity of these indicators.

In conclusion, these preliminary findings illustrated the development of the fetal hip joint in the second and third trimesters. As the development of fetus, the coverage of anterior and posterior cartilage acetabulum of the femoral head continues to decrease to a minimum value at full term, while the coverage of anterior and posterior bony acetabulum of the femoral head keeps increasing. As a normative reference, these data have the potential to alert clinicians to the early detection of abnormal hip development during intrauterine life.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Guangzhou Woman and Children's Medical Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ZL is responsible for writing the paper. HLi is responsible for the collection of cases. SW is responsible for the evaluation of the results. QW is responsible for data statistics. HLiu is the instructor of the entire study. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the General project of Natural Science Foundation of Guangdong Province (2020A1515010164).

REFERENCES

1. Giorgi M, Carriero A, Shefelbine SJ, Nowlan NC. Effects of normal and abnormal loading conditions on morphogenesis of the prenatal hip joint: application to hip dysplasia. *J Biomech.* (2015) 48:3390–7. doi: 10.1016/j.jbiomech.2015.06.002
2. Mulpuri K, Schaeffer EK, Andrade J, Sankar WN, Williams N, Matheney TH, et al. What risk factors and characteristics are associated with late-presenting dislocations of the hip in infants? *Clin Orthop Relat Res.* (2016) 474:1131–7. doi: 10.1007/s11999-015-4668-0
3. Tomlinson J, O'Dowd D, Fernandes JA. Managing developmental dysplasia of the hip. *Indian J Pediatr.* (2016) 83:1275–9. doi: 10.1007/s12098-016-2160-9
4. Hashimoto R, Kihara I, Otani H. Perinatal development of the rat hip joint with restrained fetal movement. *Congenit Anom.* (2002) 42:135–42. doi: 10.1111/j.1741-4520.2002.tb00863.x
5. Jouve JL, Glard Y, Garron E, Piercecchi MD, Dutour O, Tardieu C, et al. Anatomical study of the proximal femur in the fetus. *J Pediatr Orthop B.* (2005) 14:105–10. doi: 10.1097/01202412-200503000-00009
6. Masłoń A, Sibiński M, Topol M, Krajewski K, Grzegorzewski A. Development of human hip joint in the second and the third trimester of pregnancy; a cadaveric study. *BMC Dev Biol.* (2013) 13:19. doi: 10.1186/1471-213X-13-19
7. Lee MC, Eberson CP. Growth and development of the child's hip. *Orthop Clin North Am.* (2006) 37:119–32. doi: 10.1016/j.ocl.2005.12.001
8. Baróti B, Pap Z, Pánti Z, Buruian MM, Pávai Z. Morphometric and ultrasonographic study of the human fetal hip joint during intrauterine development. *Rom J Morphol Embryol.* (2013) 54:977–81.
9. Graf R. The diagnosis of congenital hip-joint dislocation by the ultrasonic Combound treatment. *Arch Orthop Trauma Surg.* (1980) 97:117–33. doi: 10.1007/BF00450934
10. Storer SK, Skaggs DL. Developmental dysplasia of the hip. *Am Fam Physician.* (2006) 74:1310–6. doi: 10.1002/ebch.1891
11. Pinelli G, Sénès FM, Asquasciati G, Becchetti S, Di Stadio M, Franchi L, et al. Study of foetal hip: intrauterine positions and sonographic aspects. *J Perinat Med.* (1994) 1:117–20. doi: 10.1515/jpme.1994.22.s1.117
12. Whitby EH, Bell MJ, Rigby AS, Burton M. Measuring hip development using magnetic resonance imaging. *J Pediatr Orthop.* (2007) 27:898–902. doi: 10.1097/bpo.0b013e31815a5ff1
13. Cheng H, Liu L, Yu W, Zhang H, Luo D. Zheng G. Comparison of 25D and 3D quantification of femoral head coverage in normal control subjects and patients with hip dysplasia. *PLoS ONE.* (2015) 10:143498. doi: 10.1371/journal.pone.0143498
14. Miyasaka D, Ito T, Imai N, Suda K, Minato I, Dohmae Y, et al. Three-dimensional assessment of femoral head coverage in normal and dysplastic hips: a novel method. *Acta Med Okayama.* (2014) 68:277–84. doi: 10.18926/AMO/52896
15. Buckley SL, Sponseller PD, Magid D. The acetabulum in congenital and neuromuscular hip instability. *J Pediatr Orthop.* (1991) 11:498–501. doi: 10.1097/01241398-199107000-00015
16. Harnroongroj T, Suangyanon P, Tharmviboonsri T, Harnroongroj T. Posterior acetabular arc angle of the femoral head assesses instability of posterior fracture-dislocation of the hip. *Int Orthop.* (2013) 37:1141–5. doi: 10.1007/s00264-013-1870-0
17. Killick R, Eckley I. Changepoint: an R pack- age for changepoint analysis. *J Stat Softw.* (2014) 58:1–19. doi: 10.18637/jss.v058.i03
18. Rális Z, McKibbin B. Changes in shape of the human hip joint during its development and their relation to its stability. *J*

Bone Joint Surg Br. (1973) 55:780–5. doi: 10.1302/0301-620X.55B4.780
19. Horii M, Kubo T, Inoue S, Kim WC. Coverage of the femoral head by the acetabular labrum in dysplastic hips: quantitative analysis with radial MR imaging. *Acta Orthop Scand.* (2003) 74:287–92. doi: 10.1080/00016470308540842
20. Walker JM, Goldsmith CH. Morphometric study of the fetal development of the human hip joint: significance for congenital hip disease. *Yale J Biol Med.* (1981) 54:411–37.
21. Gunay C, Atalar H, Dogruel H, Yavuz OY, Uras I, Sayli U. Correlation of femoral head coverage and Graf alpha angle in infants being screened for developmental dysplasia of the hip. *Int Orthop.* (2009) 33:761–4. doi: 10.1007/s00264-008-0570-7
22. Hansen BJ, Harris MD, Anderson LA, Peters CL, Weiss JA, Anderson AE. Correlation between radiographic measures of acetabular morphology with 3D femoral head coverage in patients with acetabular retroversion. *Acta Orthop.* (2012) 83:233–9. doi: 10.3109/17453674.2012.684138

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Liu, Li, Wang, Wu and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 14 February 2022
doi: 10.3389/fsurg.2022.843982

Clinical Analysis of the Treatment of Primary Trigeminal Neuralgia by Percutaneous Balloon Compression

Hui Wang†, Chunhui Chen†, Da Chen†, Fengsheng Li†, Shan Hu†, Wenqian Ding†, Jun Wang† and Wanghua Chen†*

Department of Neurosurgery, Pingkuang General Hospital, Pingxiang, China

Purpose: To summarize the technical points and clinical effects of percutaneous balloon compression (PBC) in the treatment of primary trigeminal neuralgia.

Methods: The clinical data of 13 patients with trigeminal neuralgia who received PBC from April 2020 to July 2021 were retrospectively analyzed. VAS, VRS-4 and PPI were used to evaluate the postoperative pain relief. Different postoperative complications were analyzed.

Results: All patients had a smooth operation, the inflation volume of the balloon was 0.7 ml, the average compression time was 120 s, and there was no balloon rupture during the operation. On the day after operation, 12 patients (92.3%) had complete pain relief, and 1 patient (7.7%) was not satisfied with pain relief, but the pain disappeared 2 weeks after the operation. After operation, there were 12 patients with facial numbness in the affected side (92.3%), 3 patients with masseter muscle weakness (23.0%), 1 patient with herpes around the mouth (7.6%), and 1 patient with diplopia (7.6%).

Conclusion: PBC is an effective minimally invasive surgical method for the treatment of primary trigeminal neuralgia. It is suitable for the elderly and infirm people, those who cannot tolerate general anesthesia or are afraid of surgery, and patients who had undergone surgery but relapsed after surgery. However, it is necessary to pay attention to the serious facial numbness and postoperative masticatory weakness. These discomforts are generally relieved after half a year.

Keywords: trigeminal neuralgia, percutaneous balloon compression, pain, clinical effect, minimally invasive surgical

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Chengke Luo,
Central South University, China
Yang Liu,
The First Medical Center of Chinese PLA General Hospital, China

***Correspondence:**
Hui Wang
wanghui18575160@163.com

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *27 December 2021*
Accepted: *20 January 2022*
Published: *14 February 2022*

Citation:
Wang H, Chen C, Chen D, Li F, Hu S, Ding W, Wang J and Chen W (2022) Clinical Analysis of the Treatment of Primary Trigeminal Neuralgia by Percutaneous Balloon Compression. Front. Surg. 9:843982. doi: 10.3389/fsurg.2022.843982

INTRODUCTION

Trigeminal neuralgia is the most common facial neuralgia in clinic. The clinical onset is mainly unilateral pain. Most of the initial pain is a short-term phenomenon, which only appears for a few seconds or minutes. After the initial pain, it may be accompanied by a period of painless remission, and then it will attack again, with typical paroxysmal pain, severe pain, and discharge-like pain (1, 2). Under normal circumstances, the clinical manifestations of patients with trigeminal neuralgia are not obvious between the two attacks, but with the development of the disease, dull pain or even persistent pain may occur in the later stage of the disease, and the pain may last for more than 1 h. Investigations have shown that the prevalence of trigeminal neuralgia in the population ranges from 4/100,000 to 27/100,000, and the most common age is over 50 years old

(3). The pathogenesis of primary trigeminal neuralgia has not been uniformly recognized by the medical community, but at present, most scholars believe that it is related to the central lesion theory and the peripheral pathogen theory. Trigeminal neuralgia not only makes the patient's language dysfunction and eating difficulty, but also may cause the patient to have bad psychology such as anxiety, irritability and depression, which has a some negative impact on the patient's daily life (4). Therefore, it is necessary to take active measures to solve trigeminal neuralgia clinically. When the trigeminal neuralgia is diagnosed for the first time, drug therapy is the first choice. Carbamazepine, as the first-line drug at present, can effectively relieve the pain. However, after taking it for a long time, the curative effect will decrease, and the patient finally stops taking the medicine because of the pain that cannot be tolerated and seek surgical treatment (5, 6).

In recent years, with the continuous development of imaging technology and nerve intervention, surgical treatment has gradually developed to be more mature. In 1983, Mullan's team first used percutaneous puncture to treat diseases, and achieved certain results. This laid the foundation for the germination of percutaneous balloon compression (PBC) in our country (7). The principle of PBC is to selectively damage the myelinated coarse fibers that conduct tactile sensation through balloon compression, while retaining the unmyelinated fine fibers that conduct pain, which is different from the known thermocoagulation radiofrequency because thermocoagulation radiofrequency can cause selective injury. It can be used as a useful supplement of microvascular decompression (MVD) for trigeminal neuralgia (8). PBC is not easy to cause corneal fiber injury. On the one hand, it may reduce the afferent sensation impulse and turn off the trigger switch of trigeminal nerve pain conduction pathway. On the other hand, it also relieves the nerve entrapment that may exist in the semilunar segment of the trigeminal nerve, so it has obvious advantages in the treatment of the I and II branches of trigeminal neuralgia (9).

Based on this, we observed 13 patients with primary trigeminal neuralgia in our hospital from April 2020 to July 2021, and discussed the therapeutic effect of PBC. The report was as follows.

MATERIALS AND METHODS

Case Data

From April 2020 to July 2021, 13 patients with primary trigeminal neuralgia were treated in our hospital. Diagnosis criteria (10): (a) Pain history ≥3 months, and sudden and recurrent pain; There are no clinical symptoms during pain relief; (b) Pain distribution and one or more branches of the trigeminal nerve distribution region; The nature of pain is "cutting" or "electric shock;" Having a definite trigger point; (c) No positive signs on nervous system examination; (d) The attack form is fixed and rigid. Thirteen patients including eight females and five males. The average age of the patients was 71 years, left side pain in seven cases, right side pain in six cases, and the history of pain was 1–23 years, with an average of 5.3 years. All patients had received carbamazepine, oxcarbazepine, and other drug treatment, but with the prolongation of the course of disease, the patients gradually tolerated or could not tolerate the toxic and side effects of drugs, and all the patients were willing to undergo surgery. Two cases had undergone PBC and four cases had undergone microvascular decompression. Two patients underwent radiofrequency, PBC and MVD operations. The follow-up time ranged from 3 months to 1 year, with an average of 5 months. Before operation, all patients were routinely examined by MRI + trigeminal neurovascular imaging and 64-slice CT skull reconstruction to check the location and direction of foramen ovale. Exclusion criteria: Secondary trigeminal neuralgia caused by intracranial tumor compression; Complicated with intracranial aneurysm, cerebral and craniofacial vascular diseases or malformations, hydrocephalus and other neurological related diseases; Unable to tolerate surgery; Bilateral trigeminal neuralgia. Before operation, patients were informed of other alternative treatment schemes and asked to sign.

Methods

Preoperative Preparation

Trigeminal cardiac inhibitory reflexes have often occurred during PBC procedures, manifesting as transient but pronounced bradycardia during balloon filling. Before foramen ovale puncture, giving patients an appropriate amount of atropine and remifentanil could alleviate this reaction. Instructed patients to take supine position, and performed routine preoperative disinfection and towel spreading. Heart rate, blood pressure, and blood oxygen saturation were monitored in the whole process, and ambulatory arterial blood pressure was monitored in real time. Tracheal intubation, general anesthesia and breathing control, neck slightly extended, with the patient's nose as the highest point, and semilunar ganglion puncture surgery were carried out under the instructions of cross-line screen. (1) 64-slice CT skull reconstruction was performed before surgery, Hartel's anterior approach to the semilunar ganglion of trigeminal nerve was used, and the foramen ovale was the puncture target (**Figure 1**). The M-shaped puncture needle with a needle core was used as the puncture tool. The puncture point was 2.5–3 cm outside the mouth angle of the affected side, which basically corresponds to the root of the first molar. The other two reference points were the direction of the pupil on the same side, the outer canthus of the corner of the eye on the same side was connected to the external auditory canal, and the connection was 3 cm above the external auditory canal. Took the intersection of the two as the direction of the foramen ovale. (2) The needle was inserted from the puncture point, and the needle should be carefully inserted, it should be careful not to pierce the oral mucosa, and reached the foramen ovale under the instructions of the fluorescent screen, but to avoid penetrating the foramen ovale. The needle core was pulled out, and the blunt end of the 0.5 Kirschner wire was inserted into the catheter at the center of the introduction. The Kirschner wire and cannula were measured and fixed before the operation, so that the head end of the needle exceeds the puncture needle tip by 1–2 cm forward and enters into the semilunar segment's Meckel's cave (**Figure 2**). Until the needle feels obvious resistance, the needle core was pulled out. When the posterior margin of the upper palate,

FIGURE 1 | (A) 64-slice CT skull reconstruction was performed before surgery to check the direction and size of the foramen ovale; **(B)** Determine the direction of the patient's puncture.

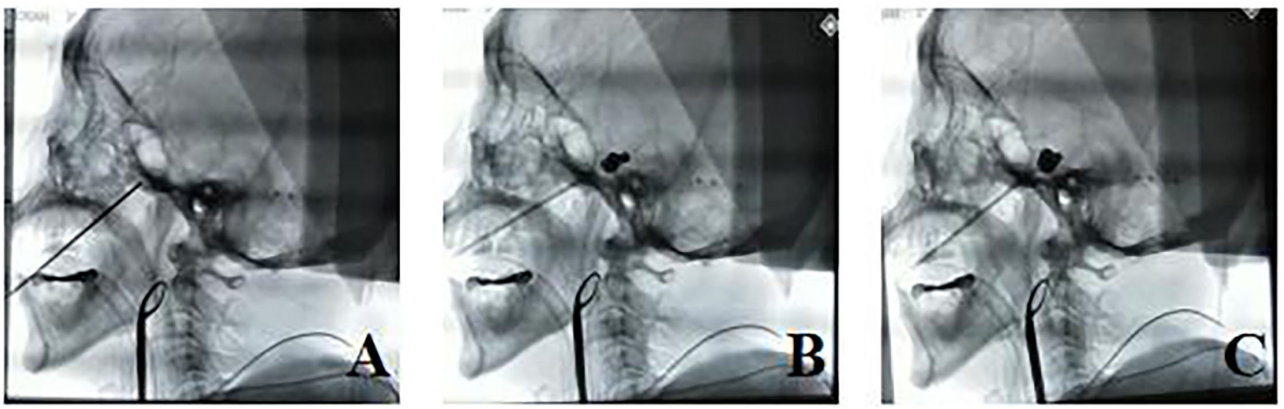


FIGURE 2 | (A–C) After the puncture was in place during the operation, the balloon was filled, and the puncture point had to be inside Meckel's cave and formed an effective "pear" shape.

temporomandibular joint, and external auditory canal overlap, it was considered a standard lateral position, and the balloon was filled with the contrast agent iohexol under standard lateral DSA fluoroscopy, until the protrusion toward the posterior cranial fossa appeared "pear" shape (**Figures 3**, **4**). If the puncture was not ideal, the cannula direction needed to be adjusted in time to re-puncture. The filling fluid of the balloon was 0.45–0.75 ml. It took 120–180 s to compress the semilunar segment, the contrast agent in the balloon was discharged, the catheter was pulled out, and the compression at the puncture point was about 5 min.

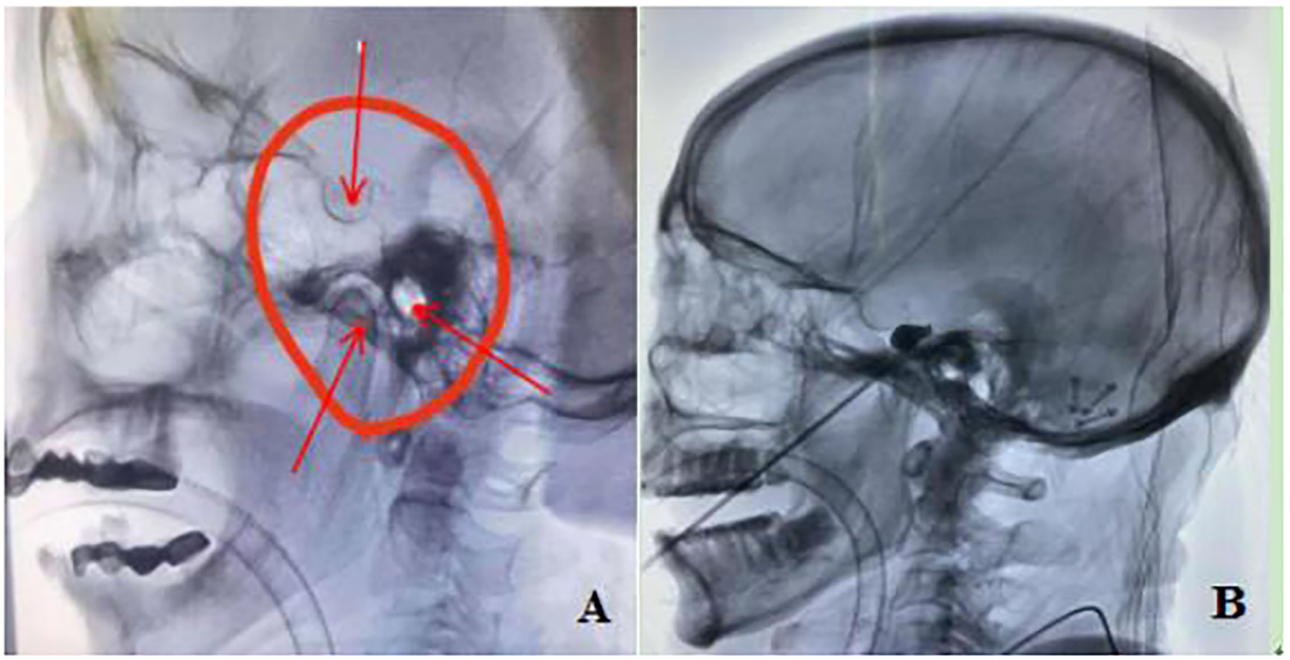


FIGURE 3 | (A) When the posterior margin of the upper palate, temporomandibular joint and external auditory canal overlap (shown by arrow), it was considered a standard lateral position; **(B)** After the puncture needle pierces the dura mater of foramen ovale, it needs to be kept outside the skull to avoid further penetration, and the balloon will form an "inverted pear" shape after filling.

Patients were taken into ICU for postoperative observation, and returned to ward after waking up.

Evaluation Methods

VAS, VRS-4, and PPI were used to evaluate the postoperative pain relief. Complete pain relief: VAS $<$ 10 points, VRS-4 0 grade or PPI 0 grade; Pain relief: VAS 10-40 points, VRS-4 1 grade, or PPI 1-2 grade: pain relief unsatisfactory: VAS $\geq$ 40 points, VRS-4 $\geq$ 2 grade, or PPI $\geq$ 3 grade. Different postoperative complications were analyzed, including facial numbness, masseter muscle weakness, herpes around the mouth, diplopia and so on.

RESULTS

All patients had a smooth operation, the inflation volume of the balloon was 0.7 ml, the average compression time was 120 s, and there was no balloon rupture during the operation. On the day after operation, 12 patients (92.3%) had complete pain relief, and 1 patient (7.7%) was not satisfied with pain relief, but the pain disappeared 2 weeks after the operation. After operation, there were 12 patients with facial numbness in the affected side (92.3%), three patients with masseter muscle weakness (23.0%), one patient with herpes around the mouth (7.6%), and one patient with diplopia (7.6%). Follow-up was conducted 3 months after operation, among which 13 cases were effectively followed up, and 1 patient had delayed effect due to the gradual reduction of oxcarbazepine after operation. The pain of this patient improved 1 month after operation, and the total effective rate was 92.3%. Twelve patients (92.3%) had slight numbness in the side of operation, and one patient had severe numbness in the side of operation with ulcer of the affected side, which was photophobia, which had certain influence on the quality of life of patients.

DISCUSSION

At present, the surgical treatment of trigeminal neuralgia can be roughly divided into four categories: MVD, stereotactic gamma knife, PBC, and radiofrequency thermocoagulation with glycerol injection (11). After MVD, the complete pain relief rate can reach 90%, and after 10 years, the complete relief rate can be maintained at about 70%, and the incidence of surgical complications is low, which is the most ideal surgical scheme at present (12). However, this operation is complicated, which requires high technical requirements for the operator, and is not suitable for patients who are weak, old, or have serious systemic diseases and cannot tolerate craniotomy under general anesthesia. Stereotactic gamma knife, as a non-invasive treatment method, was first applied in 1953. Although the long-term follow-up results show that gamma knife has a certain curative effect on trigeminal neuralgia, there are a large number of literature reports that the early postoperative complete pain relief rate is quite different (21.8–80%), and the rate of complete pain relief 10 years later was lower (45.3%), and the related surgical complications (such as facial sensory disturbance and numbness) and the recurrence rate of pain are also high (13). The rate of postoperative pain relief in PBC was 88.9–97.3%, and the rate of complete pain relief was about 62% in more than 10 years of follow-up. PBC also has a good curative effect on recurrent trigeminal

FIGURE 4 | The puncture process was guided under the direction of DSA.

neuralgia after microvascular decompression, the complete pain relief rate reached 82.7% in 3 years after operation (14). The effective relief rate of postoperative pain in this study was 92.3%, which was similar to previous reports and equivalent to the therapeutic effect of MVD. Compared with other surgical methods, PBC has four advantages. First, the wound is small, and the puncture needle is inserted beside the patient's mouth, only the pinhole size, less bleeding, less patient injury, less side effects, and fewer complications, etc. Second, the operation time is short, and the whole operation process can be completed in about 30 min. Third, the hospitalization time is short, and the patient can be discharged from hospital within 2–3 days after operation. Fourthly, the patient is well-tolerated, accepts the whole operation under general anesthesia, and the patient has less pain and discomfort during the operation (15–19).

Early balloon compression surgery lasts for a long time. Although the pain relief rate is high and the effective duration is long, facial sensory disturbance and myasthenia gravis tend to be severe and last for a long time, and there are many postoperative complications, so it is not recommended that the compression time be too long (20). The shorter the compression time, the higher the recurrence rate. Chen's team concluded that the appropriate compression time was 90 s, which not only ensured a high pain relief rate, but also did not increase the incidence of complications (21). In this study, the average time of compression was 120 s, range from 30 to 180 s. The filling volume of the balloon determines the pressure damage suffered by the semilunar ganglion nerve, which not only directly affects the pain relief effect after operation, but also leads to decreased facial sensation, numbness, and weakened masseter muscles. Clinical research has shown that surgery can't achieve the expected therapeutic effect when the balloon filling pressure was lower than 600 mmHg 0.45 ml, and surgery is suitable when the balloon pressure was 750–1,250 mmHg 0.65 ml (22). However, the pressure of each part of the balloon is not uniform, and the pressure at the semilunar node is the highest, which is significantly higher than that at the foramen ovale and the distal end. At present, few hospitals in China are equipped with pressure monitoring devices during surgery, and the general experience of surgeons is to inject 0.5–0.8 ml of non-ionic contrast agent. The average contrast agent injected in this group was 0.702 ml. Early balloon compression surgery will continue to have numbness at 1 year after operation, which can't be alleviated. Patients who experienced severe numbness after early balloon compression surgery, none of the patients improved, and the masseter muscle was atrophied and facial changes appeared afterwards (23, 24). In this study, six patients with severe numbness on the affected side of the face had an ideal "inverted pear" shaped balloon filling shape during the operation, the balloon filling volume was 0.7 ml, and the balloon filling time was 20–25 min. Compared with other patients, there was no special situation, it was speculated that the serious numbness on the affected side of the face was caused by anatomical factors: the Meckel's cave volume of the patient was too small, although the balloon was filled with the same volume of contrast agent, the pressure generated in the semilunar ganglion was obviously high, resulting in extensive destruction of nerve fibers. Patients with PBC with a long duration of intraoperative compression often have severe postoperative facial numbness, but the relative relief of postoperative facial pain is more obvious. Therefore, clinically, it is necessary to appropriately extend or shorten the compression time according to the severity of preoperative pain, but it should be within a reasonable range.

CONCLUSION

PBC is a minimally invasive, safe, effective, and minimally invasive treatment with minor complications. The indications of PBC for trigeminal neuralgia are: (1) Those who are afraid of craniotomy and refuse craniotomy; (2) Elderly and infirm people with more basic diseases; (3) Patients with poor general health; (4) Patients who have side effects on drugs; (5) Patients with ineffective microvascular decompression or postoperative pain recurrence; (6) Patients with secondary trigeminal neuralgia who have poor craniotomy treatment effect or can't tolerate drug (25, 26). Compared with other surgical methods, the biggest advantage of PBC is that it is easy to master, which is conducive to the popularization and development of primary hospitals. However, we should also realize that even if the balloon filling volume and filling compression time are reasonable, a small number of patients will still be accompanied by severe facial numbness and muscular atrophy after operation, which will affect the quality of life to a certain extent. How to reduce postoperative complications is the focus of our attention in the future, and whether there is recurrence or not in the 3 and 5 year follow-up period after surgery is also the focus of our attention in the future. Comparative analysis of a large number of cases with different surgical methods is the most effective means to evaluate the surgical efficacy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Pingkuang General Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HW was the instructor of the study. CC and DC were responsible for the design of the study. FL and SH were responsible for collecting clinical data. WD and JW were responsible for data evaluation and recording. WC was responsible for data statistical analysis and papers of writing. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Nurmikko TJ. Toward an etiology-based management of trigeminal neuralgia. *Pain Manag.* (2017) 7:149–54. doi: 10.2217/pmt-2016-0054
2. Gerwin R. Chronic facial pain: trigeminal neuralgia, persistent idiopathic facial pain, and myofascial pain syndrome-an evidence-based narrative review and etiological hypothesis. *Int J Environ Res Public Health.* (2020) 17:7012. doi: 10.3390/ijerph17197012
3. Wang Y, Yang Q, Cao D, Seminowicz D, Remeniuk B, Gao L, et al. Correlation between nerve atrophy, brain grey matter volume and pain severity in patients with primary trigeminal neuralgia. *Cephalalgia.* (2019) 39:515–25. doi: 10.1177/0333102418793643
4. Fan X, Xu F, Ren H, Lu Z, Bu H, Ma L, et al. The analysis of percutaneous balloon compression on efficacy and negative emotion in the treatment of recurrent trigeminal neuralgia after surgical procedures. *Pain Physician.* (2021) 24:E1255–62.
5. Bendtsen L, Zakrzewska JM, Heinskou TB, Hodaie M, Leal PRL, Nurmikko T, et al. Advances in diagnosis, classification, pathophysiology, and management of trigeminal neuralgia. *Lancet Neurol.* (2020) 19:784–96. doi: 10.1016/S1474-4422(20)30233-7
6. Di Stefano G, De Stefano G, Leone C, Di Lionardo A, Di Pietro G, Sgro E, et al. Real-world effectiveness and tolerability of carbamazepine and oxcarbazepine in 354 patients with trigeminal neuralgia. *Eur J Pain.* (2021) 25:1064–71. doi: 10.1002/ejp.1727
7. Mullan S, Lichtor T. Percutaneous microcompression of the trigeminal ganglion for trigeminal neuralgia. *J Neurosurg.* (1983) 59:1007–12. doi: 10.3171/jns.1983.59.6.1007
8. Xu W, Jiang C, Yu C, Liang W. Percutaneous balloon compression for persistent or recurrent trigeminal neuralgia after microvascular decompression: personal experience of 28 patients. *Acta Neurol Belg.* (2018) 118:561–6. doi: 10.1007/s13760-017-0858-8
9. Scranton RA, Shah K, Cohen-Gadol AA. Alternative customized instrumentation and technique for percutaneous balloon compression rhizotomy for trigeminal neuralgia. *J Neurosurg.* (2019) 132:1938–41. doi: 10.3171/2019.2.JNS182896
10. Bendtsen L, Zakrzewska JM, Abbott J, Braschinsky M, Di Stefano G, Donnet A, et al. European Academy of Neurology guideline on trigeminal neuralgia. *Eur J Neurol.* (2019) 26:831–49. doi: 10.1111/ene.13950
11. Green TH, Girgis F. Trigeminal neuralgia: medical management and surgical options. *J Pain Palliat Care Pharmacother.* (2019) 33:32–3. doi: 10.1080/15360288.2019.1624676
12. Zhao G, Sun X, Zhang Z, Yang H, Zheng X, Feng B. Clinical efficacy of MVD combined with PSR in the treatment of primary trigeminal neuralgia. *Exp Ther Med.* (2020) 20:1582–8. doi: 10.3892/etm.2020.8871
13. Alvarez-Pinzon AM, Wolf AL, Swedberg HN, Barkley KA, Cucalon J, Curia L, et al. Comparison of percutaneous retrogasserian balloon compression and gamma knife radiosurgery for the treatment of trigeminal neuralgia in multiple sclerosis. *World Neurosurg.* (2017) 97:590–4. doi: 10.1016/j.wneu.2016.10.028
14. Chaves JPG, De Oliveira TVHF, Francisco AN, Trintinalha MO, Carvalho NVP. Trigeminal neuralgia recurrence: a comparison of microvascular decompression and percutaneous balloon compression: a five years follow-up study. *Arq Neuropsiquiatr.* (2021) 79:51–5. doi: 10.1590/0004-282x-anp-2020-0115
15. Qin Q, Wang Y. Recurrent trigeminocardiac reflex in percutaneous balloon compression for trigeminal neuralgia: a case report. *Medicine.* (2020) 99:e22467. doi: 10.1097/MD.0000000000022467
16. Tan S, Wang D, Chi Z, Li W, Shan Y. Study on the interaction between typical phthalic acid esters (PAEs) and human haemoglobin (hHb) by molecular docking. *Environ Toxicol Pharmacol.* (2017) 53:206–11. doi: 10.1016/j.etap.2017.06.008
17. Li MW, Jiang XF, Niu CS. Efficacy of and risk factors for percutaneous balloon compression for trigeminal neuralgia in elderly patients. *Br J Neurosurg.* (2021) 35:280–4. doi: 10.1080/02688697.2020.1787341
18. Zhang W, Jiang X, Wang Y. Percutaneous balloon compression for trigeminal neuralgia because of pontine cavernous angioma. *World Neurosurg.* (2020) 137:137–9. doi: 10.1016/j.wneu.2019.12.167
19. Grewal SS, Kerezoudis P, Garcia O, Quinones-Hinojosa A, Reimer R, Wharen RE. Results of percutaneous balloon compression in trigeminal pain syndromes. *World Neurosurg.* (2018) 114:e892–9. doi: 10.1016/j.wneu.2018.03.111
20. Wang Q, Chen C, Guo G, Li Z, Huang D, Zhou H, et al. Prospective study to examine the association of the foramen ovale size with intraluminal pressure of pear-shaped balloon in percutaneous balloon compression for trigeminal neuralgia. *Pain Ther.* (2021) 10:1439–50. doi: 10.1007/s40122-021-00311-7
21. Chen JN Yu WH, Du HG, Jiang L, Dong XQ, Cao J. Prospective comparison of redo microvascular decompression and percutaneous balloon compression as primary surgery for recurrent trigeminal neuralgia. *J Korean Neurosurg Soc.* (2018) 61:747–52. doi: 10.3340/jkns.2017.0196
22. Wang Q, Guo GW, Huang D, Li ZX, Zhou HC. Correlation of preoperative reconstruction of foramen ovale parameters and intraluminal balloon pressure during percutaneous balloon compression for trigeminal neuralgia. *Zhonghua Yi Xue Za Zhi.* (2021) 101:3549–53. doi: 10.3760/cma.j.cn112137-20210824-01924
23. Noorani I, Lodge A, Vajramani G, Sparrow O. The effectiveness of percutaneous balloon compression, thermocoagulation, and glycerol rhizolysis for trigeminal neuralgia in multiple sclerosis. *Neurosurgery.* (2019) 85:E684–92. doi: 10.1093/neuros/nyz103
24. Unal TC, Unal OF, Barlas O, Hepgul K, Ali A, Aydoseli A, et al. Factors determining the outcome in trigeminal neuralgia treated with percutaneous balloon compression. *World Neurosurg.* (2017) 107:69–74. doi: 10.1016/j.wneu.2017.07.132
25. Huang B, Yao M, Chen Q, Du X, Li Z, Xie K, et al. Efficacy and safety of awake computed tomography-guided percutaneous balloon compression of trigeminal ganglion for trigeminal neuralgia. *Pain Med.* (2021) 22:2700–7. doi: 10.1093/pm/pnab228
26. Asplund P, Blomstedt P, Bergenheim AT. Percutaneous balloon compression vs percutaneous retrogasserian glycerol rhizotomy for the primary treatment of trigeminal neuralgia. *Neurosurgery.* (2016) 78:421–8. doi: 10.1227/NEU.0000000000001059

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang, Chen, Chen, Li, Hu, Ding, Wang and Chen. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 15 February 2022
doi: 10.3389/fsurg.2022.843913

Analysis of Clinical Characteristics, Treatment, and Prognostic Factors of 106 Breast Cancer Patients With Solitary Pulmonary Nodules

*Lihong He†, Xiaorui Wang†, Xiaodong Liu, Yongsheng Jia, Weipeng Zhao, Xiaochen Jia, Yuehong Zhu, Wenjing Meng and Zhongsheng Tong**

Key Laboratory of Cancer Prevention and Therapy, Department of Breast Cancer, National Research Center for Cancer, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Li Genlin,
University of South China, China
Jiangang Liu,
The Second Affiliated Hospital of Shandong First Medical University, China

***Correspondence:**
Zhongsheng Tong
15222566488@163.com

†These authors share first authorship

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *27 December 2021*
Accepted: *17 January 2022*
Published: *15 February 2022*

Citation:
He L, Wang X, Liu X, Jia Y, Zhao W, Jia X, Zhu Y, Meng W and Tong Z (2022) Analysis of Clinical Characteristics, Treatment, and Prognostic Factors of 106 Breast Cancer Patients With Solitary Pulmonary Nodules. Front. Surg. 9:843913. doi: 10.3389/fsurg.2022.843913

Objective: The clinical features of solitary pulmonary nodules (SPN) in breast cancer patients were retrospectively analyzed, and the clinical features of primary lung cancer (PLC) and metastatic pulmonary breast cancer (MBC) in breast cancer patients were compared, and the treatment plan, curative effect and influencing factors were analyzed.

Methods: The clinical data of 106 patients of SPN combined with breast cancer surgery in our hospital from January 2015 to June 2020 were analyzed. There were 65 patients of PLC and 41 patients of MBC. Record the characteristics of the primary breast cancer lesion in our patient, the interval between the initial diagnosis of breast cancer and the appearance of SPN, the previous treatment history of our patient, and the characteristics and surgical method of SPN. The survival status of all patients during the follow-up period was recorded.

Results: The onset age, interval, maximum nodule diameter, ER expression positive rate and radiotherapy history ratio of PLC patients were higher than those of MBC patients, and the lymph node positive rate and triple negative rate were lower than those of MBC patients ($P < 0.05$). Median survival was 51 months in patients with PLC and 37 months in patients with MBC. The 1, 3, and 5 year overall survival rates in patients with PLC were higher than those in patients with MBC ($P < 0.05$). Vascular tumor thrombus, SPN type and chemotherapy were all independent factors affecting the prognosis of patients with breast cancer combined with SPN ($P < 0.05$).

Conclusion: PLC patients and MBC patients have significant differences in pathological characteristics, like the onset age, interval, maximum nodule diameter, ER expression positive rate, radiotherapy history ratio, the lymph node positive rate, and triple negative rate. Septum, vascular tumor thrombus, SPN type, and chemotherapy are all independent factors that affect the curative effect of breast cancer patients with SPN. Based on the nature of SPN, it can provide reference for clinicians to decide the treatment plan, improve patients' quality of life and prolong their survival time.

Keywords: breast cancer, primary lung cancer, metastatic pulmonary breast cancer, treatment, prognosis

INTRODUCTION

Breast cancer is one of the most common malignant tumors in women, and its incidence is extremely high (1). With the application of radiotherapy, chemotherapy, and targeted therapy, the survival time of breast cancer patients is prolonged, but the risk of secondary primary cancer is increasing gradually. Studies have shown that the primary malignant tumors secondary to breast cancer mainly include endometrial cancer, blood tumor, lung cancer, and so on (2). It is the second most common primary cancer patients with breast cancer, and the lung is also the common metastatic site of breast cancer (3, 4). When an isolated pulmonary nodule (SPN) is found in patients with breast cancer, it is easy to diagnose metastatic pulmonary breast cancer (MBC) clinically, and the treatment direction will be biased toward breast cancer, leading to the change of treatment choice (5). The clinical diagnosis and treatment of MBC need to be differentiated, but the epidemiological and clinicopathological features of secondary lung cancer after breast cancer have not been fully revealed, and multi-center research lacks the support of big data. Therefore, when finding SPN in breast cancer patients, the first clinical problem to be solved to accurately diagnose the nature of SPN and distinguish between primary lung cancer (PLC) and MBC, which is of great significance to guide breast cancer patients and SPN patients to choose the best individualized treatment scheme (6, 7). In this study, we retrospectively analyzed the clinical characteristics of breast cancer patients with SPN, compared the clinical characteristics of PLC and MBC, and analyzed the efficacy of patients and the related factors affecting the prognosis of breast cancer patients with SPN, in order to provide clinical basis for the treatment and prognosis of breast cancer patients with SPN.

TABLE 1 | Comparison of clinical characteristics between patients with PLC and MBC disease (n, $\bar{x}\pm$ s).

Clinical pathological features	PLC ($n = 65$)	MBC ($n = 41$)	t/χ^2 value	P-value
Onset age (years)	55.42 ± 11.08	43.72 ± 9.85	5.523	0.027
Interval (years)	5.47 ± 1.53	2.86 ± 1.07	6.542	0.008
Maximum diameter of nodule (mm)	22.39 ± 8.94 patients with	16.24 ± 10.53	3.218	0.042
Pathological type of breast cancer			0.239	0.624
Invasive ductal carcinoma	48 (73.85%)	32 (78.05%)		
Invasive lobular carcinoma	17 (26.15%)	9 (21.95%)		
Histological grading			0.025	0.985
Level 1	12 (18.46%)	8 (19.51%)		
Level 2	31 (47.69%)	19 (46.34%)		
Level 3	22 (33.85%)	14 (34.15%)		
Lymph node status			6.154	0.013
Positive	30 (46.15%)	29 (70.73%)		
Negative	35 (53.85%)	12 (29.27%)		
ER expression			4.391	0.036
Positive	42 (64.62%)	18 (43.90%)		
Negative	23 (35.38%)	23 (56.10%)		
PR expression			0.331	0.566
Positive	37 (56.92%)	21 (51.22%)		
Negative	28 (43.08%)	20 (48.78%)		
HER-2 expression			0.095	0.758
Positive	25 (38.46%)	17 (41.46%)		
Negative	40 (61.54%)	24 (58.54%)		
Triple negative			4.352	0.037
Yes	12 (18.46%)	15 (36.59%)		
No	53 (81.54%)	26 (63.41%)		
History of radiotherapy			5.221	0.029
Yes	37 (56.92%)	16 (39.02%)		
No	28 (43.08%)	25 (60.98%)		
Chemotherapy history			0.351	0.554
Yes	58 (89.23%)	38 (92.68%)		
No	7 (10.77%)	3 (7.32%)		
History of endocrine therapy			2.107	0.146
Yes	44 (67.69%)	22 (53.66%)		
No	21 (32.31%)	19 (46.34%)		

TABLE 2 | Comparison of overall survival rates between patients with PLC and MBC disease (*n*, %).

Group	Overall survival rate		
	1 year	3 years	5 years
PLC (n = 65)	59 (90.77%)	47 (72.31%)	20 (30.77%)
MBC (n = 41)	34 (82.93%)	17 (41.46%)	8 (19.51%)
χ^2-value	3.437	5.998	5.512
P-value	0.041	0.012	0.016

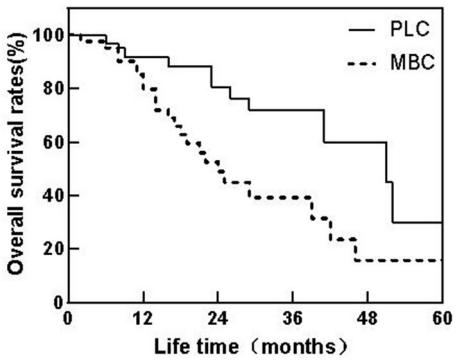


FIGURE 1 | Patient survival curves of PLC and MBC.

DATA AND METHODS

General Information

The clinical data of 106 patients of SPN combined with breast cancer diagnosed and treated in our hospital from January 2015 to June 2020 were analyzed. All patients chose the treatment plan according to their specific condition, and they met the patient inclusion criteria.

Inclusion Criteria

SPN was found during postoperative follow-up of breast cancer, and confirmed as PLC or MBC; By biopsy or post-operative pathological examination; Breast cancer was the first primary cancer; Clinical data of diagnostic immunohistochemistry; and postoperative treatment of breast cancer were complete.

Exclusion Criteria

Benign pulmonary nodules diagnosed by pathological examination; Patients with history of metastases of other malignant tumors or other sites; Follow-up universal periodic review failed; and follow-up data was lost.

All the patients were female, and 65 patients with PLC and 41 patients with MBC were diagnosed pathologically from SPN. Among the 65 PLC patients, there were 29 patients with lung squamous cell carcinoma, 22 patients with lung adenocarcinoma, 11 patients with small cell lung cancer, and 3 patients with large cell lung cancer.

Research Methods

The characteristics of primary breast cancer lesions in our patient were recorded, including pathological type, histological grade, lymph node status, expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), and vascular tumor thrombi. HER-2 was determined to be negative based on 0 or + by immunohistochemistry and positive based on + + + by fluorescence *in situ* hybridization. ER or PR positivity is defined as the proportion of cells positive for immunohistochemical staining reaching more than 1%. The triple negativity was negative for ER, PR, and HER-2. Record the interval between the initial diagnosis of breast cancer and the appearance of SPN, the previous treatment history of the patient, and the characteristics and surgical method of SPN. Patients were followed up to June 2021, and their post-treatment survival (from surgery to time of death or follow-up deadline) was recorded.

Statistical Methods

SPSS22.0 software was used for processing. The measurement data of experimental data were expressed as mean standard deviation ($\bar{x}\pm$ s), and the enumeration data were expressed as (%). *t*-test was used for pairwise comparison of measurement data between groups, and χ^2 test was used for enumeration data. Kaplan-Meier method was used to draw the survival curve. Multivariate Logisitic regression model was used to analyze the related factors affecting the postoperative efficacy of patients with breast cancer combined with SPN. The test level was $\alpha = 0.05$, and $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of Clinical Characteristics Between Patients With PLC and MBC Disease

The differences in age at onset, interval, maximum nodule diameter, lymph node status, ER expression, triple negative, and radiotherapy history between PLC patients and MBC patients were statistically significant ($P < 0.05$), while the differences were not statistically significant in pathological type, histological grade, PR expression, HER-2 expression, chemotherapy history, and endocrine treatment history ($P > 0.05$) as shown in **Table 1**.

Treatment of Patients With PLC and MBC Disease

Among 65 patients with primary liver cancer, 23 patients underwent radical lobectomy plus chemotherapy plus radiotherapy, 39 patients underwent wedge resection plus chemotherapy, and 3 patients underwent radiotherapy plus chemotherapy. Among 41 patients with MBC, 13 patients received wedge resection plus endocrine therapy, 21 patients received chemotherapy plus radiotherapy plus endocrine therapy, and seven patients received radiotherapy and chemotherapy.

TABLE 3 | Univariate analysis of prognosis of patients with breast cancer combined with SPN (*n*, %).

Clinical pathological features	Survival ($n = 28$)	Death ($n = 78$)	χ^2-value	*P*-value
Onset age (years)			0.394	0.531
≥50	17 (60.71%)	42 (53.85%)		
<50	11 (39.29%)	36 (46.15%)		
Interval time (years)			10.118	0.001
≥3	22 (78.57%)	34 (43.59%)		
<3	6 (21.43%)	44 (56.41%)		
Vascular cancer thrombi			13.562	<0.001
Yes	7 (25.00%)	51 (65.38%)		
No	21 (75.00%)	27 (34.62%)		
Pathological type			1.192	0.275
Invasive ductal carcinoma	19 (67.86%)	61 (78.21%)		
Invasive lobular carcinoma	9 (32.14%)	17 (21.79%)		
Histological grading			1.088	0.581
Level 1	7 (25.00%)	13 (16.67%)		
Level 2	13 (46.43%)	37 (47.44%)		
Level 3	8 (28.57%)	28 (35.89%)		
Lymph node status			0.034	0.853
Positive	16 (57.14%)	43 (55.13%)		
Negative	12 (42.86%)	35 (44.87%)		
Maximum diameter of nodule (mm)			5.782	0.016
≥20	22 (78.57%)	41 (52.56%)		
<20	6 (21.43%)	37 (47.44%)		
Type of SPN			4.639	0.024
PLC	20 (71.43%)	45 (57.69%)		
MBC	8 (28.57%)	33 (42.31%)		
Surgical approach			0.535	0.464
Lobectomy	10 (35.71%)	13 (16.67%)		
Wedge resection/tumor resection	18 (64.29%)	34 (43.59%)		
Chemotherapy			5.319	0.021
Yes	28 (100.00%)	65 (83.33%)		
No	0 (0.00%)	13 (16.67%)		
Endocrine therapy			0.063	0.802
Yes	6 (21.43%)	15 (19.23%)		
No	22 (78.57%)	63 (80.77%)		

TABLE 4 | Assignment for multivariate analysis of factors.

Factors	Variables	Assignment
Interval time	X1	≥3 years = 0, <3 years = 1
Vascular tumor thrombus	X2	Yes = 1, No = 0
Maximum diameter of nodules	X3	≥20 mm = 0, <20 mm = 1
Type of SPN	X4	PLC = 0, MBC = 1
Chemotherapy	X5	Yes = 1, No = 0

Prognosis of Patients With PLC and MBC Disease

The median survival time of patients with PLC was 51 months, and the overall survival rates of 1, 3, and 5 years were 90.77, 72.31, and 30.77%, respectively. The median survival time of patients with MBC was 37 months, and the overall survival rates of 1, 3, and 5 years were 82.93, 41.46, and 19.51%, respectively. The median survival time of PLC patients is longer than that of MBC patients, and the Log-rank test is $P = 0.034$, the difference is statistically significant. The 1, 3, and 5 years overall survival rates of patients with PLC were higher than those of patients with MBC, and the differences were statistically significant ($P < 0.05$) as shown in **Table 2**, **Figure 1**.

Univariate Analysis of Prognosis of Patients With Breast Cancer Combined With SPN

Univariate analysis showed that the prognosis of breast cancer patients with SPN was related to the interval time, the presence or absence of vascular tumor thrombus, the maximum diameter of nodules, the type of SPN and chemotherapy ($P < 0.05$) as shown in **Table 3**.

Analysis of Multiple Factors Affecting the Prognosis of Patients With Breast Cancer Combined With SPN

Multivariate analysis showed that interval, vascular tumor thrombus, the type of SPN, and chemotherapy were all independent factors affecting the prognosis of patients with breast cancer combined with SPN ($P < 0.05$) as shown in **Tables 4**, **5**.

DISCUSSION

Lung metastasis is a common site of postoperative recurrence and metastasis of breast cancer. The differentiation of SPN in breast cancer patients has always been a difficult problem (8). Clinically, when looking for SPN in patients with a breast cancer history, the first thing to consider is usually the occurrence of lung metastasis from breast cancer. However, for SPN in the lung, breast cancer combined is mostly combined with PLC, and MBC or benign lung diseases are the second most important place (9).

TABLE 5 | Multi-factor analysis of prognosis of patients with breast cancer combined with SPN.

Factor	*B*	*SE*	*Walds*	*P*	*OR*	*95% CI*
Interval time	2.381	1.053	5.113	0.031	10.816	1.373–15.190
Vascular tumor thrombus	2.195	0.956	5.272	0.024	8.980	1.379–9.484
Maximum diameter of nodules	1.086	0.734	2.189	0.298	2.962	0.702–12.486
Type of SPN	2.534	0.862	8.642	0.016	12.604	2.327–18.273
Chemotherapy	2.254	0.864	6.806	0.018	9.526	1.752–11.803

Studies have shown that compared with the normal population, breast cancer patients are more likely to be accompanied by PLC, which may be related to the common genetic factors and hormone genes of the two diseases, and has a certain correlation with the survival time of breast cancer patients (10). With the development and popularization of modern video-assisted thoracoscopy technology, the clinical diagnosis rate of SPN is increasing. Obtaining pathological diagnosis is the gold standard for clinical diagnosis. Therefore, for SPN whose nature cannot be clearly defined, it is feasible to first remove the focus and make a definite diagnosis. According to SPN, the next treatment plan includes anti-inflammation, endocrine therapy, chemotherapy, and targeted therapy (11, 12). Accurate identification of PLC or MBC in time, and determination of the next treatment plan according to the nature of SPN, is an important basis for rational clinical treatment (13).

In this study, the clinical data of patients with breast cancer complicated with PLC and MBC were retrospectively analyzed. The results showed that there were significant differences between PLC patients and MBC patients in onset age, interval, maximum nodule diameter, lymph node status, ER expression, triple negative, and radiotherapy history and so on. Compared with MBC patients, PLC patients have older onset age, longer interval and larger nodule diameter, which may be related to the preference of PLC for elderly patients, as well as the fact that some advanced MBC patients have more tumors are prone to lung metastasis (14, 15). Patients with negative lymph nodes, positive ER expression, less triple-negative, and more radiotherapy history are more likely to be diagnosed with PLC, which may be related to the longer survival time of these patients, and chemotherapy significantly reduces the probability of local recurrence of breast cancer (16, 17). Radiotherapy plays an important role in reducing local recurrence of breast cancer and increasing survival rates. Studies have shown that chemotherapy can lead to an increased incidence of Hodgkin's lymphoma complicated with lung cancer. In addition, estrogen is closely related to the occurrence of lung cancer, and many lung cancer cells are also accompanied by over-expression of ER (especially ERβ) (18, 19).

Excision of the lesion can clearly diagnose the nature of SPN, so as to determine the next treatment plan in clinic, including radiotherapy, chemotherapy, and endocrine therapy (20). Among 65 PLC patients, 23 patients underwent radical lobectomy + chemotherapy + radiotherapy, 39 patients underwent wedge resection + chemotherapy, and three patients underwent radiotherapy + chemotherapy. Among 41 MBC patients, 13 underwent wedge resection plus endocrine therapy, 21 underwent chemotherapy plus radiotherapy plus endocrine therapy, and seven underwent radiotherapy plus chemotherapy. The 5-year overall survival rate of patients with PLC was significantly higher than that of MBC patients. For breast cancer patients combined with PLC, surgical resection of lung diseases is an important means of treatment (21). For MBC patients, general palliative treatment is mainly used, and chemotherapy and endocrine therapy can effectively improve the survival rate (22). If the surgical treatment can be tolerated, whether surgical resection of solitary pulmonary metastases is meaningful to improve the quality of life and prolonging the survival time of MBC patients remains to be verified by prospective research results. The survival time of PLC in breast cancer is mainly determined by lung cancer. After radical resection, the clinical prognosis is good and the survival rate is high within 5 years. Once MBC appears, it is divided into the fourth stage. Even after comprehensive treatment, the prognosis is poor and the overall survival rate is significantly lower than that of breast cancer combined with PLC patients (23, 24).

The results of this study show that the curative effect of breast cancer patients with SPN was related to the interval time, the presence or absence of vascular tumor thrombus, the maximum diameter of nodules, the type of SPN, chemotherapy, and other factors. Further multivariate analysis showed that interval time, vascular tumor thrombus, SPN type, and chemotherapy were independent factors that affected the curative effect of breast cancer patients with SPN. The longer the interval between the diagnosis of breast cancer and the discovery of SPN, the PLC nature of SPN in breast cancer patients with SPN show the characteristics of better prognosis and longer survival time (25). The absence of vascular tumor thrombi and the longer survival time of patients undergoing chemotherapy may be related to the fact that the tumor load of patients is low, and chemotherapy is conducive to the removal of micro metastases throughout the body.

To sum up, compared with MBC patients, there are significant differences in the onset age, interval, maximum diameter of nodules, lymph node status, ER expression, triple negative, and radiation history among PLC patients. Septum, vascular tumor thrombus, SPN type and chemotherapy are all independent factors that affect the curative effect of breast cancer patients

with SPN. Based on the nature of SPN, it can provide reference for clinicians to decide the treatment plan, improve patients' quality of life and prolong their survival time.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of Tianjin Medical University Cancer Institute and Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LH and XW were mainly responsible for the design of the study and the writing of the manuscript. XL and YJ were mainly responsible for the collection of case data. WZ and XJ were responsible for the data recording. YZ and WM were responsible for the data statistical analysis. ZT was the instructor of the whole study. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by Key Task Project of Tianjin Health and Family Planning Commission (16KG128), Anticancer Key Technologies R&D Program of Tianjin (12ZCDZSY16200), Natural Science Foundation of Tianjin (18JCYBJC91600), amd Scientific research program of Tianjin Education Commission (2020KJ139).

REFERENCES

1. Tsang JYS, Tse GM. Molecular Classification of Breast Cancer. *Adv Anat Pathol.* (2020) 27:27–35. doi: 10.1097/PAP.0000000000000232
2. Cai WL, Greer CB, Chen JF, Arnal-Estapé A, Cao J, Yan Q, et al. Specific chromatin landscapes and transcription factors couple breast cancer subtype with metastatic relapse to lung or brain. *BMC Med Genomics.* (2020) 13:33. doi: 10.1186/s12920-020-0695-0
3. Jin L, Han B, Siegel E, Cui Y, Giuliano A, Cui X. Breast cancer lung metastasis: Molecular biology and therapeutic implications. *Cancer Biol Ther.* (2018) 19:858–68. doi: 10.1080/15384047.2018.1456599
4. Medeiros B, Allan AL. Molecular mechanisms of breast cancer metastasis to the lung: clinical and experimental perspectives. *Int J Mol Sci.* (2019) 20:2272. doi: 10.3390/ijms20092272
5. Peart O. Metastatic breast cancer. *Radiol Technol.* (2017) 88:519–39.
6. Liu C, Li H, Xu K, Song S, He Y, Cai X, et al. Multiple primary lung cancer versus intrapulmonary metastatic cancer: a case of multiple pulmonary nodules. *Thorac Cancer.* (2019) 10:352–8. doi: 10.1111/1759-7714.12918
7. Yousefi M, Nosrati R, Salmaninejad A, Dehghani S, Shahryari A, Saberi A. Organ-specific metastasis of breast cancer: molecular and cellular mechanisms underlying lung metastasis. *Cell Oncol.* (2018) 41:123–40. doi: 10.1007/s13402-018-0376-6
8. Li K, Xu C, Du Y, Junaid M, Kaushik AC, Wei DQ. Comprehensive epigenetic analyses reveal master regulators driving lung metastasis of breast cancer. *J Cell Mol Med.* (2019) 23:5415–31. doi: 10.1111/jcmm.14424
9. Macherey S, Mallmann P, Malter W, Doerr F, Heldwein M, Wahlers T, et al. Lung metastasectomy for pulmonary metastatic breast carcinoma. *Geburtshilfe Frauenheilkd.* (2017) 77:645–50. doi: 10.1055/s-0043-108252
10. Neves M, Fumagalli A, van den Bor J, Marin P, Smit MJ, Mayor F. The role of ACKR3 in 8. *Mol Pharmacol.* (2019) 96:819–25. doi: 10.1124/mol.118.115279
11. Xu H, Pu XH Yu TF, Shi HB, Wu YL, Xu YM, et al. Incidence and natural course of CT-detected pulmonary ground-glass nodules in Chinese women with breast cancer: a retrospective, single-center, long-term follow-up study in 4682 consecutive patients. *Acta Radiol.* (2020) 61:175–83. doi: 10.1177/0284185119856259
12. Hammer MM, Mortani Barbosa EJ Jr. Predictive factors for malignancy in incidental pulmonary nodules detected in breast cancer patients at baseline CT. *Eur Radiol.* (2017) 27:2802–9. doi: 10.1007/s00330-016-4627-5
13. Song Z, Ye T, Ma L, Xiang J, Chen H. Surgical outcomes of isolated malignant pulmonary nodules in patients with a history of breast cancer. *Ann Surg Oncol.* (2017) 24:3748–53. doi: 10.1245/s10434-017-6067-0
14. Lin S, Mo H, Li Y, Guan X, Chen Y, Wang Z, et al. Clinicopathological characteristics and survival outcomes in patients with synchronous lung metastases upon initial metastatic breast cancer diagnosis in Han population. *BMC Cancer.* (2021) 21:1330. doi: 10.1186/s12885-021-09038-2
15. He KW, Wei W, Liu ZY, Song X, Zhuo PY, Ma QH, et al. [Clinicopathological features of second primary lung cancer and pulmonary metastasisin patients with breast cancer]. *Zhonghua Zhong Liu Za Zhi.* (2018) 40:201–5. doi: 10.3760/cma.j.issn.0253-3766.2018.03.008
16. Kwapisz D. Oligometastatic breast cancer. *Breast Cancer.* (2019) 26:138–46. doi: 10.1007/s12282-018-0921-1
17. Liu B, Xia H. Progress in Surgery for Pulmonary Metastases. *Zhongguo Fei Ai Za Zhi.* (2019) 22:574–8. doi: 10.3779/j.issn.1009-3419.2019.09.04
18. Xie L, Lin C, Zhang H, Bao X. Second malignancy in young early-stage breast cancer patients with modern radiotherapy: a long-term population-based study (A STROBE-compliant study). *Medicine.* (2018) 97:593. doi: 10.1097/MD.0000000000010593
19. Meng W, Liao Y, Chen J, Wang Y, Meng Y, Li K, et al. Upregulation of estrogen receptor beta protein but not mRNA predicts poor prognosis and may be associated with enhanced translation in non-small cell lung cancer: a systematic review and meta-analysis. *J Thorac Dis.* (2021) 13:4281–300. doi: 10.21037/jtd-21-658
20. Latorzeff I, Bourgier C, Pinel B, Hennequin C, Jimenez G, Chapet O, et al. Traitement de la maladie primitive (cancers du sein, du poumon non à petites cellules et de la prostate), par irradiation, au stade d'emblée métastatique [Treatment of primary disease (breast, non-small cell lung and prostate cancers) with irradiation in case of de novo metastatic cancer]. *Cancer Radiother.* (2019) 23:486–95. doi: 10.1016/j.canrad.2019.08.004
21. Cruickshank A, Stieler G, Ameer F. Evaluation of the solitary pulmonary nodule. *Intern Med J.* (2019) 49:306–15. doi: 10.1111/imj.14219
22. Xiao W, Zheng S, Liu P, Zou Y, Xie X, Yu P, et al. Risk factors and survival outcomes in patients with breast cancer and lung metastasis: a population-based study. *Cancer Med.* (2018) 7:922–30. doi: 10.1002/cam4.1370
23. Wang JC Li GY, Wang B, Han SX, Sun X, Jiang YN, et al. Metformin inhibits metastatic breast cancer progression and improves chemosensitivity by inducing vessel normalization via PDGF-B downregulation. *J Exp Clin Cancer Res.* (2019) 38:235. doi: 10.1186/s13046-019-1211-2
24. Urooj T, Wasim B, Mushtaq S, Shah SNN, Shah M. Cancer cell-derived secretory factors in breast cancer-associated lung metastasis: their mechanism and future prospects. *Curr Cancer Drug Targets.* (2020) 20:168–86. doi: 10.2174/1568009620666191220151856

25. Chen MT, Sun HF, Zhao Y, Fu WY, Yang LP, Gao SP, et al. Comparison of patterns and prognosis among distant metastatic breast cancer patients by age groups: a SEER population-based analysis. *Sci Rep*. (2017) 7:9254. doi: 10.1038/s41598-017-10166-8

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 He, Wang, Liu, Jia, Zhao, Jia, Zhu, Meng and Tong. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 15 February 2022
doi: 10.3389/fsurg.2022.842884

Major Risk Factors Analysis of Pruritus Complicated by Type 2 Diabetes Mellitus and the Effect of Comprehensive Nursing Intervention

Qiu Ping Yang[1†], *Yuan Yuan Chen*[2†], *Zhenzhen Li*[3] *and Mingming Xu*[2*]

[1] *Endocrinology Ward, Shenzhen Traditional Chinese Medicine Hospital (The Fourth Clinical Medical School of Guangzhou University of Chinese Medicine), Shenzhen, China,* [2] *Nursing Department, Shenzhen Traditional Chinese Medicine Hospital (The Fourth Clinical Medical School of Guangzhou University of Chinese Medicine), Shenzhen, China,* [3] *Surgery Ward 3-4, Shenzhen Traditional Chinese Medicine Hospital (The Fourth Clinical Medical School of Guangzhou University of Chinese Medicine), Shenzhen, China*

Objective: To observe the main risk factors for pruritic skin evidence complicating type 2 diabetes mellitus (T2DM) and the effectiveness of interventions with comprehensive care measures.

Methods: Two hundred and twenty four patients with T2DM admitted to our hospital from June 2020 to November 2021 were selected and divided into Diabetic pruritus group (DP group, $n = 71$) and T2DM group ($n = 153$) according to the patients' complications of pruritus. General information such as gender, age, body mass index (BMI), duration of illness, family history, treatment modalities, other comorbidities, underlying illnesses were collected from all patients. Fasting plasma glucose (FPG), renal function [Serum creatinine (Scr), urea nitrogen (BUN), uric acid (BUA)], lipid levels [total cholesterol (TC), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)] were measured in all patients on day 2 after admission. Risk factors for pruritus complicating T2DM were identified by single multifactorial analysis. Meanwhile, patients in the DP group were divided into group A ($n = 35$) and group B ($n = 36$) using the random number table method. Group A adopted the conventional care mode and group B patients adopted the comprehensive care interventions to compare the care effects [visual analog score (VAS) before and after care, treatment efficiency, care satisfaction rate] of patients in groups A and B; the levels of pruritus mediator indicators [substance P,β-endorphin (β-EP) and γ-interferon (INF-γ)] before and after care.

Results: Risk factors for pruritus in T2DM were age, duration of DM, combined Diabetic peripheral neuropathy (DPN), combined diabetic retinopathy (DR), combined diabetic kidney disease (DKD) and serum FPG levels ($P<0.05$). Satisfaction rate of nursing care, treatment efficiency, post-care improvement in VAS scores, serum substance P, β-EP and INF-γ levels and other mediators of pruritus were better in Group B with integrated nursing intervention than in group A with conventional care only ($P < 0.05$).

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Qiang Wang,
Guizhou University, China
Lihu Xie,
University of South China, China

***Correspondence:**
Mingming Xu
szszyyhlb2@163.com

[†] *These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *24 December 2021*
Accepted: *17 January 2022*
Published: *15 February 2022*

Citation:
Yang QP, Chen YY, Li Z and Xu M (2022) Major Risk Factors Analysis of Pruritus Complicated by Type 2 Diabetes Mellitus and the Effect of Comprehensive Nursing Intervention. Front. Surg. 9:842884. doi: 10.3389/fsurg.2022.842884

Conclusion: Pruritus in T2DM is associated with age, duration of DM, combined DPN, combined DR, combined DKD and FPG levels. Comprehensive care according to the above risk factors can effectively relieve patients' clinical symptoms and signs, improve the level of pruritus mediators and patient-care relationship.

Keywords: type 2 diabetes mellitus, pruritus, risk factors, comprehensive care, pruritic medium

INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic disorders characterized by a chronic increase in plasma glucose levels due to a variety of causes (1, 2). Prolonged disturbances in the metabolism of carbohydrates, fats and proteins can be detrimental to multiple organ systems and lead to chronic progressive hypofunction of tissues and organs (3). The prevalence and incidence of DM have shown a dramatic increase in recently years, which is a worldwide public health problem that seriously threatens human health, according to the statistics of the International Diabetes Federation in 17 years (4). With the prolongation of the disease, long-term hyperglycemia can cause microvascular and neurological damage, resulting in a variety of complications. The skin is the organ with the most extensive distribution of nerves and blood vessels throughout the body, and the skin damage caused by diabetes is called diabetic skin disease (5).

Diabetic skin disease has a high incidence in DM patients, and diabetic pruritus is one of the common skin complications. Patients with DM complicated by pruritus usually show generalized or localized pruritus without primary skin damage, or secondary skin damage such as scratch marks, crusts, pigmentation and eczema-like changes after scratching (6, 7). Diabetic pruritus (DP) is often worse at night, which not only affects the quality of life and sleep, but also causes psychological and mental abnormalities such as irritability, anxiety and depression due to the unbearable itching symptoms (8, 9). Although pruritus in DM patients is not a direct threat to patients' lives, it has a serious impact on patient's quality of life and physical and mental health, reduces patients' compliance with treatment and is detrimental to the control of their condition, thus increasing their long-term mortality (10, 11). In recent years, there has been an increasing number of research treatments for pruritus in patients with MD, but with little success (12, 13). Therefore, analysis of the causes of pruritus in DM patients, establishment of a suitable assessment system, and interventions targeting them to evaluate the effects of interventions have great clinical and social significance in improving the quality of life of DP patients.

Based on such a background, this study examines both the causes of pruritus and interventions in patients with T2DM. On the one hand, the causes of pruritus in T2MD patients were analyzed through a survey of pruritus in T2MD patients in our hospital, while on the other hand, different modes of care were applied to patients with pruritus in T2MD who were treated in our hospital, thus helping to control the symptoms of pruritus in DP patients.

METHODS

Subjects of Observation

Two hundred and twenty four patients with T2DM admitted to our hospital from June 2020 to November 2021 were selected and divided into Diabetic pruritus group (DP group, 71 patients) and T2DM group (153 patients) according to the patients' complications of pruritus. Inclusion criteria: 1. The diagnosis of T2DM was based on the 1999 WHO Expert Committee on Diabetes Mellitus diagnostic criteria (14). The diagnosis of DP (15) was based on dermatologic venereology: the patient has only pruritus without an obvious primary rash, which may be accompanied by dry skin, scratching and crusting, and the pruritus lasts for 2 weeks or more. Pruritus may be localized or generalized, including the trunk, lower legs, anus, and perineum. 2. had not applied corticosteroids within 2 weeks prior to admission and had not taken antihistamines or (and) topical corticosteroids within 1 week; 3. gave informed consent to the study care protocol. 4. Occupation for civil servants or retirees. Exclusion criteria: 1. pruritus caused by primary skin conditions such as psoriasis, eczema or atopic dermatitis; 2. patients who have used medication for pruritus or medication that can cause pruritus in the last 30 days; 3. patients with severe liver or renal abnormalities; 4. Patients with combined immune system diseases, Blood system diseases, neurological diseases and malignant tumors; 5. patients with combined severe psychological or psychiatric diseases. At the same time, patients in the DP group were divided into group A (35 cases) and group B (36 cases) using the random number table method, with group A taking conventional nursing measures during hospital treatment and group B taking comprehensive nursing interventions during hospital treatment.

Research Methodology

General information on the patient's gender, age, body mass index (BMI), duration of illness, family history, treatment modalities, other comorbidities [Diabetic peripheral neuropathy (DPN), diabetic retinopathy (DR), diabetic kidney disease (DKD)], underlying illnesses, etc. were collected on the day of admission by means of a medical history enquiry. 10 mL of fasting peripheral venous blood was collected on day 2 after admission, and fasting plasma glucose (FPG), renal function [Serum creatinine (Scr), urea nitrogen (BUN), uric acid (BUA)]

and lipid levels [total cholesterol (TC), triacylglycerol (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C)] were measured.

Treatment Methods

Patients in Groups A and B received the usual symptomatic treatment for DP evidence on admission, including lowering blood glucose (insulin and oral hypoglycaemic drugs), improving vascular microcirculation (prostilbestrol injection), nerve nourishment (methylcobalamin injection), and anti-itch medication such as oven-glycerine lotion or (and) oral loratadine on the itchy skin.

Nursing Care Methods

Group A

Routine nursing programme was adopted, i.e., keeping the room environment clean and quiet with appropriate room temperature and humidity to avoid irritation to the skin by various adverse factors; changing bed sheets and covers regularly to keep them dry and tidy; routine health education and psychological intervention.

Group B

Integrated intensive care interventions were used in Group A's, which included the following. ①Enhance skin care: The patients were instructed not to scratch the itchy areas repeatedly in order to maintain the integrity of the patient's skin and to clean the patient's skin regularly and the patient's family was instructed to relieve the patient's itching symptoms by patting and massaging, while communicating more with the patient to divert his attention. Distract the patient from the itchy skin by playing music, reading, exercising and playing recreational games to avoid or reduce the risk of aggravating the condition by scratching and rubbing, which can cause skin breakdown and infection. It is also important to keep the nails trimmed with curved edges to avoid breaking the skin when scratching. ②Strengthen psychological intervention: Patients with DP were mostly of advanced age and have a long disease duration, and they were prone to tension, anxiety, pessimism and other emotions when they were troubled by symptoms for a long time. Emotional de-escalation of the patient should be reinforced at this time, by communicating positively and enthusiastically with the patient, using empathy and breathing to reduce stress to distract the patient from the illness. Assist patients to develop a correct attitude toward the disease and maintain a good state of mind so that they can actively cooperate with treatment and care. ③Strengthen dietary regimen: High blood sugar can cause itchy skin in patients, so sugar control should be strengthened in the daily diet. Given the patient a high-protein, high-vitamin, low-fiber, easy-to-digest diet, maintain water-electrolyte balance, avoid spicy and stimulating foods and beef, sheep and seafood, and instructed the patient to quit smoking and limit alcohol. ④Strengthen medication care: standardize the medication according to the duration of action of different hypoglycaemic drugs, and monitor blood glucose regularly, pay attention to prevent adverse reactions such as hypoglycaemia and complications such as liver and kidney function impairment, allergy and oedema. If the blood sugar was not well controlled, contact the physician to adjust the treatment plan in a timely manner; if there was hyperalgesia and neuropathy, give the appropriate treatment and care according to the doctor's prescription; as the itching sensation is stronger at night, sleep-promoting drugs can be given. ⑤Strengthening health education: Through PPT lectures, seminars and health education booklets, we explain to the nursing clients the knowledge about pruritus complicated by DM, the serious adverse outcomes that may result from scratching behavior, the importance of active cooperation with treatment and the scientific diet of diabetes, so that the patients can grasp the relevant knowledge and develop health behaviors such as consciously controlling diet, taking medication on time and regularly monitoring blood sugar.

Observation Indicators

Risk Factors

Information on gender, age, body mass index (BMI), disease duration, family history and treatment modality was collected from patients in the pruritus group and the T2DM group, and one-way and multi-way logistic regression analyses were used to explore the main risk factors for T2DM complicating pruritus evidence.

Effectiveness of Care

Information on pruritus scores, lesion healing time and treatment efficiency were collected and compared between the two groups before and after the nursing intervention. Pruritus scores were evaluated using visual analog scoring (VAS) (16). According to the severity of the patient's symptoms, a score from 0 to 10 was assigned from no itching symptoms to severe itching and inability to sleep, respectively, with higher scores indicating more severe itching symptoms. Satisfaction rates were measured using a hospital-made nursing satisfaction questionnaire and patients were surveyed after the nursing intervention The internal consistency Cronbach's α coefficient of the questionnaire was 0.823. The patients were classified into four levels, A, B, C and D, according to their satisfaction with the nursing interventions, representing "very satisfied," "quite satisfied," "average" and "dissatisfied," respectively. The satisfaction rate is the percentage of the sum of the number of cases in each group of A, B and C grades compared with the total number of cases in each group. Treatment efficiency was assessed according to the relevant literature (17, 18). The efficacy of the patients was also divided into four grades, A, B, C, and D, which stand for "cure," "significantly effective," "effective" and "ineffective," respectively, and the total effective rate is the percentage of the total number of cases in grades A, B, and C compared with the total number of cases in each group.

Pruritus Mediator Levels

5 mL of fasting peripheral venous blood was collected from patients before and after the nursing intervention, and the levels of pruritus mediators such as serum substance P, β-endorphin (β-EP) and γ-interferon (INF-γ) were determined by Enzyme-linked immunosorbent assay (ELISA) using a fully automated enzyme-labeled instrument and compared.

TABLE 1 | General information of patients in the DP group compared with the T2DM group [($\bar{x}\pm s$) (n,%)].

Information		DP group (n = 71)	T2DMgroup (n = 153)	t/χ^2value	P-value
Gender	Male	42 (59.15)	87 (56.86)	0.104	0.747
	Female	29 (40.85)	66 (43.14)		
Age (years)		64.52 ± 12.18	58.77 ± 13.26	3.582	<0.001
BMI(kg/m^2)		23.68 ± 5.79	21.81 ± 4.77	2.547	0.012
Duration of DM disease (years	)	13.57 ± 7.64	10.09 ± 8.25	3.006	0.003
Family history of DM	Yes	30 (42.25)	49 (32.03)	2.222	0.136
	No	41 (57.75)	104 (67.97)		
Use of insulin	Yes	60 (84.51)	66 (43.14)	33.726	<0.001
	No	11 (15.49)	87 (56.86)		
Co-morbidities	Hyperlipidaemia	36 (50.70)	47 (30.72)	8.305	0.004
	Hypertension	48 (67.61)	94 (61.44)	0.795	0.373
	Coronary heart disease	14 (19.72)	31 (20.26)	0.009	0.925
Other complications	DPN	48 (67.61)	36 (23.53)	40.198	<0.001
	DR	43 (60.56)	34 (22.22)	31.602	<0.001
	DKD	45 (63.38)	32 (20.92)	38.767	<0.001
Chronic smoking	Yes	31 (43.66)	48 (31.37)	3.208	0.073
	No	40 (56.34)	105 (68.63)		
Alcohol abuse	Yes	26 (36.62)	41 (26.80)	2.232	0.135
	No	45 (63.38)	112 (73.20)		
FPG (mmol/L)		10.46 ± 2.58	7.09 ± 3.24	7.701	<0.001
Scr (μmol/L)		152.58 ± 96.42	80.22 ± 61.20	6.797	<0.001
BUA (μmol/L)		359.74 ± 113.25	303.82 ± 127.51	3.159	0.002
BUN (mmol/L)		10.58 ± 5.23	6.69 ± 3.42	6.642	<0.001
TC (mmol/L)		4.79 ± 2.06	5.17 ± 2.43	1.140	0.255
TG (mmol/L)		3.24 ± 1.52	3.48 ± 1.37	1.178	0.240
HDL-C (mmol/L)		1.14 ± 0.61	1.06 ± 0.70	0.828	0.409
LDL-C (mmol/L)		2.73 ± 1.09	2.90 ± 1.16	1.040	0.300

Statistical Methods

The trial applied EXCEL to collate the relevant data, SPSS 20.0 was applied to calculate the statistical results of the data, and Prism 8.0 was applied to draw the pictures. The measurement data were expressed as mean ± standard deviation (±s), and if the data obeyed normal distribution, the paired t-test was applied to compare the difference between itself before and after treatment within the group, and the t-test of two independent samples was applied to compare the difference between treatment between groups; the count data were expressed as (n,%), and the χ^2 test was used for non-rank count data, and the rank sum test was used for rank data. Logistic regression models were used to analyse the main risk factors for T2DM complicated by pruritus. $P < 0.05$ was taken as statistically significant.

RESULTS

General Information of Patients in the DP Group Compared With the T2DM Group

A comparison of the information collected from DP patients and those with T2DM alone showed statistically significant differences in age, BMI, duration of DM, insulin use, combined hyperlipidaemia, combined DPN, combined DR, combined DKD, and serum levels of FPG, Scr, BUA and BUN ($P < 0.05$). There were no statistically significant differences between the two groups in terms of gender, combined hypertension, combined coronary artery disease, long-term smoking, alcohol abuse, serum levels of TC, TG, HDL-C and LDL-C ($P > 0.05$, see **Table 1** for details).

Single Factor Logistic Regression Analysis of Pruritus in Combined T2DM

Age, BMI, duration of DM, use of insulin, comorbid hyperlipidaemia, comorbid DPN, comorbid DR, comorbid DKD, serum levels of FPG, Scr, BUA and BUN were used as independent variables (see **Table 2** for assignments) and whether the patient had comorbid pruritus (assignments: 0 = no, 1 = yes) was used as the dependent variable in a one-way logistic regression analysis. The results showed that age, duration of DM, combined DPN, combined DR, combined DKD and FPG serum levels may be associated with combined pruritus in patients with T2DM ($P < 0.05$, **Table 3**).

Multivariate Logistic Regression Analysis of Pruritus in Combined T2DM

The indicators with significant differences in the univariate analysis were used as independent variables (assigned as in the univariate analysis), and whether the patients had comorbid pruritus (assigned as in the univariate analysis) was used as the dependent variable in the multivariate logistic regression analysis, and the results showed that age, duration of DM, comorbid DPN, comorbid DR, comorbid DKD and serum FPG level were independent risk factors for combined pruritus in patients with T2DM ($P < 0.05$, **Table 4**).

Comparison of Care Outcomes Between Group A and Group B

The pre-intervention VAS score, post-intervention VAS score, nursing satisfaction rate, and treatment effectiveness rate in group A were (7.49±2.51) points, (4.33 ± 1.60) points, 77.14, and 71.43%, respectively. The pre-intervention VAS score, post-intervention VAS score, nursing satisfaction rate, and treatment effectiveness rate in group B were (7.56 ± 2.63) points, (3.42 ± 1.20) points, 97.22, and 94.44%, respectively. The difference in VAS scores between the two groups before the intervention was not statistically significant ($P > 0.05$), and the VAS scores after the intervention were significantly lower than those before the intervention in both groups ($P < 0.05$). The VAS scores after the intervention in group B were lower than those in group A, and the satisfaction rate of care and treatment efficiency were higher than those in group A, and the difference was statistically significant ($P < 0.05$) (**Figures 1A,B**).

TABLE 2 | Assignment for multivariate analysis of factors.

Influencing factors	Assignment
Age	<65 years = 0, ≥65 years = 1
BMI	<24 kg/m^2 = 0, ≥24kg/m^2 = 1
Duration of DM	No = 0, Yes = 1
Using insulin	No = 0, Yes= 1
Combined hyperlipidaemia	No = 0, Yes = 1
Combined DPN	No = 0, Yes = 1
Combined DR	No = 0, Yes = 1
Combined DKD	No = 0, Yes = 1
FPG	<9 mmol/L = 0, ≥9 mmol/L = 1
Scr	<110 μmol/L = 0, ≥110 μmol/L = 1
BUA	<420 μmol/L = 0, ≥420 μmol/L = 1
BUN	<7.1 mmol/L=0, ≥7.1 mmol/L=1

Comparison of Serum Pruritic Mediator Levels Between Group A and Group B

The serum pruritic mediators levels such as substance P, β-EP and INF-γ in the two groups before and after the intervention were compared. The results were as follows: There was no statistical difference in the levels of serum substance P, β-EP, and INF-γ between the two groups before the nursing intervention. Academic significance ($P > 0.05$). After the nursing intervention, the levels of serum substance P and INF-γ in both groups decreased significantly, and the levels of serum β-EP increased significantly in both groups ($P < 0.05$); the levels of serum substance P and INF-γ in group B after the nursing intervention were significantly lower than those in group A, and the levels of serum β-EP were significantly higher than those in group B ($P < 0.05$) (**Figures 2A–C**).

DISCUSSION

With rising living standards and an aging population, the prevalence of diabetes is increasing worldwide, with serious implications for health systems worldwide. Increased blood glucose causes damage to many types of cells such as endothelial cells, neurons, renal cells, fibroblasts and keratin-forming cells, leading to multisystem damage and various complications, of which pruritus is one of the common complications of DM, accounting for approximately one third of the incidence (19–21). The main clinical manifestations of DP are pruritus, or with

TABLE 3 | Single factor Logistic regression analysis of pruritus in combined T2DM.

Influencing factors	*B*	SE	Walds	OR	95%CI	*P*-value
Age	0.082	0.09	92.245	1.085	1.066∼1.105	<0.001
BMI	0.041	0.030	3.126	1.042	0.982∼1.105	0.071
Duration of DM	0.517	0.159	9.453	1.677	1.228∼2.290	0.002
Using insulin	0.364	0.251	2.015	1.439	0.880∼2.354	0.153
Combined hyperlipidaemia	0.391	0.326	1.025	1.478	0.780∼2.801	0.733
Combined DPN	1.022	0.231	26.38	2.779	1.767∼4.370	<0.001
Combined DR	0.759	0.146	13.597	2.136	1.605∼2.844	<0.001
Combined DKD	0.635	0.158	12.248	1.887	1.384∼2.572	<0.001
FPG	0.543	0.102	10.258	1.721	1.409∼2.102	0.001
Scr	0.151	0.213	0.230	1.630	0.766∼1.766	0.611
BUA	0.058	0.051	0.633	1.060	0.959∼1.171	0.510
BUN	0.129	0.323	0.124	1.138	0.604∼2.143	0.836

TABLE 4 | Multivariate logistic regression analysis of pruritus in combined T2DM.

Influencing factors	*B*	SE	Walds	OR	95%CI	*P*-value
Age	0.074	0.011	40.875	1.077	1.054∼1.100	<0.001
Duration of DM	0.504	0.139	10.146	1.655	1.261∼2.173	0.001
Combined DPN	0.958	0.264	19.330	2.606	1.554∼4.373	<0.001
Combined DR	0.744	0.128	13.112	2.104	1.637∼2.704	<0.001
Combined DKD	0.336	0.106	5.879	1.399	1.137∼1.722	0.011
FPG	0.487	0.125	7.326	1.627	1.274∼2.079	0.009

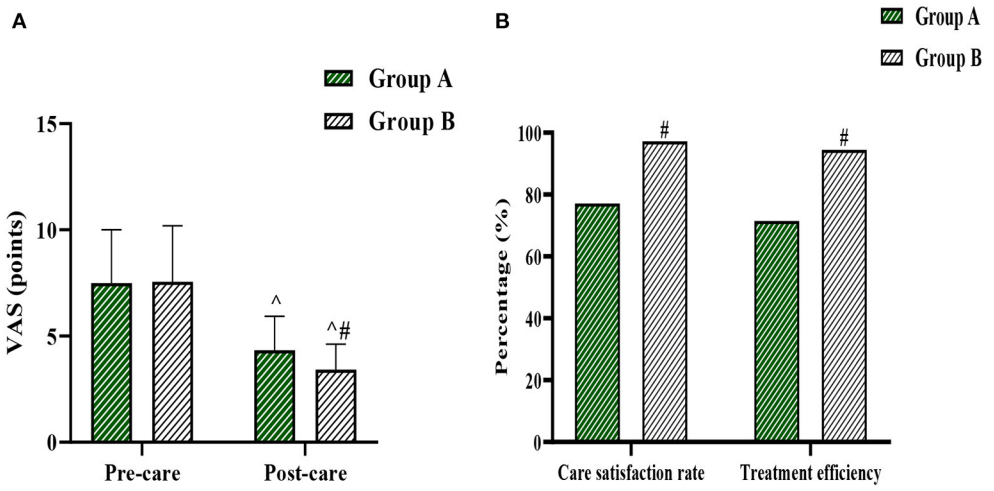


FIGURE 1 | (A) shows the comparison of VAS scores between the two groups, and **(B)** shows the comparison of nursing satisfaction rate and treatment efficiency between the two groups. Compared with the same group before care, $^P < 0.05$, and compared with the same period in Group A, $\#P < 0.05$.

secondary scratching, crusting, hyperpigmentation, secondary eczema-like and mossy lesions. Although these symptoms do not endanger patients' life and health, patients are prone to negative emotions such as anxiety and pessimism, and even rebellious psychology and do not actively cooperate with treatment, which eventually leads to the prolongation and aggravation of the disease. Therefore, it is necessary to improve the behavior and psychology of patients with DP with active and appropriate nursing interventions in the clinical treatment (22, 23). The previous model of care, which was based on symptomatic treatment and compliance with medical advice, lacked specificity and was not effective in the further development of the patient's pruritus condition (24). Moreover, the observation of risk factors for DM complicated by pruritus is still rare in the domestic and international literature, so this study aimed to identify the main risk factors for DM patients complicated by pruritus, in order to provide theoretical guidance for identifying corresponding nursing countermeasures. In addition, T2DM is about 90% of DM patients in China (25), thus the present research was performed focusing on T2DM patients.

The results of this study showed that T2DM patients with high age, high BMI, long duration of DM, insulin use, combined hyperlipidaemia, combined DPN, combined DR, combined DKD, high serum FPG, Scr, BUA and BUN levels had a higher prevalence of pruritus. Further results from a single multifactorial analysis showed that age, duration of DM, combined DPN, combined DR, combined DKD and FPG levels were the main risk factors for pruritus in patients with T2DM. The higher risk of pruritus in elderly T2DM patients may be related to factors such as aging, atrophy and thinning, dryness, reduced function of various glands, poor repair capacity, reduced skin barrier function and susceptibility to external irritation in the elderly population (26). With the prolongation of diabetes, the islet function of T2DM patients gradually declines, making it more difficult to control blood glucose, while poor blood glucose control can further reduce islet function to form a vicious circle (27). When the patient is in hyperglycemic state, the body tissues and plasma are in a hypertonic state, water flows autonomously and diffuses into the tissue fluid or plasma, the skin surface cells undergo dehydration effect, which stimulates the vegetative nerves and nerve endings, thus causing pruritus, and the degree of dry skin and pruritus increases with the increase of water loss (28, 29). Diabetic complications such as DPN, DR and DKD can involve the central nervous system, peripheral nerves and autonomic nerves, causing malfunction of sweat gland secretion. This is manifested by abnormal skin

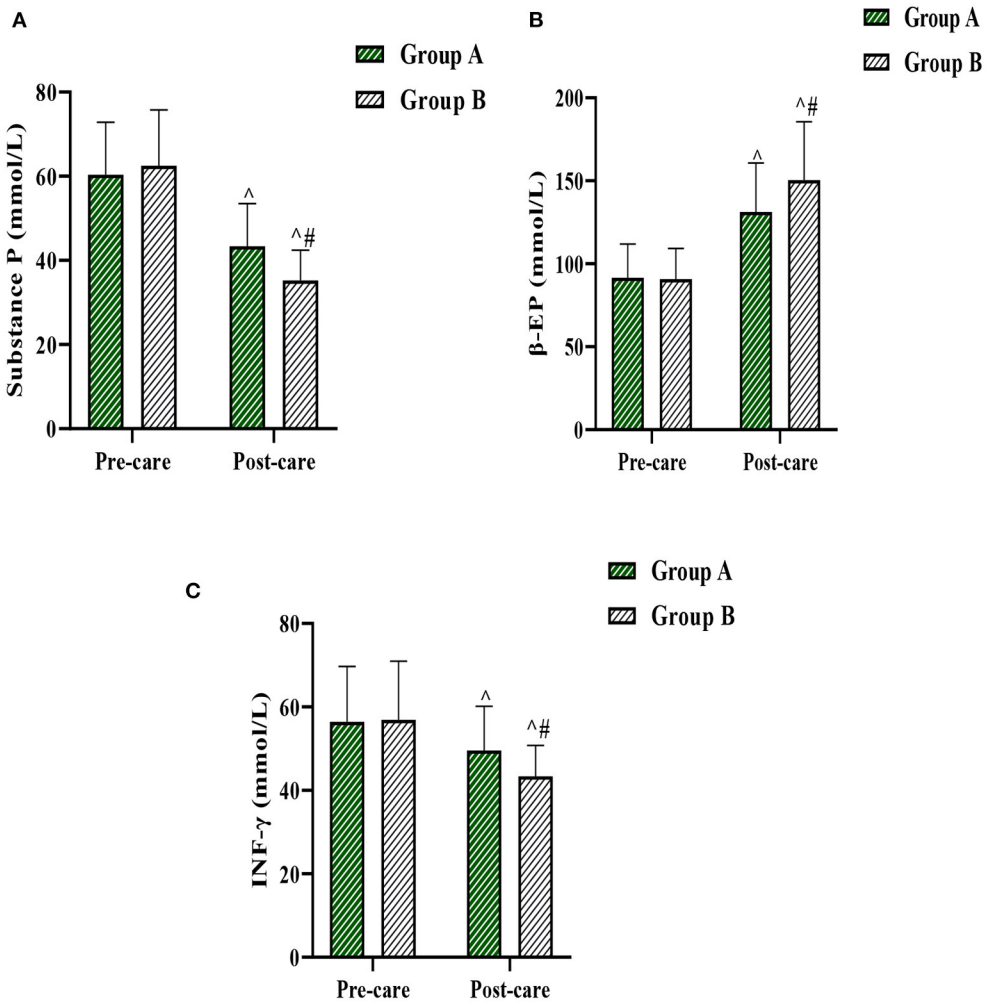


FIGURE 2 | (A–C) represent the comparison of substance P, β-EP and INF-γ levels before and after care in the two groups, respectively. Compared with the same group before care, $^P < 0.05$, and compared with the same period in Group A, $\#P < 0.05$.

perspiration, loss of nourishment of the stratum corneum and dry and damaged skin, which can cause pruritus once it is attacked by microorganisms and external stimuli (30–32). In addition, study (33) showed that the longer the duration of DM, the higher the probability of patients developing complications such as DR, DKD and DPN, further suggesting that the duration of DM is a risk factor for pruritus.

Meanwhile, this study observed the effectiveness of comprehensive care in patients with T2DM complicated by pruritus, and the results showed that satisfaction rate of nursing care, treatment efficiency, post-care improvement in VAS scores, serum substance P, β-EP and INF-γ levels and other mediators of pruritus were better in Group B with integrated nursing intervention than in group A with conventional care only. It is suggested that comprehensive care during the treatment of patients with DP could improve their pruritus symptoms more effectively, reduce the level of serum pruritus mediators, ensure the treatment effect and increase the satisfaction rate of the patients with the care work.

In conclusion, pruritus in patients with T2DM is closely related to age, duration of DM, combined DPN, combined DR, combined DKD and FPG levels, and comprehensive care based on these risk factors can effectively alleviate patients' clinical symptoms and signs, improve the level of pruritus mediators and nurse-patient relationship. However, there are many limitations in this study, such as small sample size and lack of attention to long-term effects, which need to be further explored in the future with a larger sample size and more time, in order to provide a strong reference for the clinical care of patients with DP.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committee of Shenzhen Traditional Chinese Medicine Hospital (The Fourth Clinical Medical School of Guangzhou University of Chinese Medicine). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors have made equal contributions to this study. QY is responsible for the writing of the paper. YC is responsible for the design of the study. ZL is responsible for the collection of cases and the implementation of the study. MX is responsible for the guidance of the whole study. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. *Nat Rev Nephrol.* (2020) 16:377–90. doi: 10.1038/s41581-020-0278-5
2. Eizirik DL, Pasquali L, Cnop M. Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure. *Nat Rev Endocrinol.* (2020) 16:349–62. doi: 10.1038/s41574-020-0355-7
3. Richardson A, Park WG. Acute pancreatitis and diabetes mellitus: a review. *Korean J Intern Med.* (2021) 36:15–24. doi: 10.3904/kjim.2020.505
4. Carracher AM, Marathe PH, Close KL. International diabetes federation 2017. *J Diabetes.* (2018) 10:353–6. doi: 10.1111/1753-0407.12644
5. Sanches MM, Roda Â, Pimenta R, Filipe PL, Freitas JP. Cutaneous manifestations of diabetes mellitus and prediabetes. *Acta Med Port.* (2019) 32:459–65. doi: 10.20344/amp.10738
6. Baldini E, Testa E, Voellenkle C, De Domenico E, Cianfarani F, Martelli F, et al. Dysregulation of microRNA expression in diabetic skin. *J Dermatol Sci.* (2020) 98:186–94. doi: 10.1016/j.jdermsci.2020.04.009
7. Smith A, Watkins T, Theocharidis G, Lang I, Leschinsky M, Maione A, et al. A novel three-dimensional skin disease model to assess macrophage function in diabetes. *Tissue Eng Part C Methods.* (2021) 27:49–58. doi: 10.1089/ten.tec.2020.0263
8. Sani H, Abubakar AB, Bakari AG. Prevalence and pattern of skin diseases in patients with diabetes mellitus at a tertiary hospital in Northern Nigeria. *Niger J Clin Pract.* (2020) 23:970–4. doi: 10.4103/njcp.njcp_95_19
9. De Freitas GR, Ferraz GAM, Gehlen M, Skare TL. Dry eyes in patients with diabetes mellitus. *Prim Care Diabetes.* (2021) 15:184–6. doi: 10.1016/j.pcd.2020.01.011
10. Garcia-Souto F. Localised vulvar and perianal pruritus as the first manifestation of Type 1 diabetes mellitus in a young woman. *Intern Med J.* (2021) 51:305. doi: 10.1111/imj.15192
11. Hussein Z, Aziz NA, Dhanaraj E, Brahmachari B, Kothekar M. Safety and effectiveness of a biosimilar biphasic insulin in the management of diabetes mellitus during routine clinical practice in Asian patients. *Med J Malaysia.* (2020) 75:372–8.
12. Pereira MP, Zeidler C, Storck M, Agelopoulos K, Philipp-Dormston WG, Zink A, et al. Challenges in clinical research and care in pruritus. *Acta Derm Venereol.* (2020) 100:adv00028. doi: 10.2340/00015555-3348
13. Vallely JJ, Hudson KE, Locke SC, Wolf SP, Samsa GP, Abernethy AP, et al. Pruritus in patients with solid tumors: an overlooked supportive care need. *Support Care Cancer.* (2019) 27:3897–904. doi: 10.1007/s00520-019-04693-5
14. Chevenne D, Porquet D. Génétique et critères diagnostiques du diabète sucré [Genetics and diagnostic criteria for diabetes mellitus]. *Ann Biol Clin.* (1999) 57:427–35.
15. Afsar B, Elsurer Afsar R. HbA1c is related with uremic pruritus in diabetic and nondiabetic hemodialysis patients. *Ren Fail.* (2012) 34:1264–9. doi: 10.3109/0886022X.2011.560401
16. Mimouni M, Shamir RR, Cohen AD, El-Yaniv R, Cohen MJ, Joskowicz L, et al. A Comparison of different scoring terminations rules for visual acuity testing: from a computer simulation to a clinical study. *Curr Eye Res.* (2019) 44:790–5. doi: 10.1080/02713683.2019.1589524
17. Serra E, Campo C, Novák Z, Majorek-Olechowska B, Pulka G, García-Bea A, et al. Efficacy and safety of bilastine in reducing pruritus in patients with chronic spontaneous urticaria and other skin diseases: an exploratory study. *J Dermatolog Treat.* (2020) 31:270–8. doi: 10.1080/09546634.2019.1590522
18. Thériné C, Brenaut E, Barnetche T, Misery L. Efficacy of systemic treatments of psoriasis on pruritus: a systemic literature review and meta-analysis. *J Invest Dermatol.* (2018) 138:38–45. doi: 10.1016/j.jid.2017.05.039
19. Viigimaa M, Sachinidis A, Toumpourleka M, Koutsampasopoulos K, Alliksoo S, Titma T. Macrovascular complications of type 2 diabetes mellitus. *Curr Vasc Pharmacol.* (2020) 18:110–6. doi: 10.2174/1570161117666190405165151
20. Noren Hooten N, Evans MK. Extracellular vesicles as signaling mediators in type 2 diabetes mellitus. *Am J Physiol Cell Physiol.* (2020) 318:C1189–99. doi: 10.1152/ajpcell.00536.2019
21. Huang DD, Shi G, Jiang Y, Yao C, Zhu C. A review on the potential of Resveratrol in prevention and therapy of diabetes and diabetic complications. *Biomed Pharmacother.* (2020) 125:109767. doi: 10.1016/j.biopha.2019.109767
22. Sharma S, Schaper N, Rayman G. Microangiopathy: is it relevant to wound healing in diabetic foot disease? *Diabetes Metab Res Rev.* (2020) 36:e3244. doi: 10.1002/dmrr.3244
23. Ramos-Garcia P, Roca-Rodriguez MDM, Aguilar-Diosdado M, Gonzalez-Moles MA. Diabetes mellitus and oral cancer/oral potentially malignant disorders: a systematic review and meta-analysis. *Oral Dis.* (2021) 27:404–21. doi: 10.1111/odi.13289
24. Huang AH, Kaffenberger BH, Reich A, Szepietowski JC, Ständer S, Kwatra SG. Pruritus associated with commonly prescribed medications in a tertiary care center. *Medicines.* (2019) 6:84. doi: 10.3390/medicines6030084
25. Wu CZ, Yuan YH, Liu HH, Li SS, Zhang BW, Chen W, et al. Epidemiologic relationship between periodontitis and type 2 diabetes mellitus. *BMC Oral Health.* (2020) 20:204. doi: 10.1186/s12903-020-01180-w
26. Berger TG, Shive M, Harper GM. Pruritus in the older patient: a clinical review. *JAMA.* (2013) 310:2443–50. doi: 10.1001/jama.2013.282023
27. Murao S, Murao K. Multiple skin ulceration and itch-scratch cycle in a diabetic patient. *J Diabetes Investig.* (2021) 12:2102–3. doi: 10.1111/jdi.13560
28. Hernandez A, Zeidan B, Desai P, Frunzi J. Diabetic ketoacidosis secondary to new onset type 1 diabetes mellitus related to pembrolizumab therapy. *Cureus.* (2021) 13:e13302. doi: 10.7759/cureus.13302
29. Mutsuyoshi Y, Hirai K, Morino J, Kaneko S, Minato S, Yanai K, et al. Idiopathic hypereosinophilic syndrome in hemodialysis patients: case reports. *Medicine (Baltimore).* (2021) 100:e25164. doi: 10.1097/MD.0000000000025164
30. Lehmann M, Cazzaniga S, Simon D, Perruchoud DL, Borradori L, Rammlmair A. Patterns among patients with chronic pruritus: a retrospective analysis of 170 patients. *Acta Derm Venereol.* (2020) 100:adv00068. doi: 10.2340/00015555-3405
31. Stiefelhagen P. Juckreiz, blasen, anhidrose: wie diabetes der haut zusetzt [pruritus, blisters, anhidrosis: how diabetes effects the skin]. *MMW Fortschr Med.* (2012) 154:30. doi: 10.1007/s15006-012-0233-x
32. Ko MJ, Chiu HC, Jee SH, Hu FC, Tseng CH. Postprandial blood glucose is associated with generalized pruritus in patients with type 2 diabetes. *Eur J Dermatol.* (2013) 23:688–93. doi: 10.1684/ejd.2013.2100

33. de Macedo GM, Nunes S, Barreto T. Skin disorders in diabetes mellitus: an epidemiology and physiopathology review. *Diabetol Metab Syndr.* (2016) 8:63. doi: 10.1186/s13098-016-0176-y

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Yang, Chen, Li and Xu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 15 February 2022
doi: 10.3389/fsurg.2022.842047

Clinical Efficacy of Different Thoracoscopic Surgeries for Patients With Non-small Cell Lung Cancer

Tao Wang, Xi Liu†, Lei Chen, Tao Liang and Xiaokuang Ning*

Department of Thoracic Surgery, The First Medical Center of PLA General Hospital, Beijing, China

Background: The aim of this study was to analyze the clinical efficacy of different thoracoscopic procedures in patients with non-small cell lung cancer and their correlation with matrix metalloproteinase-7 mRNA (MMPs-7 mRNA) and soluble major histocompatibility complex class I molecule A (sMICA), as well as their effect on T-cell subsets.

Methods: A total of 100 patients with non-small cell lung cancer who received different thoracoscopic surgeries were divided into the Control group (three-port thoracoscopic surgery) and the study group (single-port thoracoscopic surgery). The two groups were evaluated to compare the perioperative indicators, MMPs-7 mRNA, sMICA expression levels, T-cell subsets, postoperative pain, complication rates, and prognostic outcomes at 1-year follow-up.

Results: The operation time, blood loss, drainage tube placement time, incision length, and hospital stay in the study group were less than those in the control group ($P < 0.05$). There was no significant difference in the number of lymph node dissections between the two groups ($P > 0.05$). After 3 days, the expression levels of MMPs-7 mRNA and sMICA in the study group were lower than those in the control group ($P < 0.05$); CD4 +, CD8 +, and CD4 +/CD8 + in the study group were higher than those in the control group ($P < 0.05$). On days 1, 3, and 5, the visual analog score (VAS) of the study group was lower than that of the control group ($P < 0.05$); there was no significant difference in the complication rate between the two follow-up groups ($P > 0.05$), in which all patients completed the follow-up. After 1 year of follow-up, there was no significant difference in the tumor-free survival rate and overall survival rate between the two groups ($P > 0.05$).

Conclusion: Compared with three-port thoracoscopic surgery, single-port thoracoscopic surgery can improve perioperative expression, shorten hospital stay, reduce serum tumor micrometastasis levels, improve immune metastasis mechanisms and reduce pain, which is of great significance to patients with non-small cell lung cancer. It is an effective, convenient, and safe surgical option that deserves wide clinical reference.

Keywords: non-small cell lung cancer, single-port thoracoscopic surgery, three-port thoracoscopic surgery, MMPs-7 mRNA, sMICA, T cell subsets

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Pengyun Wang,
Xian Hospital of Traditional Chinese Medicine, China
Weiguo Wang,
Affiliated Hospital of Shandong University of Traditional Chinese Medicine, China

****Correspondence:***
Tao Wang
tao428139170373@126.com

†These authors have contributed equally to this work

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *23 December 2021*
Accepted: *17 January 2022*
Published: *15 February 2022*

Citation:
Wang T, Liu X, Chen L, Liang T and Ning X (2022) Clinical Efficacy of Different Thoracoscopic Surgeries for Patients With Non-small Cell Lung Cancer. Front. Surg. 9:842047. doi: 10.3389/fsurg.2022.842047

INTRODUCTION

Lung cancer has become one of the malignant tumor diseases that seriously endanger human health and safety in China, and the incidence rate is increasing year by year. According to incomplete statistics, the incidence of lung cancer accounts for about 82% of the total incidence of lung cancer, with a high risk of death (1). At present, surgery, chemoradiotherapy, and other treatments are mostly advocated in clinical practice, of which surgery can play an ideal role in early cell lung cancer. With the development of medical technology in recent years, thoracoscopic surgery has been introduced, which has the advantages of less trauma, high safety, and rapid recovery, and has become the standard for cell lung cancer (2). In the past, three-hole thoracoscopic surgery was commonly used. Although it could achieve a certain effect, the incisions are large and significantly traumatic, with significant post-operative pain. With the continuous penetration of the minimally invasive concept, single-hole thoracoscopic surgery has emerged, fully reflecting the advantages of minimally invasive techniques (3). Metalloproteinase-7 mRNA (MMPs-7 mRNA), soluble major histocompatibility complex class I molecule A (sMICA), and T-cell subsets are correlated with lung cancer staging and prognosis. In view of this, this study analyzed the clinical efficacy of different thoracoscopic procedures for non-small cell lung cancer patients and their effects on MMPs-7mRNA, sMICA, and T-cell subsets to provide a theoretical basis for the subsequent clinical selection of the appropriate surgical approach.

MATERIALS AND METHODS

General Information

This study was approved by the ethics committee of the Chinese People's Liberation Army (PLA) General Hospital. A total of 100 patients with non-small cell lung cancer admitted to our hospital from December 2018 to December 2019 were selected and treated with different thoracoscopic surgery for non-small cell lung cancer. They were divided into control group and study group according to different perforations, 50 cases for each group. By calculating the baseline data of the two groups, statistical analysis showed $p > 0.05$, which has a comparable value. Refer to **Table 1** for details.

TABLE 1 | The baseline data of the two groups.

	Control group ($n = 50$)	Study group ($n = 50$)	X^2/t-value	P-value
Age (years)	63.15 ± 10.90	64.03 ± 11.18	0.399	0.691
Gender (male/female)	31/19	30/20	0.042	0.838
TNM stage				
Stage I	31	29	0.181	0.914
Stage II	13	14		
Stage III	6	7		
Differentiation				
Poorly differentiated	5	4	0.204	0.903
Moderately differentiated	36	35		
Well differentiated	9	11		

Inclusion Criteria

(1) All patients have been diagnosed with non-small cell lung cancer and meet the indications of video-assisted thoracoscopic surgery; (2) No metastasis was found by imaging examination before operation; (3) All patients have not received radiotherapy or chemotherapy before operation; (4) The postoperative tumor-node-metastasis (TNM) stage was I-III; (5) All patients signed informed consent and participated voluntarily.

Exclusion Criteria

(1) Those whose expected survival time was <6 months; (2) Those had severe mental illness history, Alzheimer's disease, or poor sense of self-cooperation; (3) Patients had severe heart, liver, and kidney insufficiency; (4) Those had coagulation dysfunction; (5) there is a history of other thoracic operations; (6) Patients were encountered other malignant tumors.

Surgical Methods

The study group underwent single-hole thoracoscopic surgery for non-small cell lung cancer, guided patients to take healthy lateral positions, performed tracheal intubation general anesthesia, and confirmed one-lung ventilation after satisfactory anesthesia. An incision with a length of about 3 cm was made between the L4 or L5 ribs at the front axillary line, and the elastic rubber protective sleeve was placed in the hole as the operation hole. Then an incision with a length of about 1.5 cm was made between the L7 ribs at the back axillary line, and Trocar trocar was placed as the observation hole. Under the direct vision of the thoracoscope, the lung lobe (segment) was removed, and the hilar and mediastinal lymph nodes were dissected. The pathological specimens were sent for inspection, and the drainage tube was indwelling.

The control group received three-hole thoracoscopic non-small cell lung cancer surgery. Under the operation of the study group, an auxiliary operation hole was added, that is, an incision of about 2 cm in length was made in the L7 or L8 intercostal space of the subscapular corner line as the auxiliary operation hole, and exposure and traction were performed through the auxiliary operation hole. Under the direct thoracoscopic vision, the lobe (segment) was removed, and hilar and mediastinal lymph node dissection procedures were completed, the pathological specimen was submitted for examination, a drainage tube was indwelled, and the operation was completed.

TABLE 2 | Comparison of perioperative indexes between the two groups (X ± s, $n = 50$).

Group	Operative Time (min)	Intraoperative blood loss (ml)	Drain Placement Time (d)	Incision length (cm)	Hospital stay (d)	Number of dissected lymph nodes (pieces)
Study group	119.86 ± 9.12	124.65 ± 8.04	4.76 ± 1.02	4.19 ± 0.51	7.86 ± 1.37	13.45 ± 3.99
Control group	150.01 ± 11.36	158.11 ± 11.92	6.99 ± 1.13	10.08 ± 1.22	9.70 ± 1.25	14.70 ± 4.10
t	14.634	16.456	10.359	31.497	7.016	1.545
P	0.000	0.000	0.000	0.000	0.000	0.126

TABLE 3 | Comparison of MMPs-7 mRNA and sMICA expression levels between the two groups ($\bar{X} \pm s$).

Group	*N*	MMPs-7 mRNA		SMICA (pg/mL)	
		Pre-op	3 d after operation	Pre-op	3 d after operation
Study group	50	29.30 ± 7.16	20.38 ± 4.49	382.61 ± 81.45	291.49 ± 65.28
Control group	50	30.15 ± 6.94	24.51 ± 6.40	379.22 ± 82.06	322.13 ± 74.50
t	-	0.603	3.736	0.207	2.187
P	-	0.548	0.000	0.836	0.031

TABLE 4 | Comparison of T cell in the two groups ($\bar{X} \pm s$).

Group	*N*	Operation time	CD4 + (%)	CD8 + (%)	CD4 +/CD8 +
Study group	50	Pre-op	42.30 ± 2.89	38.65 ± 4.27	1.21 ± 0.23
		3d after operation	40.18 ± 4.16	27.70 ± 3.51	1.46 ± 0.19
Control group	50	Pre-op	41.65 ± 3.11	39.27 ± 3.30	1.22 ± 0.35
		3d after operation	32.23 ± 2.83	38.30 ± 2.40	0.96 ± 0.24
Intra-group comparison (*t*/*p*)	-	1.564/0.121	1.215/0.227	1.185/0.239	
Comparison in control group (*t*/*p*)	-	10.964/0.000	12.078/0.000	4.332/0.000	
Three days after operation, intra-group comparison (*t*/*p*)	-	7.097/0.000	8.980/0.000	4.620/0.000	

Observation Indicators

(1) We evaluated and compared the perioperative indicators of the two groups, and recorded the operation time, blood loss, drainage tube placement time, incision length, number of lymph node dissections, and hospital stay. (2) The expression of MMPs-7mRNA and sMICA were measured by RT-PCR and ELISA, respectively, before and 3 days after the operation. (3) T-cell subsets, CD4 +, CD8 +, and CD4+/CD8 + were measured and recorded by flow cytometry before and 3 days after the operation. (4) Visual analog scale (VAS) was used for postoperative pain degree, and the highest score was 10 points. The higher the score, the stronger the pain. (5) We record the postoperative complication rate of patients. (6) Prognostic results were followed up for 1 year. All patients were followed up throughout the whole process. The tumor-free survival rate and overall survival rate were counted after 1-year follow-up.

Statistical Analysis

The data were analyzed by SPSS 22 software (IBM, Armonk, NY, USA), and the measurement data were tested by *t*-tests. The Chi-square test was used for counting data, and $P < 0.05$ was statistically significant.

RESULTS

Comparison of Indicators Between the Two Groups

The operation time, blood loss, drainage tube placement time, incision length, and hospitalization time in the study group were less than those in the control group ($P < 0.05$). There was no significant difference in the number of lymph node dissections between the two groups ($P > 0.05$). Refer to **Table 2** for details.

Comparison of MMPs-7 MRNA and SMICA Expression Levels Between the Two Groups

On the 3rd day after the operation, the values of MMPs-7mRNA and sMICA in the study group were lower than those in the control group ($P < 0.05$). Refer to **Table 3** for details.

Comparison of T Cells Between the Two Groups

The levels of CD4 +, CD8 +, and CD4+/CD8 + in the study group were higher than those in the control group on the 3rd

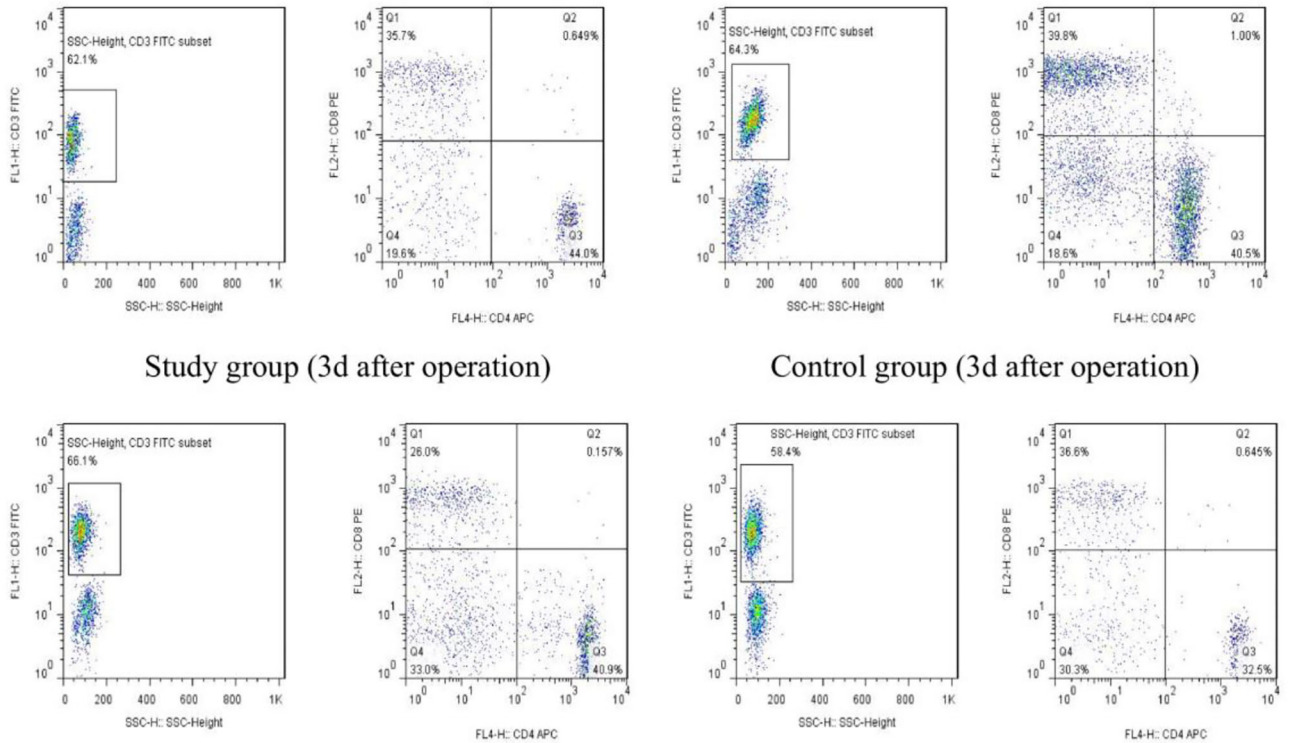


FIGURE 1 | The changes of T-cell subsets (CD4 + and CD8 +) in the observation group and the control group were detected by flow cytometry before and 3 days after the operation.

day after the operation (P <0.05). Refer to **Table 4**, **Figure 1** for details.

Comparison of VAS Score Between the Two Groups

On the 1st, 3rd, and 5th day after surgery, the VAS of the study group was lower than that of the control group ($P < 0.05$). Refer to **Table 5** for details.

Comparison of Postoperative Complication Rate Between the Two Groups

There was no significant difference in the complication rate between the two groups ($P > 0.05$). Refer to **Table 6** for details.

Comparison of Prognostic Results Between the Two Groups After 1-Year Follow-Up

All patients were followed up for 1 year. There was no significant difference in tumor-free survival rate and overall survival rate between the two groups ($P > 0.05$). Refer to **Table 7** for details.

DISCUSSION

Non-small cell lung cancer is characterized by high morbidity and high mortality, and minimally invasive surgery has become the first choice for the treatment of non-small cell lung cancer (4). It has been pointed out that for early-stage lung cancer patients, the clinical treatment effect of video-assisted thoracoscopic surgery is similar to that of traditional open-heart surgery, but video-assisted thoracoscopic surgery has the advantages of the clear and wide surgical field, small incision, low complication rate, and short recovery time, which are widely used in the treatment of lung cancer (5). In recent years, with the improvement, optimization, and development of video-assisted thoracoscopic techniques, three-hole video-assisted thoracoscopic lobectomy has achieved good results in the treatment of early-stage lung cancer. This procedure has the advantages of ease of operation, high visibility, and good exposure. However, the accessory surgical hole was found to be in a special location between the L7 or L8 ribs in the subscapularis angle line. This area is distributed with many muscle groups and has a small intercostal space, making it prone to intraoperative bleeding and injury, as well as postoperative pain in the posterior chest wall (6–8). In addition, the length of the three-hole incision is large, which will undoubtedly form postoperative scars, thus

TABLE 5 | Comparison of VAS scores between the two groups ($\bar{X} \pm s$, min).

Group	*N*	1d after operation	3rd day after operation	5th day after operation
Study group	50	3.09 ± 1.05	1.98 ± 0.70	1.02 ± 0.44
Control group	50	4.87 ± 1.42	3.26 ± 1.31	2.69 ± 1.05
t	-	7.127	3.094	10.373
P	-	0.000	0.000	0.000

TABLE 6 | Comparison of postoperative complication rate between the two groups [*n* (%)].

Group	*N*	Wound infection	Atelectasis	Pneumothorax	Complication Rate
Study group	50	2 (4.00)	1 (2.00)	1 (2.00)	4 (8.00)
Control group	50	3 (6.00)	2 (4.00)	0 (0.00)	5 (10.00)
X^2	-	0.421	0.687	2.020	0.244
P	-	0.516	0.407	0.155	0.621

TABLE 7 | Comparison of 1-year follow-up outcomes between the two groups [n (%)].

Group	*N*	Tumor free survival	Overall survival
Study group	50	49 (98.00)	50 (10.00)
Control group	50	48 (96.00)	50 (100.00)
X^2	-	0.687	-
P	-	0.407	-

affecting the aesthetics. With the development of minimally invasive technology and increasing the research on non-small cell lung cancer, single-hole thoracoscopic lobectomy was born. As early as 2005, some studies clearly pointed out that single-hole thoracoscopic lobectomy for early lung cancer has high feasibility and safety (9). After research and analysis, the main reason is that the operation is done at L4 or L5 intercostal space in the axillary front line, where the intercostal space is relatively wide and the muscle group is not abundant, so the risk of bleeding and injury is reduced to a certain extent (10). The operation time and the incision length of single-hole thoracoscopic surgery are short, and it is difficult to form obvious scars after the operation, which meets the aesthetic requirements of patients. In addition, the operation is a single-hole operation, which can effectively avoid muscle injury and nerve damage caused by the auxiliary operation hole, speed up the postoperative rehabilitation progress, and shorten the hospitalization time (11).

However, no matter what kind of operation, it will cause a stress reaction of the body, which will lead to the decline of immune function, thus prone to infection and tumor micrometastasis. Especially for tumor patients, immune function can determine the spread, recurrence, and recovery progress of tumors after the operation (12). Therefore, reducing the stress response and improving immunity are particularly critical to reducing the level of tumor micrometastasis factors.

This study shows that the operation time, blood loss, drainage tube placement time, incision length, and hospitalization time of the study group were less than those of the control group. It is suggested that compared with three-hole thoracoscopic surgery, single-hole thoracoscopic surgery for non-small cell lung cancer has a shorter operation time, can reduce intraoperative bleeding, ensure early extraction of the drainage tube, and has shorter incision length, which is beneficial to rapid healing of the incision and less hospital stay. There was no significant difference in the number of lymph node dissections between the two groups, suggesting that the number of lymph node dissections in three-hole thoracoscopic surgery was similar to that in single-hole thoracoscopic surgery. According to the data, postoperative tumor micrometastasis will be affected by extracellular matrix remodeling, immune mechanism, and other aspects, and has a close relationship with the prognosis of patients with non-small cell lung cancer (13, 14). Through tumor cytology examination, MMP-7 was highly expressed in patients with tumor (15). During the apoptosis of tumor cells, MICA protein on the cell surface falls off and finally forms sMICA, which can hinder the killing activity of T cell subsets (CD8 +) (16). Three days after the operation, the values of MMPs-7mRNA and sMICA in the study group were lower than those in the control group, suggesting that the expression level of serum tumor micrometastasis factor can be reduced by single-port thoracoscopic surgery for non-small cell lung cancer, thus ensuring the improvement of tumor metastasis microenvironment. It has been reported that T lymphocyte subsets can accurately reflect cellular immune function (17). CD4 +, CD8 +, and CD4+/CD8 + in the study group were higher than those in the control group, suggesting that single-port thoracoscopic surgery for non-small cell lung cancer can effectively protect cellular immune function. The main reason is that single-hole thoracoscopic surgery has a short operation time and less bleeding, which can obviously reduce the impact on the immune mechanism of the body (18). In addition, this operation has less trauma, and at the same time, it can effectively preserve the integrity of the thorax, avoid muscle and nerve damage, and

has a low-stress response, which can promote the immunity to return to normal (19, 20). On the 1st, 3rd, and 5th day after the operation, the VAS of the study group was lower than that of the control group, suggesting that the application of single-hole thoracoscopic surgery for non-small cell lung cancer can reduce the postoperative pain, relieve its pain and improve the surgical tolerance and compliance. There is no significant difference in complication rate between the two groups, suggesting that three-hole/single-hole thoracoscopic surgery for non-small cell lung cancer is not easy to cause postoperative complications such as incision infection, atelectasis, and pneumothorax, and the operation is safe. All patients were followed up for 1 year. There was no significant difference in tumor-free survival rate and overall survival rate between the two groups, suggesting that there was no significant difference in the influence of different thoracoscopic surgery on the 1-year survival rate after surgery. However, in this study, the number of samples is small, the follow-up time is short, and there is no comparison of long-term recurrence and metastasis of single-hole/three-hole thoracoscopic surgery for non-small cell lung cancer. In the future, it is necessary to expand the sample size and extend the follow-up time to further confirm the practical application value of the above two operations.

CONCLUSIONS

In conclusion, compared with three-port thoracoscopic surgery, single-port thoracoscopic surgery in patients with non-small cell lung cancer can optimize perioperative indicators, shorten hospital stay, reduce the expression level of serum tumor micrometastatic factors, improve immune mechanisms, and be less painful. It is of great significance for patients with non-small cell lung cancer and is an effective, convenient, and safe surgical option, which is worthy of extensive clinical reference.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of PLA General Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TW and XL designed the study and prepared the manuscript. LC and TL collected the data. TW, XL, and XN analyzed the data. All authors read and approved the final manuscript.

REFERENCES

1. Wang J, Fu J, Shen Q, Zhang F, Wang Y, Wu LL. Identification and diagnostic value of pleural fluid periostin and serum periostin of malignant pleural effusions in patients with non-small-cell lung cancer. *J Clin Lab Anal.* (2019) 33:e22943. doi: 10.1002/jcla.22943
2. Ma M, He F, Lv X, Wang X, Dong S, Liu C, et al. Feasibility and effectiveness of thoracoscopic pulmonary segmentectomy for non-small cell lung cancer. *Medicine.* (2020) 99:e18959. doi: 10.1097/MD.0000000000018959
3. Schneider T, Hoffmann H, Dienemann H, Herpel E, Heussel CP, Enk AH, et al. Immune response after radiofrequency ablation and surgical resection in nonsmall cell lung cancer. *Semin Thorac Cardiovasc Surg.* (2016) 28:585–92. doi: 10.1053/j.semtcvs.2016.02.008
4. Xu Q, Shi NJ, Zhang H, Zhu YM. Effects of combined general-epidural anesthesia and total intravenous anesthesia on cellular immunity and prognosis in patients with nonsmall cell lung cancer: a comparative study. *Mol Med Rep.* (2017) 16:4445–54. doi: 10.3892/mmr.2017.7144
5. Bendixen M, Jorgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. *Lancet Oncol.* (2016) 17:836–44. doi: 10.1016/S1470-2045(16)00173-X
6. Ye Z, Zhang B, Chen Y, Lin J. Comparison of single utility port video-assisted thoracoscopic surgery (VATS) and three-port VATS for non-small cell lung cancer. *Oncol Lett.* (2019) 18:1311–7. doi: 10.3892/ol.2019.10394
7. Yang SM, Hsu HH, Chen JS. Recent advances in surgical management of early lung cancer. *J Formos Med Assoc.* (2017) 116:917–23. doi: 10.1016/j.jfma.2017.07.009
8. Tsyganov MM, Rodionov EO, Pevzner AM, Ibragimova MK, Miller SV, Cheremisina OV, et al. Prognostic significance of ERCC1, RRM1, TOP1, TOP2A, TYMS, TUBB3, GSTP1 AND BRCA1 mRNA expressions in patients with non-small-cell lung cancer receiving a platinum-based chemotherapy. *J Buon.* (2020) 25:1728–36.
9. Mimae T, Okada M. Are segmentectomy and lobectomy comparable in terms of curative intent for early stage non-small cell lung cancer? *Gen Thorac Cardiovasc Surg.* (2020) 68:703–6. doi: 10.1007/s11748-019-01219-y
10. Cao J, Yuan P, Wang Y, Xu J, Yuan X, Wang Z, et al. Survival rates after lobectomy, segmentectomy, and wedge resection for non-small cell lung cancer. *Ann Thorac Surg.* (2018) 105:1483–91. doi: 10.1016/j.athoracsur.2018.01.032
11. Sotiropoulos GP, Kotopouli M, Karampela I, Christodoulatos GS, Antonakos G, Marinou I, et al. Circulating plasminogen activator inhibitor-1 activity: a biomarker for resectable non-small cell lung cancer? *J Buon.* (2019) 24:943–54.
12. Ishikawa Y, Kojima F, Ishii T, Yoshiyasu N, Ohde S, Bando T. Early postoperative inflammatory response by procedure types: stapler-based segmentectomy versus lobectomy. *Gen Thorac Cardiovasc Surg.* (2020) 68:280–6. doi: 10.1007/s11748-019-01214-3
13. Luo QQ, Lin H, Tan Q, Huang J, Xu L. Analysis of clinical application of thoracoscopic lobectomy for lung cancer. *World J Surg Oncol.* (2014) 12:157. doi: 10.1186/1477-7819-12-157
14. Mizukami Y, Takahashi Y, Adachi H. Single-port vs. conventional three-port video-assisted thoracoscopic pulmonary wedge resection: comparison of postoperative pain and surgical costs. *Ann Thorac Cardiovasc Surg.* (2021) 27:91–6. doi: 10.5761/atcs.oa.20-00142
15. Li X, Niu C, Chen Q, Chen X. Comparison of efficacy of stereotactic body radiotherapy and thoracoscopic surgery in the treatment of early-stage non-small cell lung cancer. *J Buon.* (2020) 25:1497–503.
16. Aokage K, Yoshida J, Hishida T, Tsuboi M, Saji H, Okada M, et al. Limited resection for early-stage non-small cell lung cancer as function-preserving radical surgery: a review. *Jpn J Clin Oncol.* (2017) 47:7–11. doi: 10.1093/jjco/hyw148

17. Chen L, Fang W. [A Review on comparison of lobectomy and segmentectomy in the treatment of early stage non-small cell lung cancer]. *Zhongguo Fei Ai Za Zhi.* (2019) 22:526–31. doi: 10.3779/j.issn.1009-3419.2019.08.08
18. Tsukazan M, Terra RM, Vigo A, Fortunato GA, Camargo SM, de Oliveira HA, et al. Video-assisted thoracoscopic surgery yields better outcomes than thoracotomy for anatomical lung resection in Brazil: a propensity score-matching analysis using the Brazilian society of thoracic surgery database. *Eur J Cardiothorac Surg.* (2018) 53:993–8. doi: 10.1093/ejcts/ezx442
19. Erdogu V, Akin H, Sonmezoglu Y, Kutluk AC, Sezen CB, Dogru MV, et al. Comparison of the video-assisted thoracoscopic lobectomy versus open thoracotomy for primary non-small cell lung cancer: single cohort study with 269 cases. *Sisli Etfal Hastan Tip Bul.* (2020) 54:291–6. doi: 10.14744/SEMB.2020.60963
20. Begum SS, Papagiannopoulos K, Falcoz PE, Decaluwe H, Salati M, Brunelli A. Outcome after video-assisted thoracoscopic surgery and open pulmonary lobectomy in patients with low VO2 max: a case-matched analysis from the ESTS databasedagger. *Eur J Cardiothorac Surg.* (2016) 49:1054–8. doi: 10.1093/ejcts/ezv378

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang, Liu, Chen, Liang and Ning. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 15 February 2022
doi: 10.3389/fsurg.2022.839523

Effects of Transient Electrical Acupuncture Stimulation Combined With Rehabilitation Training on Hemorheology, Neurological Function and BDNF in Patients With Cerebral Infarction

Shuangqin Chen[1], *Jianghua Huang*[1], *Xuan Tang*[1], *Ting Wang*[2] *and Yahua Zeng*[2]*

[1] *The First Affiliated Hospital, Department of Neurology, Hengyang Medical School, University of South China, Hengyang, China,* [2] *The First Affiliated Hospital, Department of Rehabilitation, Hengyang Medical School, University of South China, Hengyang, China*

Objective: To explore the effects of transient electric acupuncture stimulation combined with rehabilitation training on hemorheology, neurological function and brain-derived neurotrophic factor (BDNF) in patients with cerebral infarction (CI).

Methods: A total of 90 patients with CI were admitted to our hospital from March 2019 to March 2021. According to the random number table method, 90 patients were divided into a control group (was treated with transient electrical acupuncture stimulation intervention treatment) and a therapy group (was treated with rehabilitation training on the basis of the control group), with 45 cases in each group. NIHSS score to detect neurological deficit; FMA score to detect motor function recovery; the clinical efficacy of the two groups of patients were compared; blood rheology analyzer to detect whole blood high shear viscosity, whole blood low shear viscosity, platelet aggregation rate and fibrinogen indicators; ELISA detects the content of BDNF in serum.

Results: There was no significant difference in NIHSS score, FMA score, clinical efficacy, hemorheology index, and BDNF content between the two groups of patients before treatment ($P > 0.05$). After treatment, the NIHSS score, whole blood high shear visible, whole blood low shear visible, platelet aggregation rate and fibrinogen index of the two groups were lower than those before treatment, and the FMA score and BDNF content of the two groups were higher than those before treatment, and all the above indicators in the therapy group changed significantly compared with the control group ($P < 0.05$). After treatment, the clinical efficacy of the therapy group was better than that of the control group ($P < 0.05$).

Conclusion: The combination of transient electrical acupuncture stimulation and rehabilitation training can inhibit the blood flow index of patients with CI, improve the nerve function, increase the content of BDNF in the patient's serum, and restore the patient's nerve function.

Keywords: instantaneous electrical acupuncture stimulation, rehabilitation training, cerebral infarction, hemorheology, nerve function, BDNF

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Jing Xu,
Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, China
Qiang Wang,
Guizhou University, China

***Correspondence:**
Yahua Zeng
14129465@qq.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *20 December 2021*
Accepted: *13 January 2022*
Published: *15 February 2022*

Citation:
Chen S, Huang J, Tang X, Wang T and Zeng Y (2022) Effects of Transient Electrical Acupuncture Stimulation Combined With Rehabilitation Training on Hemorheology, Neurological Function and BDNF in Patients With Cerebral Infarction. Front. Surg. 9:839523. doi: 10.3389/fsurg.2022.839523

INTRODUCTION

Cerebral infarction (CI), also known as ischemic stroke, accounts for 65–70% of the total number of strokes in my country, and is an acute and critical illness of cerebrovascular disease. Cerebral infarction is mainly due to cerebral hemodynamic disturbance and local brain tissue is in a state of ischemia and hypoxia, which can cause serious damage to the neurological function of the brain of patients (1). With the improvement of the modern medical level, although vascular interventions and thrombolysis can reperfuse brain tissue to a certain extent, thus effectively reducing the degree of cerebral ischemia and hypoxia, yet the endurance of nerve cells to ischemia and hypoxia is very low. Poor, more than 75% of patients with CI still have different degrees of dysfunction even after the brain tissue is restored to perfusion, which seriously affects the quality of life of the patients. While posing a great threat to the physical and mental health of patients, it also places varying degrees of burden on patients, families and society (2). A large number of studies have shown that the human brain has strong plasticity. Rehabilitation training can increase the expression level of nerve growth factor in patients with CI, stimulate the auxiliary motor cortex, and improve brain function, thereby restoring or partially restoring the control of the brain to the subcortical center and improving the motor function of the limbs (3, 4). Electroacupuncture is an important supplement/alternative treatment for cerebrovascular diseases and is widely used in clinical practice. Electroacupuncture regulates the yin and yang meridians by stimulating acupoints, and achieves the balance between yin and yang by the mutual aid of yin and yang (5). It has been confirmed that electroacupuncture combined with exercise training has a significant synergistic effect in the treatment of postoperative motor dysfunction after CI. Brain-derived neurotrophic factor (BDNF) is one of the most representative members of the nerve growth factor family. It is a basic protein with a relative molecular weight of 12,300, with the highest content in the hippocampus (6). BDNF is closely related to CI. It can promote the survival, development, differentiation and repair of a variety of neurons, promote synaptic plasticity, and participate in the enhancement of long-term memory (7). In this study, combined use of transient electrical acupuncture stimulation combined with rehabilitation training to observe its effects on hemorheology, neurological function and BDNF in patients with CI.

MATERIALS AND METHODS

General Information and Grouping

A total of 90 patients with CI were selected in our hospital from March 2019 to March 2021. According to the random number table method, 90 patients were divided into a control group and a therapy group, with 45 cases in each group. All patients met the relevant diagnostic criteria for CI in our hospital. There was no statistically significant difference between the two groups of patients in general information such as age, course of disease, and pathological location ($P > 0.05$), (**Table 1**).

TABLE 1 | Comparison of general information between the two groups of patients.

Items	Control group ($n = 45$)	Therapy group ($n = 45$)	t/χ^2	P
Age (years old)	60.30 ± 5.40	61.22 ± 5.34	0.813	0.419
Course of disease (months)	1.32 ± 0.45	1.29 ± 0.43	0.323	0.747
Male/female (cases)	23/22	21/24	0.178	0.673
Pathological location (cases)			0.184	0.912
Basal ganglia CI	21	23		
Internal capsule infarction	15	14		
Middle CI	9	8		
Basic diseases (cases)			0.239	0.971
Hypertension	17	15		
Diabetes	10	11		
Coronary heart disease	7	8		
Hyperlipidemia	11	11		
Complication (cases)			0.479	0.787
Numbness or paralysis of limbs	24	22		
Aphasia	12	15		
Coughing and dysphagia	9	8		

Inclusion and Exclusion Criteria

Inclusion Criteria

Meeting the definition of acute ischemic stroke as defined by the American Association of Neurological Surgeons (8); Patients with stable vital signs; The age was less than 80 years old; Presence of physical dysfunction; Patients voluntarily participated and signed an informed consent form.

Exclusion Criteria

Patients with previous history of mental illness or symptoms of dementia; Patients with neurological deficit symptoms or other diseases, such as hemorrhagic stroke, encephalitis, etc.; Patients with cardiogenic cerebral embolism; Patients with malignant tumors, severe heart, liver and kidney dysfunction, blood system and other diseases; Patients with incomplete medical history data; Acupuncture and other related treatment contraindications.

Treatment Methods

After admission, medical personnel should give all patients basic treatments such as blood pressure management, brain protection agents, improvement of patients' cerebral blood circulation, and anti-platelet aggregation.

Control Group

The patients were given transient electrical acupuncture stimulation intervention treatment. Transient electrical acupuncture stimulation: According to the diagnosis of brain damage, the scalp acupuncture and body acupuncture points were diagnosed. The scalp acupuncture points were the motor area, sensory area, superior temporal gyrus, transverse gyrus and lower gyrus of scalp acupuncture. Acupuncture points for body acupuncture, Lianquan, Tinggong, Yifeng, Fengchi, Jiquan and Neiguan of the paralyzed upper limbs, Shenshu, Huantiao,

Fengshi, Weizhong, Sanyinjiao, Taichong, etc. of paralyzed lower limbs. The waveform was density wave, current intensity was 10 (2 mA), and the instrument was SDZ-II Huatuo brand electronic acupuncture instrument and electric acupuncture instrument. Operation method: According to the condition, two groups of scalp acupoints and paralyzed body acupoints were taken, and the current intensity was turned on instantly to 10, within 1∼5 seconds, and then quickly returned to zero, and the stimulation was performed sequentially. Each acupuncture point was stimulated 2∼3 times, and the patient's expression and tolerance should be closely observed during the stimulation. If dizziness occurs, treatment should be stopped immediately, 4–5 times per week.

Therapy Group

The patients were treated with rehabilitation training on the basis of the control group. (1) During the treatment process, medical staff should regularly organize the patient to perform postural changes to ensure smooth blood circulation and avoid pressure injuries and other problems. (2) Medical staff should massage the patient's affected limb to ensure that they could effectively achieve reasonable passive activities, so as to achieve the improvement and optimization of the treatment effect. (3) Trauma rehabilitation training: During the treatment process, medical personnel should guide the patient to perform crossed arms and elevation training to train hip joint control. At the same time, the medical staff should guide the patient with knee flexion and lower limb extension training in prone and supine positions to lay a good foundation for subsequent weight-bearing rehabilitation training. (4) Balance training: Medical staff should actively train the patient's balance ability, including bedside standing and seat balance exercises, to effectively realize the patient's rotation activity and back and forth movement in the correct standing and sitting state. (5) Athletic training: Under the premise of ensuring the patient's safety, guiding the patient to perform appropriate walking or up and down stairs exercises. (6) Occupational therapy: During the treatment process, medical staff should guide the patient to train the functions of the hands and upper limbs, including vertebral body, wiping the table, and basketball control. At the same time, the patient should be instructed to achieve triggering activity of muscles through appropriate neurostimulation techniques. The specific content of the above rehabilitation training was selected according to the actual situation of the patient, 1 h/time, 1 time/d, and the rehabilitation training time was 1 month.

Observation Indicators

Neurological Deficits

The National Institutes of Health Stroke Scale (NIHSS) was used to score the neurological deficits of patients in the two group before and after treatment. The scale included 15 scoring items such as language, consciousness, visual field, movement, and limb ataxia. The NIHSS score ranged from 0 to 45 points; the lower the score, the lighter the neurological deficit.

TABLE 2 | Comparison of NIHSS scores before and after treatment between the two groups (M ± SD, scores).

Group	*n*	NIHSS	
		Before treatment	**After treatment**
Control group	45	26.31 ± 4.18	20.46 ± 3.25*
Therapy group	45	26.65 ± 4.27	14.52 ± 3.06*Δ
t		0.3817	8.927
P		0.7036	<0.0001

*Compared with the control group before treatment, *P < 0.05; Compared with the therapy group after treatment, ΔP < 0.05.*

Physical Motor Function

The simplified Fugl-Meyer rating scale (FMA) was used to score the recovery of motor function of hemiplegic limbs before and after treatment in the two group. The scale involved sensation, balance, movement, mobility of limbs and joints, pain and other aspects. The total score was 100 points. The higher the score, the better the motor function.

Evaluation of Clinical Efficacy

The clinical efficacy of patients was evaluated according to the evaluation criteria for clinical efficacy of stroke adopted by the Fourth National Cerebrovascular Disease Academic Conference. Get well: After treatment, the symptoms and signs of the nervous system of the patient had basically disappeared, or the NIHSS score was reduced by more than 90%, and the life was completely self-care; markedly effective: the symptoms and signs of the nervous system of the patient were significantly improved after the treatment, or the NIHSS score was reduced by 70–89%, and was able to basically take care of themselves; Effective: After treatment, the patient's nervous system symptoms and signs had improved, or the NIHSS score was reduced by 30–69%, and was able to take care of part of life; Invalid: After treatment, the patient's nervous system symptoms and signs did not improve or even worsened, or died.

Hemorheology and BNDF Content Determination

Before and after treatment, 4 mL of cubital venous blood was drawn on an empty stomach in the two groups of patients, centrifuged at 3000 r/min for 10 min, and the serum was separated and stored in a refrigerator at −20°C for examination. The LG-R-20 hemorheology analyzer (Beijing Zhongqin Shidi Scientific Instrument Co., Ltd.) measured the whole blood high shear viscosity, whole blood low shear viscosity, platelet aggregation rate and fibrinogen index before and after treatment in the two groups. ELISA method was used to detect the BDNF content in the serum of the two groups of patients. Kit was purchased from elaid biotech Co., Ltd.

Statistical Methods

Graphpad prism 8.0 software was used for data analysis, and the measurement data were expressed as $M \pm SD$. The *t*-test was in accordance with the normal distribution, and the Wilcoxon test was not in accordance with the normal distribution. The

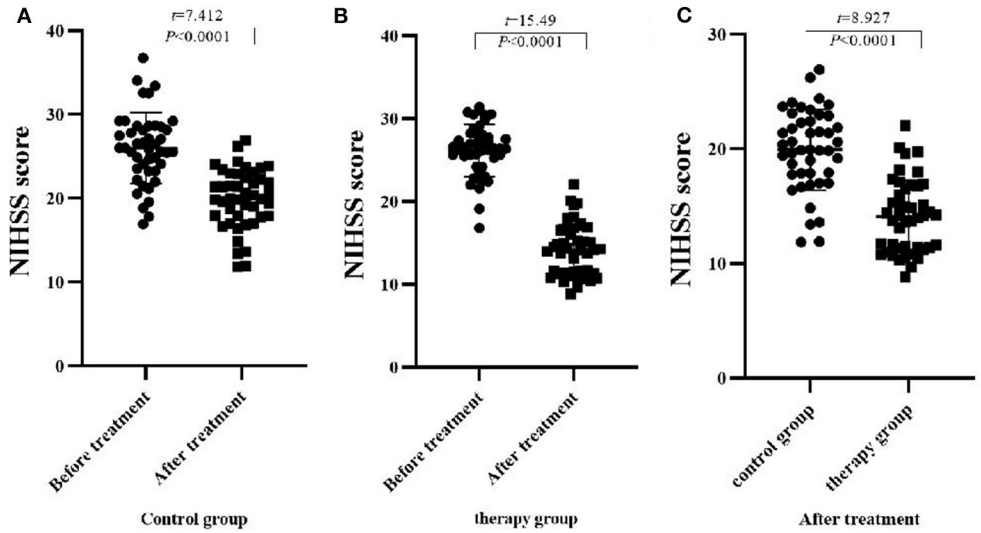


FIGURE 1 | Comparison of NIHSS scores before and after treatment between the two groups (M ± *SD*, scores). **(A)** Comparison of NIHSS scores of the control group before and after treatment; **(B)** Comparison of NIHSS scores of the therapy group before and after treatment; **(C)** Comparison of NIHSS scores of the two groups after treatment.

measurement data were expressed as % and tested by χ^2, and $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of NIHSS Scores Between the Two Groups of Patients Before and After Treatment

Before treatment, there was no significant difference in NIHSS scores between the two groups of patients ($P > 0.05$). After treatment, NIHSS scores in both groups decreased significantly, and the therapy group decreased significantly compared with the control group ($P < 0.05$), (**Table 2**, **Figure 1**).

Comparison of FMA Scores Between the Two Groups of Patients Before and After Treatment

There was no significant difference in FMA scores between the two groups before treatment ($P > 0.05$). After treatment, the FMA scores of the two groups increased significantly, and the therapy group increased significantly compared with the control group ($P < 0.05$), (**Table 3**, **Figure 2**).

Comparison of Clinical Efficacy Between the Two Groups of Patients

The total clinical effective rate of patients in the therapy group was 91.1%, and the total clinical effective rate of patients in the control group was 77.8%. Compared with the clinical efficacy between the groups, the treatment group was significantly better than the control group ($P < 0.05$), (**Table 4**, **Figure 3**).

TABLE 3 | Comparison of FMA scores before and after treatment between the two groups (M ± *SD*, scores).

Group	*n*	FMA	
		Before treatment	**After treatment**
Control group	45	30.48 ± 3.67	45.27 ± 4.16*
Therapy group	45	30.12 ± 3.25	53.81 ± 4.75*Δ
t		0.6235	9.073
P		0.4926	<0.0001

*Compared with the control group before treatment, *P < 0.05; Compared with the therapy group after treatment, ΔP < 0.05.*

Comparison of Hemorheology Between the Two Groups of Patients Before and After Treatment

There was no significant difference in hemorheology between the two groups of patients before treatment ($P > 0.05$). After treatment, the whole blood high shear viscosity, whole blood low shear viscosity, platelet aggregation rate, fibrinogen of the two groups were decreased, and the therapy group was significantly lower than that of the control group ($P < 0.05$), (**Table 5**).

Comparison of Serum BDNF Content Between the Two Groups of Patients Before and After Treatment

There was no significant difference in serum BDNF content between the two groups before treatment ($P > 0.05$). After treatment, the BDNF content of the two groups increased significantly, and the therapy group increased significantly compared with the control group ($P < 0.05$), (**Table 6, Figure 4**).

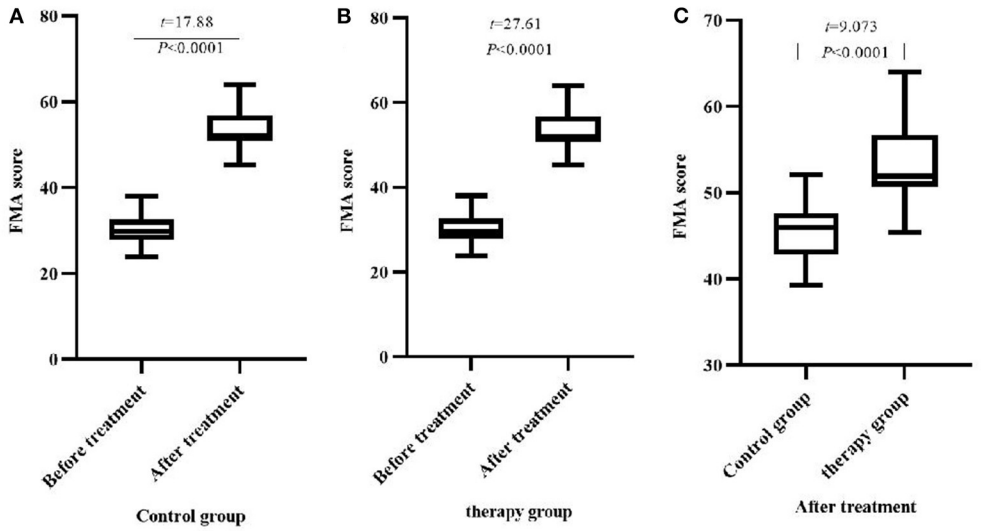


FIGURE 2 | Comparison of FMA scores before and after treatment between the two groups (M ± SD, scores). **(A)** Comparison of FMA scores of the control group before and after treatment; **(B)** Comparison of FMA scores of the therapy group before and after treatment; **(C)** Comparison of FMA scores of the two groups after treatment.

TABLE 4 | Comparison of clinical efficacy between the two groups of patients [*n* (%)].

Group	*N*	Get well	Markedly effective	Efficient	Invalid	Total effective rate
Control group	45	5	18	12	10	35 (77.8)
Therapy group	45	10	21	10	4	41 (91.1)
χ^2						23.92
P						<0.0001

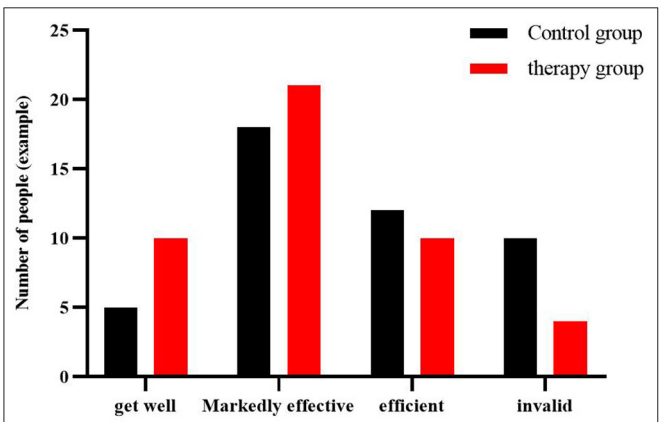


FIGURE 3 | Comparison of clinical efficacy between control group and therapy group (cases).

DISCUSSION

In recent years, the incidence of cardiovascular and cerebrovascular diseases has been increasing year by year. CI is a common critical illness that causes impairment in patients' motor and sensory functions and results in a significant decline in patients' abilities of daily living (9). The current conventional treatment methods for the treatment of CI include inhibiting platelet aggregation, reducing cerebral edema, and restoring blood supply in the infarcted area. However, the rehabilitation effect of patients is often not as expected. It is necessary to further improve the patient's limb exercise ability and self-care ability. Therefore, in this study, combined acupuncture and rehabilitation therapy was given on the basis of conventional Western medicine treatment in the hope of achieving the objective of improving the motor function and self-care ability of patients. The theory of traditional Chinese medicine believes that CI belongs to the category of stroke and dysfunction. The imbalance of kidney, liver, heart, yin and yang and the interaction of qi, fire, wind, blood, and phlegm, which causes disuse of the limbs, blockage of the veins, and dysfunction. The main manifestations are sudden fainting, unconsciousness, hemiparesis, unfavorable language and so on (10). Rescue therapy during the acute phase of CI can help patients to get out of danger, but due to the deficiency of yin in liver and kidney, the patient's qi and blood have not been restored, which can lead to hemiplegia, unfavorable speech and other sequelae. The use of acupuncture to treat CI can significantly reduce neurological damage and help the recovery of motor function (11). Traditional Chinese medicine believes that the governor pulse is the convergence of the three yang meridians of the hand

TABLE 5 | Comparison of whole blood high shear viscosity, whole blood low shear viscosity, platelet aggregation rate and fibrinogen index before and after treatment in the two groups (M ± SD, $n = 45$).

Group	Whole blood high shear viscosity (mPa.s)		Whole blood low shear viscosity (mPa.s)		Platelet aggregation rate (%)		Fibrinogen (mg/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	7.42 ± 0.51	6.38 ± 0.46*	15.79 ± 2.61	11.37 ± 0.45*	45.12 ± 2.83	40.24 ± 2.15*	5.01 ± 0.42	3.65 ± 0.37*
Therapy group	7.26 ± 0.48	4.01 ± 0.32*Δ	15.93 ± 2.65	7.26 ± 0.32*Δ	45.36 ± 2.91	26.47 ± 1.83*Δ	4.93 ± 0.38	2.15 ± 0.16*Δ
t	1.533	28.37	0.2525	49.93	0.3966	32.72	0.9475	24.96
P	0.1290	<0.0001	0.8012	<0.0001	0.6926	<0.0001	0.3460	<0.0001

*Compared with the control group before treatment, *P < 0.05; Compared with the therapy group after treatment, ΔP < 0.05.*

TABLE 6 | Comparison of serum BDNF content before and after treatment in the two groups (M ± SD, ng/mL).

Group	*n*	BDNF	
		Before treatment	After treatment
Control group	45	19.34 ± 2.16	24.61 ± 3.69*
Therapy group	45	20.08 ± 2.37	29.04 ± 4.02*Δ
t		1.548	5.446
P		0.1252	<0.0001

*Compared with the control group before treatment, *P < 0.05; Compared with the therapy group after treatment, ΔP < 0.05.*

and the three yang meridians of the foot, which can regulate the qi and blood of the yang meridians of the whole body and maintain the vitality of the whole body. Neurological and motor dysfunction in patients with CI is caused by yang deficiency, so by stimulating the head motor area, sensory area, superior temporal gyrus, transverse gyrus, inferior gyrus and various points of the upper and lower limbs, it is beneficial to the the recovery of patient's nerve and motor function, and then improve the prognosis and improve the quality of life of patients. Electrical acupuncture stimulation therapy is one of the important branches of acupuncture in traditional Chinese medicine. Its mechanism is to promote the excitability of central nerve cells and the release of central neurotransmitters by acupuncture scalp and body acupoints and applying a certain amount of current stimulation. It can make the inhibited nerve cells wake up or revive the reversible nerve cells, increase the number of neurons and nerve fibers, and then play a role in promoting nerve reconstruction (12). Relevant studies have shown that the application of instantaneous electrical acupuncture has a significant effect on neurological rehabilitation in patients with acute CI. In addition, the follow-up rehabilitation training is also an important part of the rehabilitation treatment of CI patients. Rehabilitation training can help restore the patient's body, language and brain response ability to the greatest extent. Standardized three-level rehabilitation is a standardized and holistic rehabilitation training model, which uses gradual training content to cooperate with the functional recovery of the injured nerve of the patient, and promotes the recovery of the patient's physical function by maximizing the movement of the affected limb (13, 14).

In this study, the combined treatment of transient electrical acupuncture stimulation and rehabilitation training was given to the patients, and the clinical efficacy of the therapy group was significantly better than that of the control group. In recent years, related reports have pointed out that changes in blood viscosity are an important key factor in ischemic cerebrovascular diseases, and blood viscosity in microcirculation depends on platelet aggregation and fibrinogen (15). This study observes the effects of instantaneous electroacupuncture combined with rehabilitation training on hemorheology, focusing on whole blood high shear viscosity, whole blood low shear viscosity, platelet aggregation rate and fibrinogen as the key observation indicators. The results showed that after treatment, the contents of hemorheological indexes in the two groups were lower than those before treatment, and the contents of hemorheological indexes in the therapy group were lower than those in the control group. This suggests that short-term electroacupuncture combined with rehabilitation training can effectively inhibit platelet aggregation, reduce whole blood viscosity and fibrinogen, so as to inhibit microvascular thrombosis and increase blood oxygen content. Therefore, it plays a good role in improving blood supply and nutrition of brain cells. The results of NIHSS and FMA scores before and after treatment in this study showed that the NIHSS scores of the two groups of patients after treatment were lower than those before treatment, and the FMA scores were higher than before treatment; the NIHSS score of the therapy group was lower than that of the control group, and the FMA score was higher than that of the control group. It can be seen that the combination of transient electrical acupuncture stimulation and rehabilitation training can significantly improve the neurological and motor functions of patients with CI, and improve the physiological quality of patients. It is partially consistent with the results of Sheng et al. (16).

BDNF is a member of the neurotrophic factor family and is mainly distributed in the central nervous system. It plays a very important role in maintaining the survival, growth, differentiation, repair and regeneration of injured neurons. It is essential for maintaining and protecting the survival and growth of neurons (17, 18). And the mouse model shows that the BDNF in the brain tissue can enter the blood through the blood-brain barrier, so it is speculated that the serum level can reflect the BDNF level in the brain (19). The results of this study showed that the serum BDNF content of the two

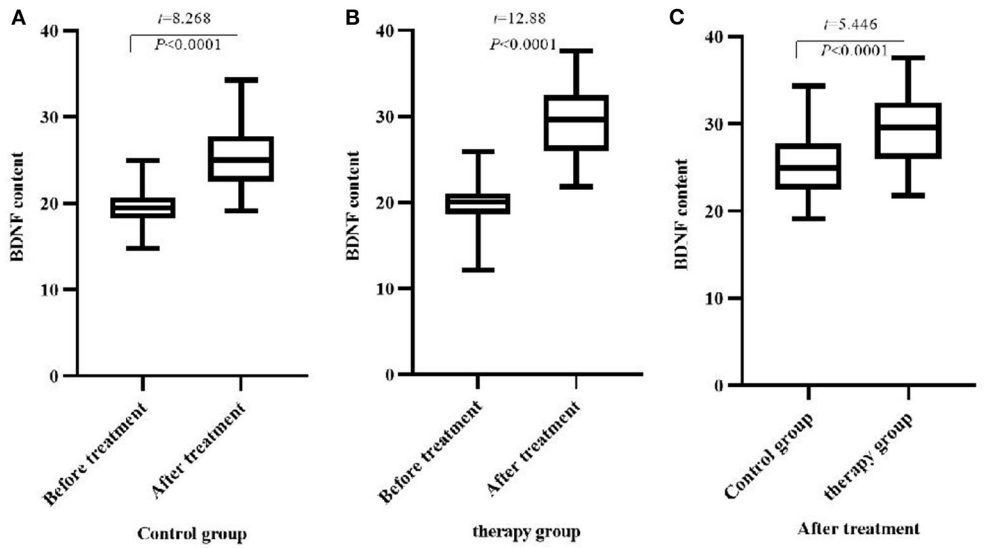


FIGURE 4 | Comparison of BDNF content before and after treatment between the two groups (M ± SD, ng/mL). **(A)** Comparison of BDNF content in the control group before and after treatment; **(B)** Comparison of BDNF content in the therapy group before and after treatment; **(C)** Comparison of BDNF content in the two groups after treatment.

groups of patients after treatment was higher than that before the treatment, and the serum BDNF content of the therapy group was higher than that of the control group. Rising levels of BDNF stimulate and promote the growth and differentiation of neural cells and promote the repair of damaged neurons, and therefore, contribute to the recovery of neurological function. In addition, modern studies have also confirmed that acupuncture can achieve the effect of improving muscle strength by inhibiting neuronal apoptosis, improving cerebral blood circulation, and reestablishing the coordination of regenerating nerves (20).

In summary, the combination of transient electrical acupuncture stimulation and rehabilitation training can inhibit the blood flow index of patients with CI, improve the nerve function, increase the content of BDNF in the patient's serum, and promotes recovery of neurological function in patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The First Affiliated Hospital of University of South China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC was responsible for the writing of the paper. JH and XT were responsible for the design of the research pair and the detection of the results. TW was responsible for the data recording and statistics. YZ was responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by subject of Hunan Provincial Health Commission (202214014506).

REFERENCES

1. Yu J, Zhang J, Chen J. The significance to determine factors related to postoperative cerebral infarction in patients with moyamoya disease. *Cerebrovasc Dis.* (2020) 49:233–4. doi: 10.1159/000506856
2. Ishii D, Osaki H, Yozu A, Ishibashi K, Kawamura K, Yamamoto S, et al. Ipsilesional spatial bias after a focal cerebral infarction in the medial agranular cortex: a mouse model of unilateral spatial neglect. *Behav Brain Res.* (2021) 401:113097. doi: 10.1016/j.bbr.2020.113097
3. Yamaguchi N, Sawano T, Fukumoto K, Nakatani J, Inoue S, Doe N, et al. Voluntary running exercise after focal cerebral ischemia ameliorates dendritic spine loss and promotes functional recovery. *Brain Res.* (2021) 1767:147542. doi: 10.1016/j.brainres.2021.147542
4. Takeda H, Yamaguchi T, Yano H, Tanaka J. Microglial metabolic disturbances and neuroinflammation in cerebral infarction. *J Pharmacol Sci.* (2021) 145:130–9. doi: 10.1016/j.jphs.2020.11.007
5. Merkler AE, Alakbarli J, Barbar T, Baradaran H, Adejumo O, Navi BB, et al. Associations between the size and location of

myocardial infarction and cerebral infarction. *J Neurol Sci.* (2020) 419:117182. doi: 10.1016/j.jns.2020.117182
6. Colaço CS, Alves SS, Nolli LM, Pinheiro WO, de Oliveira DGR, Santos BWL, et al. Toxicity of ayahuasca after 28 days daily exposure and effects on monoamines and brain-derived neurotrophic factor (BDNF) in brain of Wistar rats. *Metab Brain Dis.* (2020) 35:739–51. doi: 10.1007/s11011-020-00547-w
7. Lee SS, Kim CJ, Shin MS, Lim BV. Treadmill exercise ameliorates memory impairment through ERK-Akt-CREB-BDNF signaling pathway in cerebral ischemia gerbils. *J Exerc Rehabil.* (2020) 16:49–57. doi: 10.12965/jer.2040014.007
8. Sacks D, Baxter B, Campbell BC, Carpenter JS, Cognard C, Dippel D, et al. Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke. *Int J Stroke.* (2018) 13:612–32. doi: 10.1177/1747493018778713
9. Zhou LF, Wu XG, Zhang JC, Cao XL, Liu JW. Effects of electroacupuncture on renal function in rats with acute cerebral infarction. *J Guangxi Med Univ.* (2019) 36:669–73.
10. Xiong XJ. The meaning of "stroke" in ancient times and the experience of Xiaoxuming Decoction in Treating Cerebral Infarction and Cerebral Hemorrhage. *Chin J Chin Materia Medica.* (2020) 45:2725–34. doi: 10.19540/j.cnki.cjcmm.20200316.501
11. Yu DD, Xie Ym, Liao X, Cui DH, Wang YY. Visual analysis of research hotspots and trends in CI in traditional Chinese medicine based on CiteSpace. *Chin J Tradit Chin Med.* (2020) 35:595–8.
12. Hu PL. The effect of acupuncture and moxibustion combined with electric acupuncture stimulation combined with rehabilitation training on neurological deficits and limb motor function in stroke patients. *Chin Convales Med.* (2020) 29:337–79.
13. Jia R, Liu QF Li L, Xu DX, Wu CL, Jiang LP, et al. Observation on the effect of "sitting-standing-walking" target exercise on improving lower limb dysfunction in elderly patients with acute Cerebral Infarction. *Geriatrics Health Care.* (2020) 26:367–70. doi: 10.3969/j.issn.1008-8296.2020.03.009
14. Wang K, Li YW, Wang YL. The effect of early repetitive training of lower limbs on the recovery of lower limb function in patients with acute cerebral infarction. *Chin J Rehabil Med.* (2020) 35:949–53.
15. Lu XH. Study on the effect of Tongqiaohuoxue Decoction on the recovery of nerve function and hemorheology in patients with ischemic cerebrovascular disease. *Sichuan J Tradit Chin Med.* (2020) 38:102–5.
16. Sheng P. Effect of instantaneous electro-acupuncture combined with dihuang yinzi on neurological function reconstruction in patients with convalescent cerebral infarction. *J Mathemat Med.* (2019) 32:1288–91. doi: 10.3969/j.issn.1004-4337.2019.09.009
17. Memarpour S, Beheshti F, Baghcheghi Y, Vafaei AA, Hosseini M, Rashidy-Pour A. Neuronal nitric oxide inhibitor 7-nitroindazole improved brain-derived neurotrophic factor and attenuated brain tissues oxidative damage and learning and memory impairments of hypothyroid juvenile rats. *Neurochem Res.* (2020) 45:2775–85. doi: 10.1007/s11064-020-03128-6
18. Yang M, Sun JY, Ying CC, Wang Y, Guo YL. Adipose-derived stem cells modified by BDNF gene rescue erectile dysfunction after cavernous nerve injury. *Neural Regen Res.* (2020) 15:120–7. doi: 10.4103/1673-5374.264464
19. Liu J, Liu B, Yuan P, Cheng L, Sun H, Gui J, et al. Role of PKA/CREB/BDNF signaling in PM25-induced neurodevelopmental damage to the hippocampal neurons of rats. *Ecotoxicol Environ Saf.* (2021) 214:112005. doi: 10.1016/j.ecoenv.2021.112005
20. Pan L, Tian SS, Tian WY. Ginkgo biloba combined with acupuncture and moxibustion promotes neurological recovery after traumatic cerebral hemorrhage in rats through Nrf2/HO-1 pathway. *Med J Chin People's Liberation Army.* (2020) 32:16–21. doi: 10.3969/j.issn.2095-140X.2020.07.004

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Chen, Huang, Tang, Wang and Zeng. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 15 February 2022
doi: 10.3389/fsurg.2022.842309

Application of Operating Room Nursing Intervention to Incision Infection of Patients Undergoing Gastrointestinal Surgery Can Reduce Complications and Improve Gastrointestinal Function

*Ping Wang, Hong Chen and Qi Ji**

Operating Room, The First People's Hospital of Lianyungang, Lianyungang, China

Objective: To observe the influence of nursing intervention in operation rooms on incision infection of patients undergoing gastrointestinal surgery and the improvement of gastrointestinal function.

Methods: A total of 340 patients who underwent gastrointestinal surgery in our hospital from June 2020 to August 2021 were included. According to the random number table, they were divided into the conventional nursing group ($n = 170$) and the operating room nursing group ($n = 170$). The conventional nursing group was treated with routine nursing intervention, while the operating room nursing group was treated with operating room nursing intervention. The incision infection, healing, gastrointestinal function recovery, and complications in the two groups were compared, and the patient care satisfaction was recorded.

Results: The incidence of incision swelling, pain, and incision secretion in the operating room nursing group was significantly lower than that in the conventional nursing group ($p < 0.05$). The patients in the operating room nursing group had higher grade A healing than in the conventional nursing group, and lower grade B and grade C healing than in the conventional nursing group ($p < 0.05$). The time of anal exhaust, first defecation, and the time of gastric tube removal in the operating room nursing group were lower than those in the conventional nursing group ($p < 0.05$). The incidence of postoperative complications, such as incision infection, incision dehiscence, early inflammatory bowel adhesion, and abdominal abscess, in the operating room nursing group was lower than that in the conventional nursing group ($p < 0.05$). The total satisfaction degree in the operating room nursing group was significantly higher than that in the conventional nursing group ($p < 0.05$).

Conclusion: Nursing intervention in operation room can reduce complications and improve gastrointestinal function when applied to patients undergoing gastrointestinal surgery due to incision infection.

Keywords: gastrointestinal surgery, operating room nursing, incision infection, gastrointestinal function, complication

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Wenjie Song,
Fourth Military Medical University, China
Li Zhu,
Central South University, China

****Correspondence:***
Qi Ji
jiqicat@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *23 December 2021*
Accepted: *12 January 2022*
Published: *15 February 2022*

Citation:
Wang P, Chen H and Ji Q (2022) Application of Operating Room Nursing Intervention to Incision Infection of Patients Undergoing Gastrointestinal Surgery Can Reduce Complications and Improve Gastrointestinal Function. Front. Surg. 9:842309. doi: 10.3389/fsurg.2022.842309

INTRODUCTION

It is easy to breed bacteria in the gastrointestinal tract. Therefore, patients undergoing gastrointestinal surgery are prone to infection of surgical incision and various other complications. Incision infection accounts for 15–20%, a high proportion, of nosocomial infections (1, 2). Two to four days after gastrointestinal surgery, the incision pain and body temperature of a patient will gradually return to normal. If the incision pain is not relieved or if there are signs, such as swelling and fever in the local incision, it indicates that a degree of infection might be present (3). The dehiscence and exudation that occur after the infection of an incision prolongs its healing time. If not treated in time, the infection may worsen and may eventually lead to organ dysfunction or systemic infection and death in severe cases (4, 5).

Although the operating room is an important place for clinical rescue, it is also a department with a high infection rate. Postoperative infection has always been a clinically difficult problem (6, 7). Literature shows that nursing interventions for patients undergoing gastrointestinal surgery can effectively reduce postoperative infection rate. To further reduce the infection rate of incisions after gastrointestinal surgery, we should not only standardize the disinfection and sterilization for the operation, but also do a good job of nursing in the operating room so as to reduce the infection rate of incision, improve the operation efficiency, and reduce the economic and psychological burden of patients (8). This study discusses the influence of nursing intervention in operating rooms on wound healing and gastrointestinal peristalsis of patients undergoing gastrointestinal surgery. The results are reported as follows.

DATA AND METHODS

General Information

A total of 340 patients who underwent gastrointestinal surgery in our hospital from June 2020 to August 2021 were included in the study. They were divided into the conventional nursing group (170 patients) and the operating room nursing group (170 patients) according to the random number table. The inclusion criteria were as follows: patients undergoing elective surgery; patients who have no immune or endocrine disorders; patients with a certain have primary school education or above and can cooperate with the research. The exclusion criteria were as follows: patients with severe hepatic and renal insufficiency; patients with malignant tumor/s or mental diseases; patients with with coagulation disorders, i.e., anemia; patients who have cultural taboos on nursing measures; patients who have had failed treatment or operation and may prolong their stay in hospital; palliative surgery patients. This study was approved by the Hospital Ethics Committee, and informed consent was obtained from patients and their families.

Research Methods

Routine nursing intervention was adopted in the conventional nursing group. Nurses in this group were tasked with the following: (1) timely update of the operating room equipment level; (2) conduct regular spot checks for health care personnel infection prevention awareness and measures to understand the situation, for understanding the improper health care personnel should be strengthened education; (3) the operating room head nurse actively cooperate with infection department work, responsible for the daily infection prevention and control management; (4) for the medical staff in and out of the operating room for infection prevention measures supervision.

The operating room nursing group adopted the nursing intervention in the operation room. Before the intervention measures are implemented, a management system and process and areward and punishment system was made to encourage staff to supervise each other. In the process of implementation, staff were tasked to study and check each other regularly to correct the deficiencies. The specific measures are divided into three parts: preoperative preparation, strengthening the management of the operating room, and meticulous care of the incision. The specific measures are as follows:

(2) Pre-operation: after receiving the notice of operation, the nurses in the operating room should have carefully checked the case data of the patient and understand their condition. The purpose, method, precautions, and expected results of operation should be introduced to the patient and their family. Nurses should have patiently solved the problems raised by the patient and their family. In addition, they should have fully understood the psychological state of the patient and psychologically guide their bad emotions and enhance their confidence in treatment. At the same time, the operating room nurses should have given preoperative instructions, telling the patient that they should strictly fast from food and water 8 h before operation to prevent gastrointestinal decompression. Lastly, they must assist clinicians to complete various examinations, inspecting and checking instruments and items required for surgery.

(3) Strengthening the management of the operation room: Nurses were tasked to manage the access of personnel in the operation room. Non-emergency operations were reasonably sequenced. The interval between two operations was more than 35 min, during which the operating room environment and air were disinfected. Thirty minutes before surgery, the operating room nurses should clean and disinfect the environment and tools in the operating room. The storage and management of sterile instruments should be managed by special personnel. Before entering the room, they should strictly strengthen aseptic operation. Hand washing was conducted according to the six-step washing method. The nurse in charge of the operation room conducted a hand hygiene check on the medical staff involved in the operation. Surgeons can only stay in the sterile area of the operating room. The gloves used in the operation shall be replaced immediately if they are torn or punctured by a sharp instrument. Used instruments shall not be reused. The temperature and humidity in the operation room were controlled within an appropriate range, and the thermal measures were maintained for patients to avoid incision infection caused by too low temperature.

(4) Incision care: Before the operation, the local skin at the incision site was disinfected. The disinfected area should cover 15–20 cm around the incision before a 3 m skin

protective film is stuck on the incision. During the operation, after the abdominal cavity is opened, the incision should be protected by a full-layer protector in time to prevent bacteria or feces from polluting the incision. After applying a protective pad around the incision, the gastrointestinal tract can be cut. After the peritoneal suture was completed, the skin, subcutaneous tissue, and grass-roots layer of the incision in the patient were rinsed with 37°C normal saline. Afterwhich, the normal saline was wiped clean with gauze (the tumor flushing fluid is sterilized water for injection at 38–43°C, and the operation field is soaked for 3–5 min for 2–3 times), and the incision was sutured layer by layer. A dress with good adsorbability was applied to that incision site to avoid incision exudation.

Observation Indicators

The wound infection and healing of two groups of patients were compared. Assessment of wound healing included: Grade A healing (wound healing is good without any adverse healing), Grade B healing (inflammation such as swelling, hematoma or effusion after wound healing), and Grade C healing (wound purulent needs dressing change).

The recovery of gastrointestinal function and the incidence of complications were compared between two groups. The nurse should accurately record the gastrointestinal function indicators of patients (including anal exhaust time, first defecation time and gastric tube removal time), along with complications (including incision infection, incision dehiscence, early inflammatory bowel adhesion, and peritoneal abscess), and calculate the incidence rate.

The satisfaction of patients with nursing care in the two groups was recorded. According to the actual situation of the operating room, a nursing satisfaction score scale was set up, which mainly included the service attitude, nursing operation, operation process, health education, nursing results, and other aspects of the medical staff. There were three grades, namely, very satisfactory (score >89), satisfactory (score: 60–89 points), and dissatisfied (score < 60 points). The content reliability index of nursing satisfaction rating scale was 0.79, and the α coefficient of Kehlenbach was 0.784, which had good reliability.

Statistical Methods

SPSS22.0 software was used for processing. The measurement of the experimental data were expressed as mean SD ($x \pm s$), and the enumeration data were expressed in percent (%). *T*-test analysis was used for pairwise comparison of measurement data among groups, and the count data were tested by $\chi 2$ test. The test level was $\alpha = 0.05$, and a value of $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of General Data Between the Two Groups

There was no significant difference in general information such as gender, age, and educational background between the two groups ($p > 0.05$) as shown in **Table 1**.

Comparison of Incision Infection Between the Two Groups

The incidence of incision swelling, pain, and incision secretion in the operating room nursing group was significantly lower than in the conventional nursing group. The differences were statistically significant ($p < 0.05$) as shown in **Figure 1**.

Comparison of Wound Healing Between the Two Groups

The grade A healing rate of patients in the operating room nursing group was higher than that of the conventional nursing group, and the grade B and grade C healing rates were lower than those of the conventional nursing group. The differences were statistically significant ($p < 0.05$) as shown in **Figure 2**.

Comparison of Gastrointestinal Function-Related Indicators Between the Two Groups

Patients in the operating room nursing group had lower anal exhaust time, first defecation time, and gastric tube removal time than those in the conventional nursing group. The differences were statistically significant ($p < 0.05$) as shown in **Figure 3**.

Comparison of Postoperative Complications Between the Two Groups

The incidence of postoperative complications, such as incision infection, incision dehiscence, early inflammatory bowel adhesion, and peritoneal abscess, in the operating room nursing group was lower than that in the conventional nursing group. The difference was statistically significant ($p < 0.05$). As shown in **Figure 4**.

Comparison of Nursing Satisfaction Between the Two Groups

The total satisfaction degree of the operating room nursing group (93.53%) was significantly higher than that of the conventional nursing group (75.29%). The difference was statistically significant ($\chi^2 = 30.637$, $p < 0.001$) as shown in **Figure 5**.

DISCUSSION

Postoperative infection of gastrointestinal incision is one of the common clinical complications at present. Studies have pointed out that the infection rate of gastrointestinal surgical incisions can be as high as 25%, which makes it a common complication in operating rooms (9). Compared with other types of surgery, gastrointestinal surgery has certain particularity. Gastrointestinal flora is abundant and most of the surgical incisions for gastrointestinal operations are of Class II and III. If the incision is not treated in time, the risk of surgical incision infection will increase to a certain extent, which could easily to aggravate the condition of the patient (10, 11). Incision infection is closely related to the operating room environment, the personnel involved in the operation, and the surgical instruments. Therefore, nursing in operation room plays an important role in patient safety.

TABLE 1 | Comparison of general data of patients between the two groups.

Group	Gender		Educational background		
	Male	**Female**	**Junior secondary and below**	**Senior high school**	**Bachelor degree or above**
Conventional nursing group ($n = 170$)	81	89	61	68	41
Operating room nursing group ($n = 170$)	83	87	65	67	38
χ^2 *value*	0.047			0.248	
P value	0.828			0.883	
Group	Age (years)		Surgical type		
		Partial gastrectomy	Clearance of intestinal adhesions	Repair of duodenal perforation	Radical gastrectomy for gastric cancer
Conventional nursing group ($n = 170$)	41.82 ± 6.53	49	29	51	41
Operating room nursing group ($n = 170$)	42.59 ± 5.91	48	24	54	44
t/χ^2 *value*	1.140		1.111		
P value	0.255		0.774		

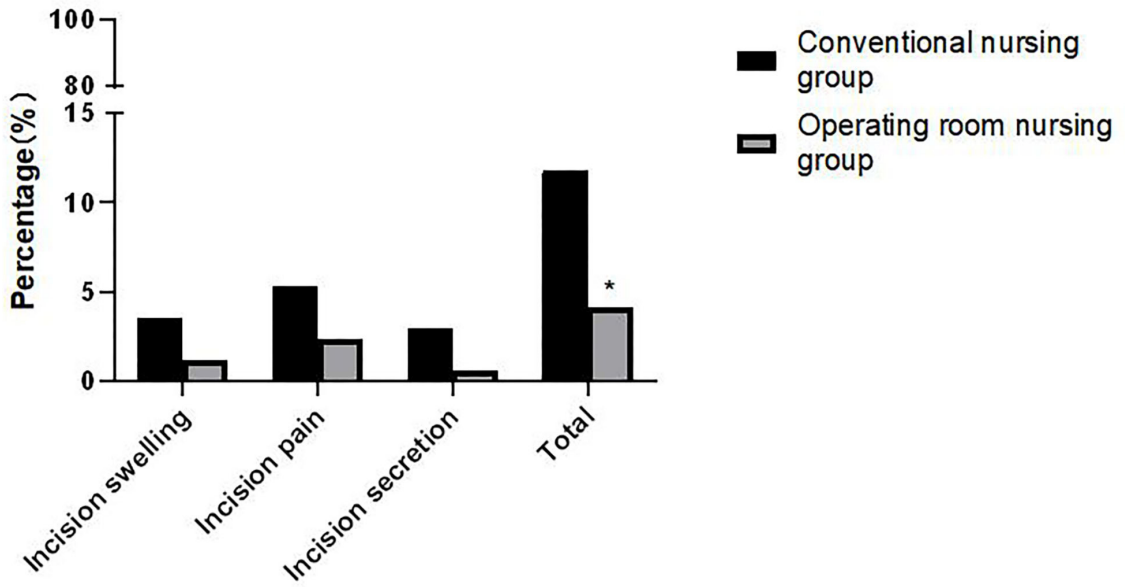


FIGURE 1 | Comparison of incision infection between the two groups. Note: Compared with the conventional nursing group, $^*p < 0.05$.

The routine nursing mode in operating rooms has a certain effect on preventing infection. However, there are still many patients with different degrees of incision infection after operation. This seriously affects the treatment quality and work efficiency and thereby increases the incidence of medical disputes (12, 13). Therefore, finding suitable operating room nursing measures that can reduce complications, such as incision infection, is the focus of the current clinical research. In this study, the incidence of incision infection in the operating room nursing group was significantly lower than in the conventional nursing group. Wound healing was also significantly better than in the conventional nursing group. It indicated that nursing in operation room had clear advantages for reducing incision infection and promoting the recovery of patients.

According to the characteristics of gastrointestinal surgery, nursing in operating room should strictly make preparation for the operation, including checking the case data of the patient, grasping the basic situation of the patient, and preparing the skin, which can reduce the chance of bacterial infection to some extent. Secondly, the whole nursing process was centered on strengthening aseptic operation, strict access control in operation rooms, and reducing the risk of cross-infection. Medical staff involved in the operation should strictly wash their hands according to the six-step washing method to ensure hand

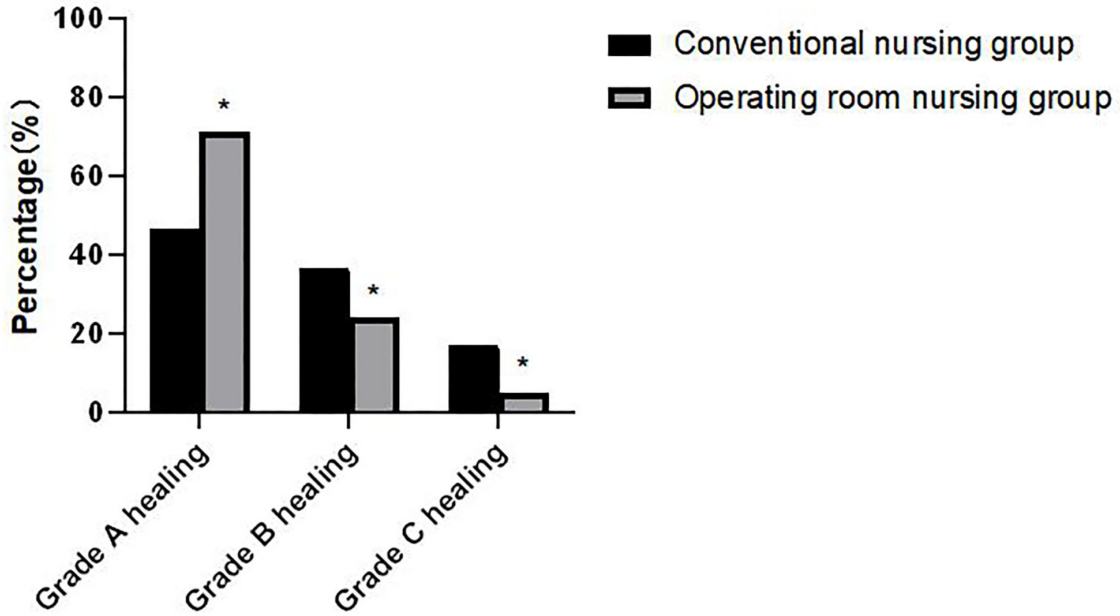


FIGURE 2 | Comparison of wound healing between the two groups. Compared with the conventional nursing group, $^{*}p < 0.05$.

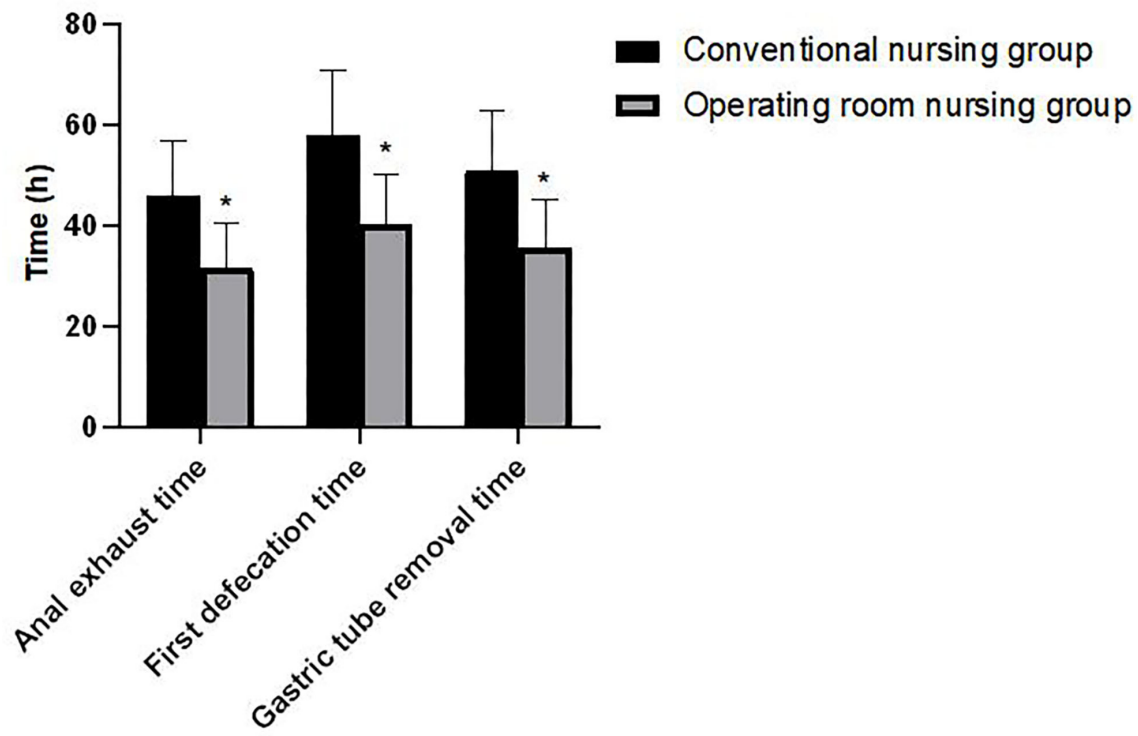


FIGURE 3 | Comparison of gastrointestinal function-related indicators between the two groups. Compared with the conventional nursing group, $^{*}p < 0.05$.

hygiene, ensure disinfection in the operation area, ensure the operating room environmental health, and reduce bacterial adhesion. Staff should also strictly control the flow of operating room staff and the number of surgical visitors to reduce the chance of airborne bacteria. Finally, they are to cooperate with surgeons during incision processing, disinfection of local skin incision, taking the full layer protector to protect treatment in time, and, after the completion of the peritoneal suture, clean the

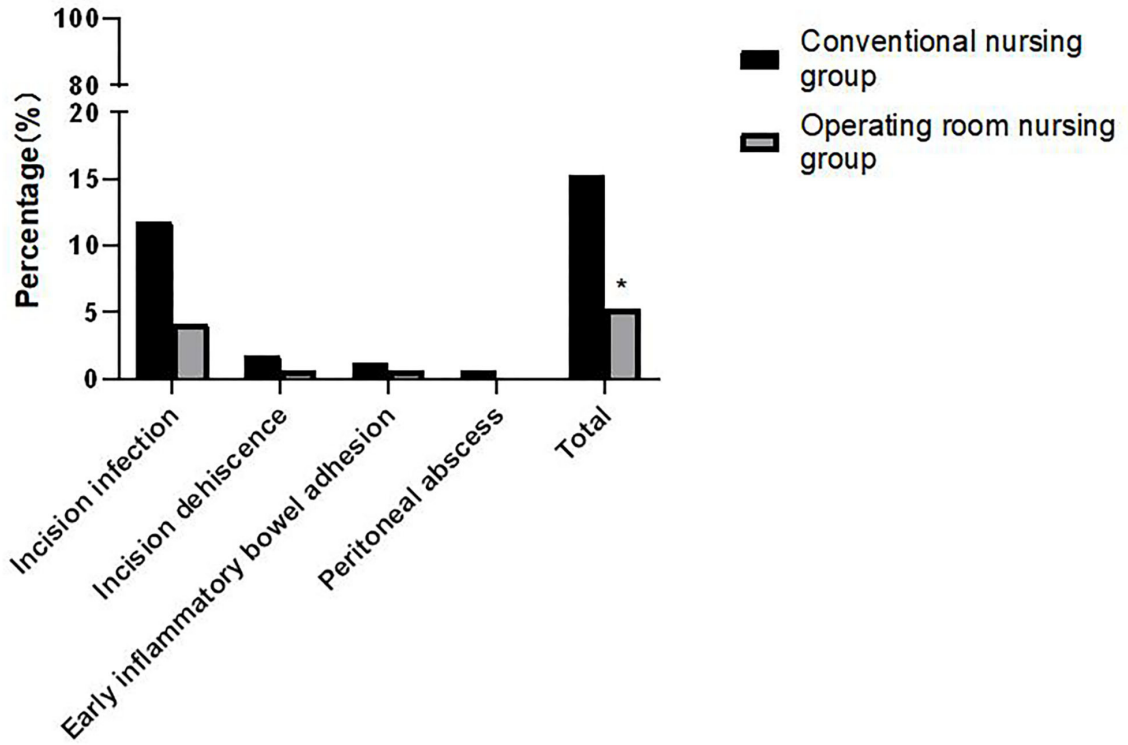


FIGURE 4 | Comparison of postoperative complications between the two groups. Compared with the conventional nursing group, $^{*}p < 0.05$.

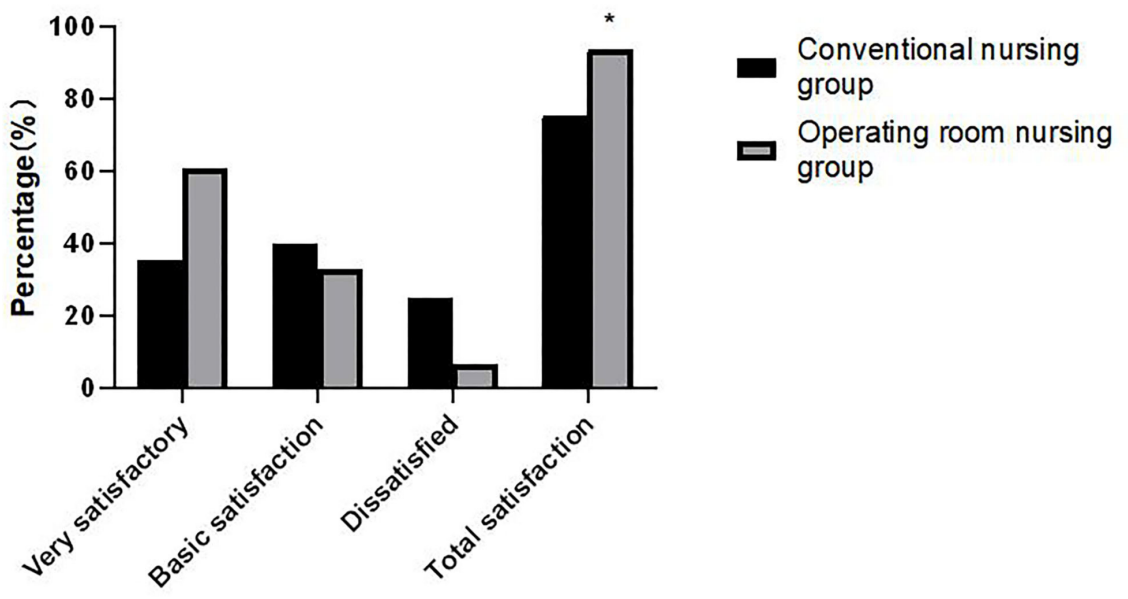


FIGURE 5 | Comparison of nursing satisfaction between the two groups. Compared with the conventional nursing group, $^{*}p < 0.05$.

incision using normal saline irrigation in order to block the path of bacterial infection, and avoid infection (14–16).

Gastrointestinal surgery can arouse the excitement and stimulation of the sympathetic nervous system of the gastrointestinal tract of patients. At the same time, due to the stimulation of anesthetics, traction and other factors, patients are very likely to suffer from inhibition of gastrointestinal peristalsis after surgery, which in turn leads to symptoms of gastrointestinal dysfunction, such as non-flatus, non-defecation and abdominal distension. This may affect the surgical effect and

rehabilitation process of patients (17–19). This study showed that the patients in the operating room nursing group had lower anal exhaust time, first defecation time, and gastric tube removal time than those in the conventional nursing group. It is proved that nursing in operating room was superior to the routine nursing in promoting the recovery of gastrointestinal function. The smooth recovery of gastrointestinal function is an important symbol for the success of the operation. If gastrointestinal dysfunction occurs, it will not only cause water and electrolyte disorders, but also other complications, such as incision infection, dehiscence, early inflammatory bowel adhesion, abdominal abscess, and, in severe cases, death (20, 21). In this study, the incidence of postoperative complications in the operating room nursing group was lower than in the conventional nursing group. Take various preventive measures to reduce the injury caused by operation and the infection rate of incision, further promote the recovery of patients' gastrointestinal function and reduce complications.

Nursing in the operating room gives comfort and encouragement to the psychology of patients. It also introduces successful operations, which may reduce patient anxiety toward similar procedures. By extension, it can improve the satisfaction of patients with the nursing service (22). The results of this study demonstrated that the total satisfaction in the operating room nursing group was significantly higher than that in the conventional nursing group.

To sum up, nursing interventions in the operating room for patients undergoing gastrointestinal surgery can effectively reduce the infection rate of incisions, promote incision healing, improve the gastrointestinal function of patients, and reduce postoperative complications.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First People's Hospital of Lianyungang. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PW was responsible for the writing of the manuscript. HC was responsible for the design of the study. QJ was mainly responsible for the guidance. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Herbert G, Perry R, Andersen HK, Atkinson C, Penfold C, Lewis SJ, et al. Early enteral nutrition within 24 h of lower gastrointestinal surgery versus later commencement for length of hospital stay and postoperative complications. *Cochrane Database Syst Rev.* (2019) 7:4080. doi: 10.1002/14651858.CD004080.pub4
2. Zhang XF, Chen J, Wang PG, Luo SM, Liu NX, Li XM, et al. Surgical site infection after abdominal surgery in China: a multicenter cross-sectional study. *Zhonghua Wei Chang Wai Ke Za Zhi.* (2020) 23:1036–42. doi: 10.3760/cma.j.cn.441530-20200810-00470
3. GlobalSurg Collaborative. Surgical site infection after gastrointestinal surgery in high-income, middle-income, and low-income countries: a prospective, international, multicentre cohort study. *Lancet Infect Dis.* (2018) 18:516–25. doi: 10.1016/S1473-3099(18)30101-4
4. Shen P, Blackham AU, Lewis S, Clark CJ, Howerton R, Mogal HD, et al. Phase II randomized trial of negative-pressure wound therapy to decrease surgical site infection in patients undergoing laparotomy for gastrointestinal, pancreatic, and peritoneal surface malignancies. *J Am Coll Surg.* (2017) 224:726–37. doi: 10.1016/j.jamcollsurg.2016.12.028
5. Maehara Y, Shirabe K, Kohnoe S, Emi Y, Oki E, Kakeji Y, et al. Impact of intra-abdominal absorbable sutures on surgical site infection in gastrointestinal and hepato-biliary-pancreatic surgery: results of a multicenter, randomized, prospective, phase II clinical trial. *Surg Today.* (2017) 47:1060–71. doi: 10.1007/s00595-017-1480-3
6. Deng YH, Yang YM, Ruan J, Mu L, Wang SQ. Effects of nursing care in fast-track surgery on postoperative pain, psychological state, and patient satisfaction with nursing for glioma. *World J Clin Cases.* (2021) 9:5435–41. doi: 10.12998/wjcc.v9.i20.5435
7. Zhong M, Liu D, Tang H, Zheng Y, Bai Y, Liang Q, et al. Impacts of the perioperative fast track surgery concept on the physical and psychological rehabilitation of total hip arthroplasty: A prospective cohort study of 348 patients. *Medicine (Baltimore).* (2021) 100:26869. doi: 10.1097/MD.0000000000026869
8. Xu Y, Wang H, Yang M. Preoperative nursing visit reduces preoperative anxiety and postoperative complications in patients with laparoscopic cholecystectomy: A randomized clinical trial protocol. *Medicine (Baltimore).* (2020) 99:22314. doi: 10.1097/MD.0000000000022314
9. Zywot A, Lau CSM, Stephen Fletcher H, Paul S. Bundles prevent surgical site infections after colorectal surgery: meta-analysis and systematic review. *J Gastrointest Surg.* (2017) 21:1915–30. doi: 10.1007/s11605-017-3465-3
10. Espin Basany E, Solís-Peña A, Pellino G, Kreisler E, Fraccalvieri D, Muinelo-Lorenzo M, et al. Preoperative oral antibiotics and surgical-site infections in colon surgery (ORALEV): a multicentre, single-blind, pragmatic, randomised controlled trial. *Lancet Gastroenterol Hepatol.* (2020) 5:729–38. doi: 10.1016/S2468-1253(20)30075-3
11. Andersson R, Søreide K, Ansari D. Surgical infections and antibiotic stewardship: in need for new directions. *Scand J Surg.* (2021) 110:110–2. doi: 10.1177/1457496919891617
12. Shao W, Wang H, Chen Q, Zhao W, Gu Y, Feng G. Enhanced recovery after surgery nursing program, a protective factor for stoma-related complications in patients with low rectal cancer. *BMC Surg.* (2020) 20:316. doi: 10.1186/s12893-020-00978-3
13. Robertson JM, Dias RD, Yule S, Smink DS. Operating room team training with simulation: a systematic review. *J Laparoendosc Adv Surg Tech A.* (2017) 27:475–80. doi: 10.1089/lap.2017.0043
14. Sandelin A, Kalman S, Gustafsson BÅ. Prerequisites for safe intraoperative nursing care and teamwork-Operating theatre nurses' perspectives: a qualitative interview study. *J Clin Nurs.* (2019) 28:2635–43. doi: 10.1111/jocn.14850
15. Xu M, Zhang H, Tang T, Zhou J, Zhou W, Tan S, et al. Potential and applications of capillary electrophoresis for analyzing traditional Chinese medicine: a critical review. *Analyst.* (2021) 146:4724–36. doi: 10.1039/D1AN00767J
16. Yang HK, Ji J, Han SU, Terashima M, Li G, Kim HH, et al. Extensive peritoneal lavage with saline after curative gastrectomy for gastric cancer (EXPEL): a

multicentre randomised controlled trial. *Lancet Gastroenterol Hepatol.* (2021) 6:120–7. doi: 10.1016/S2468-1253(20)30315-0
17. Hanssen I, Smith Jacobsen IL, Skråmm SH. Non-technical skills in operating room nursing: Ethical aspects. *Nurs Ethics.* (2020) 27:1364–72. doi: 10.1177/0969733020914376
18. Xiang J, Liu F, Wang B, Chen L, Liu W, Tan S. A literature review on maillard reaction based on milk proteins and carbohydrates in food and pharmaceutical products: advantages, disadvantages, and avoidance strategies. *Foods.* (2021) 10:1998. doi: 10.3390/foods10091998
19. Chapman SJ, Thorpe G, Vallance AE, Harji DP, Lee MJ, Fearnhead NS, et al. Systematic review of definitions and outcome measures for return of bowel function after gastrointestinal surgery. *BJS Open.* (2018) 3:1–10. doi: 10.1002/bjs5.102
20. Adiamah A, Skorepa P, Weimann A, Lobo DN. The impact of preoperative immune modulating nutrition on outcomes in patients undergoing surgery for gastrointestinal cancer: a systematic review and meta-analysis. *Ann Surg.* (2019) 270:247–56. doi: 10.1097/SLA.0000000000003256
21. Ogata H, Nakamoto S, Miyawaki H, Ueki R, Kariya N, Tatara T, et al. Association between intraoperative nociception and postoperative complications in patients undergoing laparoscopic gastrointestinal surgery. *J Clin Monit Comput.* (2020) 34:575–81. doi: 10.1007/s10877-019-00347-3
22. Ji Y, Han S, Wang B. Effects of situation-background-assessment-recommendation handover combined with detail nursing intervention on patients with infections. *Am J Transl Res.* (2021) 13:9056–62. doi: 10.1177/2374373521997733

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang, Chen and Ji. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 17 February 2022
doi: 10.3389/fsurg.2022.840420

Effect of Lung Protective Ventilation Combined With Flurbiprofen Axetil on Immune Function During Thoracoscopic Radical Resection of Lung Cancer

Jia Yuan†, *Shenghua Cen*†, *Jingjing Li, Kun Wang, Qixu Chen, Hongbin Li and Yan Zhang**

Department of Anesthesiology, Zhoushan Hospital, Zhoushan, China

The decreased immune function of patients with lung cancer has always been the focus of clinical attention. However, the stress response caused by surgery, anesthesia and pain will further reduce the body's immune function and affect the prognosis of patients to a certain extent. It was found that both protective ventilation and flurbiprofen ester pretreatment could reduce the immunosuppression caused by stress response. In this study, 120 lung cancer patients treated with video-assisted thoracoscopic radical resection were divided into group A, group B, group C and group D, which were treated with conventional mechanical ventilation, lung protective ventilation, conventional mechanical ventilation + flurbiprofen axetil and lung protective ventilation + flurbiprofen axetil, respectively. The results showed that the levels of CD3+, CD4+, CD4/CD8+, and NK in groups A, B, and C were lower than T0 on T1, T2, and T3, while those indicators in group D were lower than T0 on T1 and T2 ($P < 0.05$). The above indicators in group D were higher than those in the other three groups on T1, T2, and T3 ($P < 0.05$). The above indicators were statistically significant compared with those in group A and group C, group B and group D, and group A and group B at T1, T2, and T3 ($P < 0.05$). The comparisons of CD3+, CD4+, CD4/CD8+, and NK among the four groups within different time groups, and the repeated - measures analysis of variance (repeated - measures ANOVA) showed that there were interactions among time, group, and between groups × within groups ($P < 0.05$). It was confirmed that lung protective ventilation combined with flurbiprofen axetil could alleviate the immunosuppression of patients undergoing thoracoscopic radical lung cancer, providing a new idea for clinical treatment.

Keywords: lung cancer, lung protective ventilation, flurbiprofen axetil, thoracoscopic radical resection, immunologic function

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Yang Liu,
The First Medical Center of Chinese PLA General Hospital, China
Fenglong Sun,
Capital University of Medical Sciences, China

***Correspondence:**
Yan Zhang
zsyyzy316@163.com

†*These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *21 December 2021*
Accepted: *04 January 2022*
Published: *17 February 2022*

Citation:
Yuan J, Cen S, Li J, Wang K, Chen Q, Li H and Zhang Y (2022) Effect of Lung Protective Ventilation Combined With Flurbiprofen Axetil on Immune Function During Thoracoscopic Radical Resection of Lung Cancer. Front. Surg. 9:840420. doi: 10.3389/fsurg.2022.840420

INTRODUCTION

Lung cancer can be divided into two types of non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), and 80% of patients with NSCLC. The 5-year survival rate of lung cancer patients is low, and in recent years, the onset age of lung cancer patients also tends to be younger (1). Thoracoscopic radical resection of lung cancer is currently an important means of treatment

for lung cancer. But it needs to be performed under mechanical ventilation, which has a certain inhibitory effect on patients' autoimmunity, while narcotic drugs (especially opioids) also have an impact on immunity (2, 3). However, immunity is closely related to the patient's ability to resist external pathogen infection, and the balance regulation of immune system also plays an important role in maintaining body homeostasis. Once the immune balance is out of balance, the body is very prone to infection, and autoimmune diseases. Therefore, alleviating the immunosuppressive effects of mechanical ventilation and anesthesia is of great significance for improving the prognosis of patients undergoing video-assisted thoracoscopic radical resection of lung cancer (4).

In recent years, studies have pointed out that lung protective ventilation and flurbiprofen ester can weaken the inhibition of the above factors on the immune system of patients. On this basis, we hereby studies the effect of combination of the two on immune function in patients undergoing radical lung cancer surgery, as reported below.

MATERIALS AND METHODS

General Data

One hundred twenty patients with lung cancer who received thoracoscopic radical resection of lung cancer in our hospital from April 2017 to June 2020 were included as research objects and divided into 4 groups. The ages of group A, B, C, and D were (56.15 ± 3.65) years old, (57.24 ± 3.95) years old, (55.78 ± 7.21) years old, and (57.16 ± 3.65) years old. Male and female composition: 19/11, 17/13, 18/12, and 19/11; ASAi/ii constituted 6/24, 2/28, 7/23 and 4/26; BMI was (23.15 ± 2.39) kg/m^2, (23.36 ± 3.01) kg/m^2, (22.96 ± 2.57) kg/m^2 and (22.37 ± 5.14) kg/m^2. The mean course of disease was (6.17 ± 1.52) months, (6.25 ± 1.37) months and (6.33 ± 1.29) months. There was no difference in the general data of the four groups($P > 0.05$).

Inclusion Criteria

i) 18–69 years old; ii) The BMI was 18–28 kg/m^2; iii) Meeting the Class I–II criteria of the American Association of Anesthesiologists (5); iv) Sign informed consent form.

Exclusion Criteria

i) Combined with fever, cough and gastrointestinal ulcers; ii) Patients who took NSAIDs for a long time before entering the group; iii) Patients with combined history of consciousness disorder and mental disease; iv) Patients with pulmonary tuberculosis and bronchial asthma; v) Patients requiring blood transfusion during the operation; vi) Combined with kidney, liver, heart and other major organ dysfunction; vii) Taking glucocorticoids and immunosuppressive agents before operation; viii) Patients with coagulation abnormalities and severe endocrine diseases; ix) Allergic to drugs used in this study; x) The pathological type of lung cancer is not suitable for thoracoscopic lung cancer radical surgery.

Methods of Anesthesia and Mechanical Ventilation

Routine anesthesia: 0.5 mg penehycliane hydrochloride was intravenously injected 30 min before surgery, oxygen was inhaled via nasal catheter, peripheral venous access of the upper limb was opened, SpO_2, HR and other indicators were detected. The non-operative radial artery puncture was performed under local anesthesia, and the invasive blood pressure was monitored. The lateral internal jugular vein puncture was completed under local anesthesia ultrasound guidance, and the CVP was maintained within the range of 5–10 cmH_2O. Midazolam, etomidate, sufentanil and rocuronium were given intravenously at doses of 0.05 mg/kg, 0.2 mg/kg, 0.4 ug/kg and 0.8 mg/kg. Indwelling of the left double-lumen bronchocatheter was performed under laryngoscopy. Under the assistance of a laryngoscope, the left double-cavity bronchial catheter was placed. Localization was performed by fiberoptic bronchoscopy. Mechanical ventilation was performed with A5 anesthesia, and volumetric controlled ventilation mode was used. After the patient's position was changed, the indwelling position of the double lumen tube was observed again.

Group A underwent conventional ventilation: one-lung ventilation was performed at Vr8ml/kg and RR13–16 times/min; The bilateral lung ventilation rate was Vr10ml/kg, and RR10–12 times /min. Group B was treated with protective ventilation: One-lung ventilation was given at Vr6ml/kg and RR14–16 times/min. Two-lung ventilation was given at Vr8ml/kg and RR12–14 times /min. One-lung ventilation was performed with PEEP5 cmH_2O, oxygen flow rate of 1–2 L/min, I: E ratio of 1:2, and FIO 2100%. $PETCO_2$ was maintained at 35–45 mmHg. Anesthesia was maintained by target controlled infusion of remifentanil and propofol, with target plasma concentrations of 2–4 ng/mL and 2–4 mg/mL, respectively. During infusion, the dosage and infusion speed were adjusted according to the arterial pressure to maintain the arterial pressure fluctuation to be ≤20% of the preoperative level. Before skin incision, 0.2 ug/kg sufentanil was given intravenously, while 0.05 mg/kg atracurium besylate was given intermittently during the process, to maintain the Narcotrend index within the range of 37–64. Also, 6 mL kg/h compound sodium lactate was given intravenously during the operation. All patients stopped drug administration at the completion of the operation. After the patients were conscious and the muscle strength recovered, the double-lumen endobronchial tube was removed. Meanwhile, the same scheme of analgesic pump was used for analgesia within 24 h after the operation. In addition, in the groups C and B, flurbiprofen axetil 2 mg/Kg was given intravenously 5 min before anesthesia induction.

Observation Indicators

T0-t4 was used to represent preoperative, post-operative, postoperative 24 h, 72 h, and 7 d. At the above time, the expression of CD3+, CD4+, CD8+ and NK cells was detected by FC500 flow cytometry, and CD4+/CD8+ was calculated. 2 ml venous blood was taken in the fasting state in the morning, and heparin anticoagulant blood was taken (1: 9) 100P1 was added with monoclonal antibody, kept away from light for 12 min at

room temperature, centrifuged, washed twice by PBS, and then added with 0.5 mL 1% paraformaldehyde. Machine detection was performed. Homotype negative control was performed for each sample at the same time. The number of cells per sample was 10,000, and the percentage of positive cells was calculated.

Statistical Methods

All data were processed with SPSS 22.0 statistical software, and GraghPad prism 8 was used to make statistical graphs. Measurement data are expressed as mean ± standard deviation ($\bar{X}\pm$ s), the comparisons of four groups at different times were performed with repeated measures analysis of variance and F test. The count data between groups were expressed in percentage (%) and tested by "x^2". The difference is statistically significant when $P < 0.05$.

RESULTS

Comparison of CD3+ Expression

CD3+ in Groups A, B, and C was lower than T0 on T1, T2, and T3, while it was lower than T0 on T1 and T2 in Group D; T1, T2, and T3 in group D were higher than those of the other three groups from T1 to T3. The CD3+ expressions on T1, T2, and T3 in group A and group C, group B and group D, and group A and group B were all statistically significant ($P < 0.05$). Repeated measures analysis of variance: $F_{time} = 121.201$ ($P < 0.001$); $F_{Group} = 76.951$ ($P < 0.001$); $F_{Time\times grouping} = 65.150$ ($P < 0.001$, **Table 1**).

Comparison of CD4+ Expression

CD4+ in group A, B and C was lower than T0 at T1, T2, and T3, and lower than T0 at T1 and T2 in group D. The CD4+ of group D was higher than that of the other three groups at T1, T2, and T3. The expression of CD4+ in group A and GROUP C, group B and group D, and group A and group B was statistically significant at T1, T2, and T3 ($P < 0.05$). The comparison of CD4+ in group A and group B at T1, T2, and T3 was statistically significant ($P < 0.05$). Anova of repeated measures: $F_{time} = 89.113$ ($P < 0.001$); $F_{Group} = 89.658$ ($P < 0.001$); $F_{Time\times grouping} = 41.625$ ($P < 0.001$, **Table 2**).

Comparison of CD4+/CD8+ Expression

CD4+/CD8+ in groups A, B and C were lower than T0 on T1, T2, and T3, while CD4+/CD8+ in group D was lower than T0 on T1 and T2. Group D had higher CD4+/CD8+ values on T1, T2, and T3 than the other three groups. The comparisons of T1, T2, and T3 between group A and group C, group B and group D, and group A and group B were statistically significant ($P < 0.05$). Repeated measures analysis of variance: $F_{time} = 69.067$ ($P < 0.001$); $F_{Group} = 49.167$ ($P < 0.001$); $F_{Time\times grouping} = 29.117$ ($P < 0.001$, **Table 3**).

Comparison of NK Expression

NK in group A, B and C was lower than T0 at T1, T2, and T3, and NK in group D was lower than T0 at T1 and T2. NK in group D was higher at T1, T2, and T3 than in the other three groups. There were statistically significant differences between group A and GROUP C, group B and group D, group A and group B at T1, T2, and T3 ($P < 0.05$). Anova of repeated measures: $F_{time} = 59.621$ ($P < 0.001$); $F_{Group} = 39.651$ ($P < 0.001$); $F_{Time\times grouping} = 23.780$ ($P < 0.001$, **Table 4**).

DISCUSSION

Deficiencies of Conventional Mechanical Ventilation

Mechanical ventilation is an important supportive treatment in ICU. It can not only effectively maintain the airway patency of patients, improve oxygenation and ventilation, but also prevent carbon dioxide accumulation and hypoxia in the body, thereby enabling the body to avoid respiratory failure caused by basic lesions. However, many studies have confirmed that within 2–4 h of conventional mechanical ventilation, the susceptibility of patients to bacteremia is significantly higher than that of patients without mechanical ventilation. Excessive mechanical ventilation results in the accumulation of cytokines, white blood cells, and neutrophil-dependent tissue damage, resulting in cell activation and release of mediators, leading to alveolar inflammation (6). In addition, the observation of NK cell expression during conventional mechanical ventilation (10 ml/kg tidal volume) in infants without pulmonary diseases undergoing cardiac catheterization also showed that the activity of NK cells in peripheral blood began to decrease 2 h after the operation. The subjects of this study were lung cancer patients, and the results showed that the levels of CD3+, CD4+, CD4/CD8+, and NK in the four groups at T1 were lower than those at T0, which confirm that routine mechanical ventilation can adversely affect the patient's immune system.

Application of Lung Protective Ventilation

Lung protective ventilation strategies include appropriate PEEP and low tidal volumes (7). In animal experiments, the expression of NK cells in peripheral blood of mice with different mechanical ventilation schemes was compared and analyzed after 4 h of ventilation. It was found that high tidal volume ventilation could cause significant immunosuppression, and the decline degree of NK cells in mice with high tidal volume and without PEEP was more significant than that with high tidal volume and PEEP. And the combination of low tidal volume and PEEP could alleviate the immunosuppression caused by mechanical ventilation (8). In this study, the expression levels of the above indicators in group A were lower than those in group B from T1 to T3 ($P < 0.05$). This is due to compared with conventional mechanical ventilation, lung protective ventilation can alleviate alveolar-capillary barrier damage and inhibit inflammatory response. It was reported that 90% of patients with general anesthesia can appear atelectasis. During general anesthesia, low

TABLE 1 | Comparison of CD3+ expression among four groups ($\bar{X}\pm$ s).

Group		T0	T1	T2	T3	T4
Group A	30	65.52 ± 6.51	43.62 ± 5.36[a]	49.65 ± 7.75[a]	54.65 ± 6.97[a]	63.98 ± 8.98
Group B	30	65.15 ± 6.98	50.52 ± 8.65[a]	56.21 ± 6.99[a]	60.36 ± 5.61[a]	65.15 ± 5.87
Group C	30	64.75 ± 8.62	48.65 ± 7.16[a]	54.12 ± 5.98[a]	58.62 ± 5.67[a]	64.54 ± 8.64
Group D	30	66.65 ± 7.18	57.65 ± 5.49[a]	60.54 ± 9.65[a]	65.98 ± 7.69	65.78 ± 8.34
F/P	-	2.575/0.462	21.90/0.000	10.33/0.000	15.50/0.000	0.28/0.841
Q/P	A and B	0.275/>0.05	5.557/<0.01	4.656/<0.01	5.7101/<0.01	0.796/>0.05
Q/P	A and C	0.573/>0.05	4.052/<0.01	3.171/<0.01	3.970/<0.01	0.381/>0.05
Q/P	A and D	0.840/>0.05	11.301/<0.01	7.731/<0.01	11.330/<0.05	1.225/>0.05
Q/P	B and C	0.298/>0.05	1.506/>0.05	1.485/>0.05	1.740/>0.05	0.415/>0.05
Q/P	B and D	1.116/>0.05	5.743/<0.01	3.076/<0.01	5.620/<0.01	0.429/>0.05
Q/P	C and D	1.413/>0.05	7.249/<0.01	4.561/<0.01	7.360/<0.01	0.844/>0.05

Comparison with T0, [a]P < 0.05.

TABLE 2 | Comparison of CD4+ expression among the four groups ($\bar{X}\pm$ s).

Group		T0	T1	T2	T3	T4
Group A	30	39.12 ± 5.98	26.54 ± 4.98[a]	28.13 ± 3.65[a]	31.26 ± 4.54[a]	37.54 ± 9.54
Group B	30	39.49 ± 6.21	31.32 ± 5.15[a]	33.35 ± 5.65[a]	34.65 ± 5.45[a]	38.32 ± 6.67
Group C	30	39.06 ± 7.11	29.65 ± 3.54[a]	31.23 ± 7.45[a]	34.59 ± 5.18[a]	38.27 ± 7.14
Group D	30	38.95 ± 6.98	34.54 ± 5.24[a]	36.57 ± 5.65[a]	38.67 ± 6.87	38.14 ± 8.03
F/P	-	0.04/0.9901	14.63/0.000	11.42/0.000	8.87/0.000	0.06/0.980
Q/P	A and B	0.308/>0.05	5.480/<0.01	4.965/<0.01	3.330/<0.05	0.539/>0.05
Q/P	A and C	0.05/>0.05	3.565/<0.01	2.948/<0.05	3.271/<0.05	0.505/>0.05
Q/P	A and D	0.141/>0.05	9.171/<0.01	8.027/<0.01	7.279/<0.01	0.415/>0.05
Q/P	B and C	0.358/>0.05	1.914/>0.05	2.016/>0.05	0.059/>0.05	0.035/>0.05
Q/P	B and D	0.449/>0.05	3.691/<0.01	3.062/<0.05	3.949/<0.01	0.125/>0.05
Q/P	C and D	0.092/>0.05	5.606/<0.01	5.079/<0.01	4.008/<0.05	0.090/>0.05

Comparison with T0, [a]P < 0.05.

TABLE 3 | Comparison of CD4+/CD8+ expression among four groups ($\bar{X}\pm$ s).

Group		T0	T1	T2	T3	T4
Group A	30	2.51 ± 1.32	1.30 ± 0.39[a]	1.40 ± 0.59[a]	1.62 ± 0.41[a]	2.47 ± 0.58
Group B	30	2.52 ± 1.49	1.65 ± 0.57[a]	1.75 ± 0.32[a]	2.16 ± 0.39[a]	2.56 ± 0.52
Group C	30	2.59 ± 0.95	1.52 ± 0.32[a]	1.72 ± 0.31[a]	2.03 ± 0.40[a]	2.50 ± 0.59
Group D	30	2.60 ± 0.57	1.99 ± 0.36[a]	2.36 ± 0.29[a]	2.46 ± 0.39	2.58 ± 0.38
F/P	-	0.05/0.985	14.11/0.000	30.59/0.000	23.04/0.000	0.29/0.835
Q/P	A and B	0.048/>0.05	4.553/<0.01	4.828/<0.01	7.439/<0.05	0.940/>0.05
Q/P	A and C	0.385/>0.05	2.862/<0.01	4.414/<0.05	5.648/<0.05	0.313/>0.05
Q/P	A and D	0.433/>0.05	8.977/<0.01	13.242/<0.01	11.572/<0.01	1.149/>0.05
Q/P	B and C	0.337/>0.05	1.691/>0.05	0.414/>0.05	1.791/>0.05	0.627/>0.05
Q/P	B and D	0.385/>0.05	4.423/<0.01	8.414/<0.05	4.133/<0.01	0.209/>0.05
Q/P	C and D	0.048/>0.05	6.115/<0.01	8.828/<0.01	5.924/<0.05	0.836/>0.05

Comparison with T0, [a]P < 0.05.

pulmonary volume ventilation can lead to repeated collapse and reopening of the alveolar space, which further affects small airway epithelial cells, leading to the occurrence of atelectasis (9, 10). Driven by experimental and clinical studies, mechanical ventilation can reduce tidal volume and limit lung dilation to a certain extent. Previous studies have pointed out that when tidal volume is 15 ml/kg, end-expiratory lung volume can be improved and intraoperative atelectasis can be relieved

TABLE 4 | Comparison of NK expression among four groups ($\bar{X}\pm$ s).

Group		T0	T1	T2	T3	T4
Group A	30	22.10 ± 0.85	11.03 ± 1.65[a]	13.86 ± 1.32[a]	16.02 ± 1.36[a]	22.03 ± 1.36
Group B	30	22.03 ± 0.74	14.52 ± 1.36[a]	16.26 ± 1.47[a]	20.03 ± 2.03[a]	22.42 ± 2.45
Group C	30	21.98 ± 0.69	14.03 ± 1.59[a]	17.36 ± 2.08[a]	19.65 ± 1.99[a]	21.89 ± 1.98
Group D	30	22.19 ± 0.97	17.62 ± 1.49[a]	20.36 ± 3.65[a]	23.92 ± 2.46	22.80 ± 0.65
F/P	–	0.37/0.774	93.72/0.000	40.50/0.000	78.32/0.000	1.65/0.181
Q/P	A and B	0.468/>0.05	12.523/<0.01	5.663/<0.01	10.988/<0.01	1.223/>0.05
Q/P	A and C	0.802/>0.05	10.765/<0.01	8.259/<0.01	9.947/<0.01	0.439/>0.05
Q/P	A and D	0.601/>0.05	23.646/<0.01	15.338/<0.01	21.647/<0.01	2.415/>0.05
Q/P	B and C	0.334/>0.05	1.758/>0.05	2.596/>0.05	1.041/>0.05	1.663/>0.05
Q/P	B and D	1.069/>0.05	11.123/<0.01	9.675/<0.05	10.659/<0.01	1.192/>0.05
Q/P	C and D	1.403/>0.05	12.882/<0.01	7.079/<0.01	11.700/<0.05	2.855/>0.05

Comparison with T0, [a]$P < 0.05$.

(11). In addition, if there are no contraindications, the use of positive end-expiratory pressure and lung recruitment can also help prevent end-expiratory lung volume loss and small airway closure during anesthesia (12). Although 10 ml/kg tidal volume was mostly used in clinical practice in the past, anesthesiologists would reduce tidal volume during single ventilation. Moreover, many studies have pointed out that a tidal volume of 4–5 mL/kg can better protect lung tissue while fully satisfying the gas exchange (13). The tidal volume selected for lung protective ventilation in this study belongs to the safe range (14).

Flurbiprofen Ester Alleviates Immunosuppression

Flurbiprofen ester is a non-steroidal analgesic drug, which can inhibit coX-2 release, prostaglandin synthesis, inflammatory factor release and other mechanisms through selective aggregation in surgical incision and inflammatory tissue, and exert targeted analgesic effect. It can reduce the dose of opioids, and is currently mainly used for cancer pain treatment, postoperative analgesia and preemptive analgesia et al. (15, 16). In addition, compared with tramadol or morphine, flurbiprofen had the weakest immunosuppressive effect during postoperative analgesia (17). Previous studies have indicated that postoperative analgesia with flurbiprofen axetil can alleviate postoperative immunosuppression, and protect the immune function of cancer patients (18, 19). Zhang et al. (20) pointed out that the decrease of CD4+, CD3+, CD4+/CD8+ and NK cell activity in sufentanil combined with flurbiprofen ester was lower than that in sufentanil alone. Anova of this study showed that group and time had impact on each indicator ($P < 0.001$), which suggesting that flurbiprofen ester could relieve immunosuppression caused by anesthesia or surgery.

In summary, lung protective ventilation combined with flurbiprofen axetil in video-assisted thoracoscopic lung cancer radical surgery can alleviate immunosuppression and facilitate postoperative recovery, which is worthy of promotion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Zhoushan Hospital of Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JY and SC are mainly responsible for the writing of the paper. JL is responsible for the design of the research. KW and QC are responsible for the detection and evaluation of the results. HL is responsible for data recording and statistics. YZ is the instructor of the entire research. All authors contributed to the article and approved the submitted version.

FUNDING

This work was funded the Department of Science and Technology Program in Zhejiang Province (2018C37134) and the Health Commission of Zhejiang Province (2018KY855).

REFERENCES

1. McDonnell KK, Gallerani DG, Newsome BR, Owens OL, Beer J, Myren-Bennett AR, et al. A prospective pilot study evaluating feasibility and preliminary effects of breathe easier: a mindfulness-based intervention for survivors of lung cancer and their family members (Dyads). *Integr Cancer Ther.* (2020) 19:1872–6. doi: 10.1177/1534735420969829
2. Webb LA, Kane McDonnell K, Arp Adams S, Davis RE, Felder TM. Exploring stigma among lung cancer survivors: a scoping literature review. *Oncol Nurs Forum.* (2019) 46:402–18. doi: 10.1188/19.ONF.402-418

3. O'Gara B, Talmor D. Perioperative lung protective ventilation. *BMJ.* (2018) 362:3030. doi: 10.1136/bmj.k3030
4. Bertoni M, Spadaro S, Goligher E C. Monitoring patient respiratory effort during mechanical ventilation: lung and diaphragm-protective ventilation. *Crit Care.* (2020) 24:106. doi: 10.1186/s13054-020-2777-y
5. Amiri AA, Karvandian K, Ramezani N, Amiri AA. Short-term memory impairment in patients undergoing general anesthesia and its contributing factors. *Saudi J Anaesth.* (2020) 14:454–8. doi: 10.4103/sja.SJA_651_19
6. Schepens T, Dres M, Heunks L, Goligher EC. Diaphragm-protective mechanical ventilation. *Curr Opin Crit Care.* (2019) 25:77–85. doi: 10.1097/MCC.0000000000000578
7. Qu Z, Zhang H, Zhou S. Lung-protective ventilation in cardiac surgery: comment. *Anesthesiology.* (2020) 132:1610–1. doi: 10.1097/ALN.0000000000003292
8. Wong JJ, Lee SW, Tan HL, Ma YJ, Sultana R, Mok YH, et al. Lung-protective mechanical ventilation strategies in pediatric acute respiratory distress syndrome. *Pediatr Crit Care Med.* (2020) 21:720–8. doi: 10.1097/PCC.0000000000002324
9. Fuller B M. Help for adherence to lung-protective ventilation … for those who will accept it. *Chest.* (2020) 158:2247–8. doi: 10.1016/j.chest.2020.06.035
10. Zhou XL, Wei XJ, Li SP, Ma HL, Zhao Y. Lung-protective ventilation worsens ventilator-induced diaphragm atrophy and weakness. *Respir Res.* (2020) 21:16. doi: 10.1186/s12931-020-1276-7
11. Dianti J, Matelski J, Tisminetzky M, Walkey AJ, Munshi L, Del Sorbo L, et al. Comparing the effects of tidal volume, driving pressure, and mechanical power on mortality in trials of lung-protective mechanical ventilation. *Respir Care.* (2021) 66:221–227. doi: 10.4187/respcare.07876
12. Nyberg A, Larsson A, Jylhävä J, Hurme M, Sperber J, Lipcsey M, et al. Lung-protective ventilation suppresses systemic and hepatic vein levels of cell-free DNA in porcine experimental post-operative sepsis. *BMC Pulm Med.* (2020) 20:206. doi: 10.1186/s12890-020-01239-y
13. Piran P, Stevens R D. Lung-protective ventilation and adjunctive strategies to manage respiratory failure: are they safe in the neurological patient? *Curr Opin Crit Care.* (2021) 27:115–9. doi: 10.1097/MCC.0000000000000809
14. Sahetya S K. Searching for the optimal positive end-expiratory pressure for lung protective ventilation. *Curr Opin Crit Care.* (2020) 26:53–8. doi: 10.1097/MCC.0000000000000685
15. Ji X, Cui W, Zhang B, Shan S. Effect of lung protective ventilation on perioperative pulmonary infection in elderly patients with mild to moderate COPD under general anesthesia. *J Infect Public Health.* (2020) 13:281–6. doi: 10.1016/j.jiph.2019.11.021
16. Wang RD, Sheng XR, Guan WX, Wang M, Peng C, Yang YY, et al. Flurbiprofen axetil for postoperative analgesia in upper abdominal surgery: a randomized, parallel controlled, double-blind, multicenter clinical study. *Surg Today.* (2020) 50:749–56. doi: 10.1007/s00595-019-01951-1
17. Wang D, Yang SK, Zhao MX, Tang YZ, Ou-Yang W, Zhang H, et al. Low dose of flurbiprofen axetil decrease the rate of acute kidney injury after operation: a retrospective clinical data analysis of 9915 cases. *BMC Nephrol.* (2020) 21:52. doi: 10.1186/s12882-020-1711-5
18. Kotera A. Efficacy of flurbiprofen axetil for preventing postanesthetic shivering in patients undergoing gynecologic laparotomy surgeries. *JA Clin Rep.* (2020) 6:96. doi: 10.1186/s40981-020-00403-x
19. Wang X, Wang Y, Hu Y, Wang L, Zhao W, Wei L, et al. Effect of flurbiprofen axetil on postoperative delirium for elderly patients. *Brain Behav.* (2019) 9:1290. doi: 10.1002/brb3.1290
20. Zhang J, Zhang H, Zhao L, Gu J, Feng Y, An H. Population pharmacokinetic modeling of flurbiprofen, the active metabolite of flurbiprofen axetil, in Chinese patients with postoperative pain. *J Pain Res.* (2018) 11:3061–70. doi: 10.2147/JPR.S176475

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Yuan, Cen, Li, Wang, Chen, Li and Zhang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 18 February 2022
doi: 10.3389/fsurg.2022.841296

Analysis of the Effect of Phacoemulsification and Intraocular Lens Implantation Combined With Trabeculectomy on Cataract and Its Influence on Corneal Endothelium

Bin Wang and Liqin Tang*

Department of Ophthalmology, The First People's Hospital of Fuyang District, Hangzhou, China

Objective: This study aimed to discuss the effect of phacoemulsification and intraocular lens implantation (PHACO + IOL) combined with trabeculectomy (TRAB) on cataracts and its influence on the corneal endothelium.

Methods: We selected 120 cataract patients admitted to our hospital from January 2018 to January 2021. According to different surgical methods, they were divided into the control group and the observation group. The observation group was treated with PHACO + IOL combined with TRAB, the control group only received PHACO. The clinical effect, ophthalmic-related parameters, corneal endothelium, complications, the satisfaction of the two groups were observed.

Results: The total effective rate and total satisfaction rate of the observation group were significantly higher than the control group ($P < 0.05$). One month after the operation, the vision and central anterior chamber depth of the observation group were higher than those of the control group, and intraocular pressure (IOP) was lower than that of the control group ($P < 0.05$). One month after the operation, the corneal endothelial cell area and cell density in the observation group were not significantly different from those before operation ($P > 0.05$). There was no significant difference in the total incidence of complications between the two groups ($P > 0.05$).

Conclusion: This study concluded that PHACO + IOL combined with TRAB has a good curative effect in the treatment of cataracts, which can improve the patients' vision and IOP, keep the functional integrity of corneal endothelial cells, and does not increase the occurrence of complications, the patients' satisfaction is high.

Keywords: cataract, phacoemulsification, intraocular lens implantation, trabeculectomy, corneal endothelium

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Guilu Tao,
The Second Affiliated Hospital of Dalian Medical University, China
Feng Qin,
The Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, China

****Correspondence:***
Bin Wang
wangbin72315@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *22 December 2021*
Accepted: *14 January 2022*
Published: *18 February 2022*

Citation:
Wang B and Tang L (2022) Analysis of the Effect of Phacoemulsification and Intraocular Lens Implantation Combined With Trabeculectomy on Cataract and Its Influence on Corneal Endothelium. Front. Surg. 9:841296. doi: 10.3389/fsurg.2022.841296

INTRODUCTION

A cataract is the first kind of blinding eye disease in China and even in the whole world. Usually, the metabolic disorder of the patient's eye lens leads to degeneration of lens protein, which leads to intraocular lens opacity (1). Cataracts mostly occur in middle-aged and elderly people over 50 years old, which can be caused by age, decreased immunity, radiation, drugs, poisoning, and other

factors. However, there are cases of cataracts at birth, and congenital cataracts are mostly influenced by genetic factors, which may be closely related to maternal nutrition deficiency, metabolic disorder, bacterial virus infection during pregnancy, a large amount of harmful radiation, and other factors (2, 3). The main symptoms of cataracts are decreased vision, a spot-shaped fixed shadow in the visual field, one eye diplopia or polyopia, refractive changes, visual distortion, and finally color vision changes, resulting in blindness, these symptoms seriously affect the daily life of patients (4). According to reports, the incidence of cataracts is 60–70% during the period of 50–60 years old, and the incidence of cataracts over 70 years old can reach 80%. At the same time, it is estimated that cataract is the main cause of vision decline, accounting for about 54.20%, and blindness accounts for 17.8%. This disease has become the leading cause of blindness and visual disability in the world (5). With the development of cataract, the patient's lens enters the expansion period, its volume increases, and its anterior-posterior diameter becomes thicker, which increases the contact area between lens and iris, leading to the increase of the resistance of the posterior chamber aqueous drainage to the anterior chamber, resulting in the pupillary block. When the pressure of the posterior chamber cannot overcome the pupillary block, the peripheral iris swells obviously, leading to the stenosis of the anterior chamber angle and even the occlusion of the anterior chamber angle, which leads to glaucoma (6, 7). Therefore, effective treatment of cataract patients is needed in time.

At present, for cataract patients, the therapeutic effect of drugs is not obvious, so the operation has become the main treatment of cataracts. Phacoemulsification intraocular lens implantation (PHACO + IOL) and trabeculectomy (TRAB) are effective methods to treat cataracts, but the single treatment method is difficult to achieve the desired goal (8). In recent years, the choice of surgical scheme for cataract patients is still controversial. With the continuous improvement of medical equipment and medical technology, one-time combined operation is more and more accepted by ophthalmologists. In this study, 120 patients with cataracts were selected as the observation object, O + IOL + TRAB treatment was performed, and the clinical efficacy of this operation for cataracts was discussed. The specific report was as follows.

MATERIALS AND METHODS

Research Object

We selected 120 cataract patients admitted to our hospital from January 2018 to January 2021. According to different surgical methods, they were divided into the control group (58 cases, 81 eyes) and the observation group (62 cases, 85 eyes). There were 31 men and 27 women in the control group, with an average age of (59.34 ± 4.88) years. The average disease duration was (5.2 ± 0.6) months. Emery nuclear hardness classification: 26 eyes were grade I, 29 eyes were grade II, and 26 eyes were grade III. There were 32 men and 30 women in the observation group, with an average age of (59.6 ± 4.71) years. The average disease duration was (5.1 ± 0.7) months. Emery nuclear hardness classification: 27 eyes were grade I, 30 eyes were grade II, and 28 eyes were grade III. General data of the two groups were balanced and comparable ($P > 0.05$). Inclusion criteria include consistent with the diagnosis of cataract, lens opacity can be seen in pupil area, including vacuoles, water cracks, lamellar separation, wheel-width opacity, wedge-shaped opacity, nuclear opacity, and posterior capsular opacity, etc. Exclusion criteria include combined with other eye diseases, high myopia, having a history of an eye operation, complicated with serious organic diseases, and there was eye trauma recently.

Research Methods

Preoperative Treatment

Different intraocular pressure-lowering measures were taken according to the intraocular pressure of the patients when they were admitted to the hospital. The routine treatment was as follows: The two groups were given pilocarpine eye drops, a mydriatic agent, 10 min/time, 3–5 times in a row. Timolol maleate eye drops and tobramycin dexamethasone eye drops were used to control intraocular pressure (IOP) in affected eyes once.

Operation Technique

The observation group was treated with PHACO + IOL combined with TRAB. First of all, Eye surface anesthesia was carried out. PHACO + IOL: A conjunctival flap based on the dome was made above the limbal of the cornea, and a scleral flap with a thickness of 4 × 3 mm and a thickness of 1/2 of the sclera was made after the sclera was burned to stop bleeding. The flap was divided into transparent corneas of 1 mm, and a continuous annular capsulorhexis with a diameter of 5–6 mm was cut in the middle of the anterior capsule of the lens with a capsulorhexis tool. Water was separated and stratified, then, the hard lens nucleus was crushed into a chylous shape by Universal II phacoemulsification machine (Alcon, USA), and then sucked out. The free cortex was sucked out, then the cortex adhered to the capsule was removed. Afterward, the capsule was polished and a viscoelastic agent was inserted. The annular capsulorhexis was enlarged and the IOL was inserted into the capsule and adjusted to the appropriate position. Then TRAB was performed: 1 mm × 3 mm trabecula and the surrounding 1/3 iris were removed, the scleral flap was sutured intermittently with 10-0 nylon thread, viscoelastic agent in the anterior chamber was sucked out, the anterior chamber was formed, and filtration was checked at the same time; the conjunctiva and fascia were reduced and sutured continuously with 10-0 nylon thread. The control group only received PHACO operation, and the operation method was the same as the observation group.

Postoperative Treatment

Indomethacin was given orally, 25 mg/time, 3 times/day; acetazolamide was given orally, 250 mg/time, 2 times/day; tobramycin dexamethasone eye drops and pilocarpine eye drops were given, 1 time/day, and the medication lasted for 5–7 days.

Observation Index

(1) The curative effect was determined 1 month after the operation. The criterion of curative effect: Markedly effective:

the lesion disappeared, without discomfort in the eyes; Effective: the symptoms improved, and the patient felt that the symptoms improved; Invalid: the disease has not improved, and even worsened. Total effective rate = markedly effective rate + effective rate.

(2) Before and 1 month after the operation, the vision was measured by comprehensive refractometer, IOP was measured by non-contact tonometer, and ophthalmic related parameters such as central anterior chamber depth (cACD), lens thickness (LT), and axial length (AL) were measured by A-mode ultrasound, each eye was tested 10 times and the average value was taken.

(3) Before and 1 month after the operation, at the workstation equipped with image processing, the images of the central living area of corneal endothelial cells of patients were obtained by using a non-contact corneal endothelial cell microscope, and the corneal endothelial cell area (ECA) and corneal endothelial cell density (CD) were measured.

(4) The complications such as the shallow anterior chamber, anterior chamber hemorrhage, cellulose exudation of iris, corneal edema, corneal endothelial fold, and anterior chamber inflammation were recorded after the operation.

(5) The satisfaction questionnaire prepared by the undergraduate department was used to evaluate patients' satisfaction from the aspects of visual condition, clarity, comfort, stability, and other indicators. The Likert 5 method was used to score, and the score of very satisfaction was 90–100 points, satisfaction was 70–89 points, and dissatisfaction was < 70 points. Total satisfaction = very satisfaction rate + satisfaction rate. The self-made questionnaire in our hospital had good reliability, with a reliability of .81.

Statistical Methods

For data processing, SPSS 22 software, Armonk, NY; IBM Corporation was used, and the enumeration data were expressed as rate (%), χ^2 test was used for comparison. Measurement data were expressed as ($\bar{x} \pm$ s), t-test was used for comparison. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Clinical Effect of Two Groups

The total effective rate of the observation group was 98.82%, which was significantly higher than that of the control group (87.65%) ($P < 0.05$) (**Table 1**).

Ophthalmic Related Parameters of Two Groups

One month after the operation, the vision, IOP, cACD, and LT of the two groups were significantly different from those before operation ($P < 0.05$). One month after the operation, the vision and cACD of the observation group were higher than those of the control group, and IOP was lower than that of the control group ($P < 0.05$) (**Figure 1**).

Corneal Endothelium of Two Groups

One month after the operation, the ECA and CD in the observation group were not significantly different from those before the operation ($P > 0.05$). ECA in the observation group was lower than the control group, the CD was higher than the control group ($P < 0.05$) (**Figure 2**).

Complications of Two Groups

There was no significant difference in the total incidence of complications between the two groups ($P > 0.05$) (**Table 2**).

The Satisfaction Rate of Two Groups

The total satisfaction rate of the observation group was 88.24%, which was significantly higher than that of the control group (75.31%) ($P < 0.05$) (**Table 3**).

DISCUSSION

With the aging of the population, the number of cases of visual impairment caused by cataracts is increasing. Cataract leads to the closure of the angle of the chamber, the thickness of the lens increases in the elderly, and the relaxation of the suspensory ligament leads to the relative forward movement of the lens (9, 10). How to treat these patients effectively has become one of the key problems to be solved urgently in clinical ophthalmology. In recent years, cataract operation has made rapid development, and different surgical methods have different therapeutic effects, which significantly improves the recovery rate of patients.

Phacoemulsification (PHACO) is a surgical method for cataract treatment by using phacoemulsification instruments. The therapeutic principle of this technology is to establish surgical access in the incision of cornea or sclera through the phacoemulsification handle, then form a capsulorhexis, and use the ultrasonic needle to generate certain energy in the eyes, so as to crush the hard lens into chylous shape, and then suck out the crushed lens and free cortex with the help of perfusion suction system (11, 12). This operation can deepen the anterior chamber, enlarge the angle of the chamber, improve the pupillary block caused by the lens, and solve the anatomical factors such as lens thickening, relative forward movement of the lens position, closure of the remaining angle of the chamber in cataract patients, thus rapidly reducing the IOP of the patients (13). During the implementation of PHACO, ultrasound itself can cause the secretion function of the ciliary body to decline, and the placement of viscoelastic agent forms a passive separation effect on the corner adhesion. At the same time, it has the advantages of good sealing of surgical incision, short time, light postoperative reaction, quick recovery of vision, etc., which has received extensive attention from clinicians (14–16). However, giving cataract patients a single surgical procedure may not meet their ideal needs. The implementation of PHACO cannot change the structure of the highly pleated iris, cannot effectively solve the iris bulge, and the iris still adheres to the ciliary body. Moreover, the application of PHACO preoperative intraocular hypertension drugs will lead to the destruction of the ocular trabecular structure of patients, resulting in the continuous increase of IOP and the impaired function of corneal endothelial cells and other adverse changes. Finally, cataract patients may need a second operation, which not only increases the iatrogenic injury of patients but also increases the medical expenses (17).

TABLE 1 | Clinical effect of two groups (*n*, %).

Group	Eye number	Markedly effective rate	Effective rate	Invalid rate	Total effective rate
Control group ($n = 58$)	81	51 (62.96%)	20 (24.69%)	10 (12.35%)	71 (87.65%)
Observation group ($n = 62$)	85	59 (69.41%)	25 (29.41%)	1 (1.18%)	84 (98.82%)
χ^2 value					8.362
P value					0.004

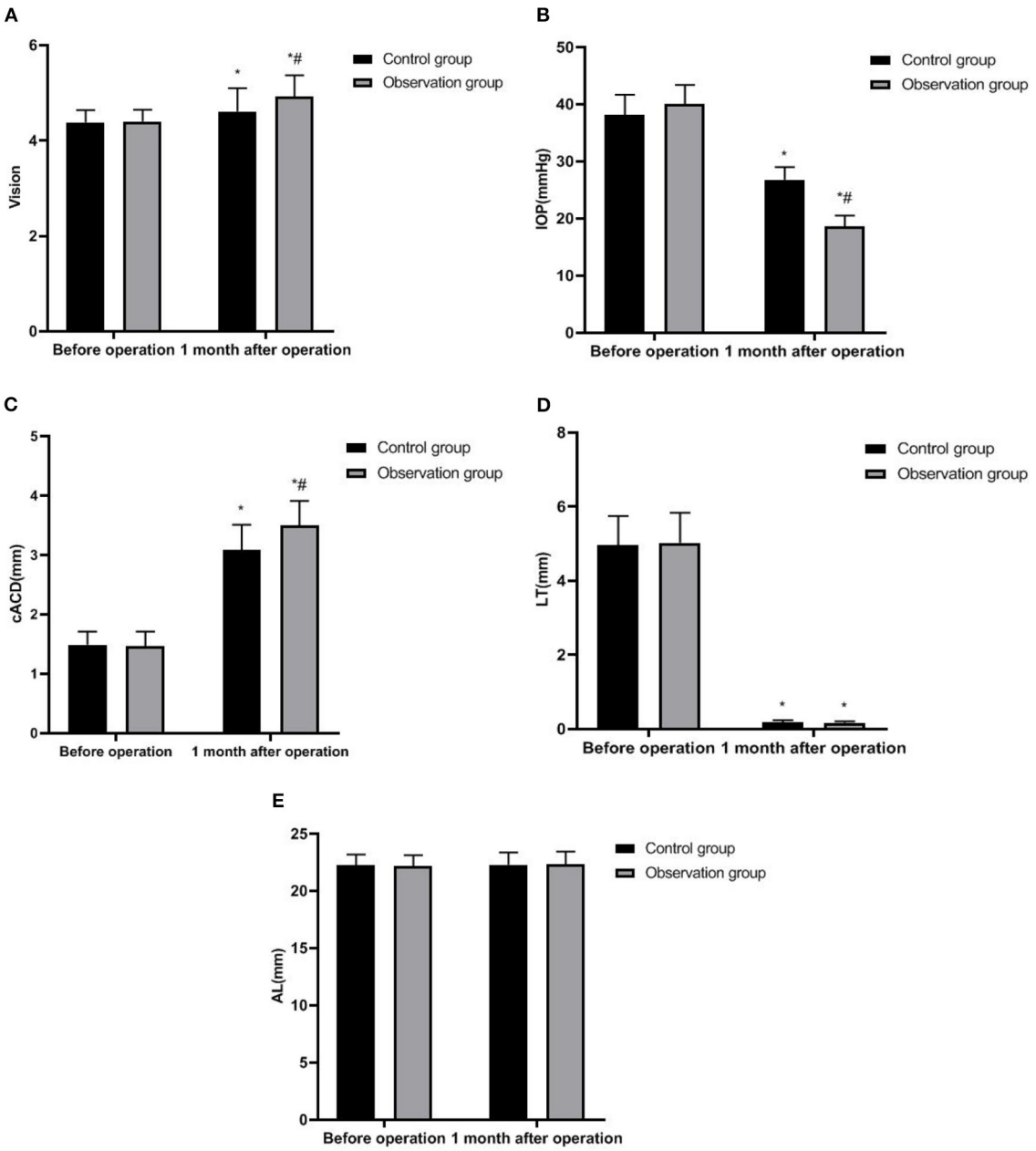


FIGURE 1 | Ophthalmic-related parameters of two groups. **(A)** Vision; **(B)** IOP; **(C)** cACD; **(D)** LT; and **(E)** AL. Compared with before operation, $^{*}P < 0.05$; Compared with the control group, $^{\#}P < 0.05$.

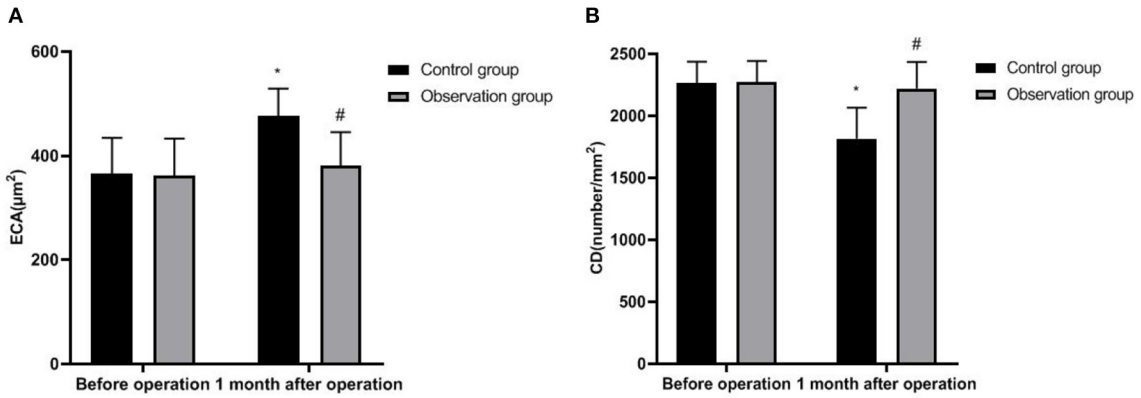


FIGURE 2 | Corneal endothelium of two groups. **(A)** ECA and **(B)** CD. Compared with before operation, $^{*}P < 0.05$; Compared with the control group, $^{\#}P < 0.05$.

TABLE 2 | Complications in two groups (*n*, %).

Group	Eye number	Shallow anterior chamber	Anterior chamber hemorrhage	Cellulose exudation of iris	Corneal edema	Other	Total incidence rate
Control group ($n = 58$)	81	2 (2.47%)	1 (1.23%)	2 (2.47%)	2 (2.47%)	2 (2.47%)	9 (11.11%)
Observation group ($n = 62$)	85	2 (2.35%)	0 (0.00%)	1 (1.18%)	1 (1.18%)	0 (0.00%)	4 (4.71%)
χ^2 value							2.357
P value							0.125

In recent years, PHACO + IOL combined with TRAB has become the focus of clinical ophthalmology. PHACO + IOL is a surgical method of implanting an intraocular lens with thickness < 1.0 mm in the capsular bag to replace the human lens with a thickness of about 5.0 mm. After the operation, the anterior chamber volume can be improved, the cACD can be significantly deepened, and the contact plane between pupil margin and lens can be moved backward, thus reducing pupil block, widening the angle of the chamber, and reducing the outflow resistance of aqueous humor, resulting in effective control of vision and IOP compared with before operation (18). TRAB was first established by Cairns's team. It is to re-establish an extra-ocular drainage channel of aqueous humor at the corneal limbus, so that part of aqueous humor in the trabecular meshwork can be drained out of the filtering bleb, which has a positive effect on lowering IOP (19). In the operation of PHACO + IOL combined with TRAB, the operator directly removes the sinus trabecular tissue and the surrounding iris tissue after implantation of intraocular lens, and in the process of cataract extraction, with the help of the operation of the ultrasonic emulsifying machine, the trabecular meshwork deposits can be removed, and the filtering effect of trabecular meshwork can be improved. The application of viscoelastic agent can compress iris blood vessels, reduce the pressure of the anterior chamber, improve the structure of the anterior chamber, adjust the lens position, further relieve pupillary block, maintain the stability of the anterior chamber, and make the IOP after operation return to normal and effectively improve (20, 21). PHACO+IOL combined with TRAB has many advantages when applied to cataract patients. ① The operation can be completed at one time, which avoids eye trauma caused by multiple operations and reduces the chance of tissue bleeding; ② It can shorten the treatment period, relieve the pain of patients and save the cost of operation; ③ Compared with the single operation, the combined operation can improve the operation quality, and achieve the better long-term effect of intraocular pressure control. It can relieve many glaucoma factors at one time (22, 23). In this study, the vision, IOP, cACD, and LT of patients in PHACO + IOL combined with the TRAB group were significantly better than those before the operation, and the total effective rate, vision, IOP, and cACD were significantly better than those in a single operation, and the patients had higher satisfaction. This is roughly consistent with the research results of Wang's team (24).

The corneal transparency of patients has an important impact on the recovery of vision in cataract patients after operation, and the structural and functional integrity of corneal endothelial cells is the main condition to ensure corneal transparency. Choi's team reported that corneal endothelial cells can only be repaired by normal cell expansion after injury, but when CD < 1,000 cells /mm^2, the damage rate of corneal endothelial cells will exceed its function compensation rate, resulting in corneal endothelial cells being unable to maintain normal function (25). Our research results have shown that the ECA of the observation group was lower than that of the control group, and the CD was higher than that of the control group, which revealed that cataract patients who only implement PHACO have more serious damage to

TABLE 3 | The satisfaction rate of two groups (*n*, %).

Group	Eye number	Very satisfactory rate	Satisfaction rate	Dissatisfaction rate	Total satisfaction rate
Control group ($n = 58$)	81	40 (49.38%)	21 (25.93%)	20 (24.69%)	61 (75.31%)
Observation group ($n = 62$)	85	46 (54.12%)	29 (34.12%)	10 (11.76%)	75 (88.24%)
χ^2 value					4.681
P value					0.031

corneal endothelial cells, and PHACO itself can cause damage to corneal endothelial cells. The degree of damage is influenced by factors such as ultrasonic energy and time, lens nucleus hardness, operator's operation proficiency, and so on, and may be related to the duration of high intraocular pressure. At the same time, we observed that there was no significant difference in ECA and CD in the observation group after operation compared with that before operation. The scheme of the PHA + IOL + TRAB combined operation is quite perfect. By suctioning out the cloudy lens, implanting intraocular lens, cutting out the trabecular sinus tissue, and other operations, the vision and IOP of patients can be improved, and the corneal endothelial cells of patients are less damaged, and the functional integrity of corneal endothelial cells can be effectively maintained. In addition, in this study, the incidence of complications of the combined operation scheme is not high, only 4.71%, and there was no corneal endothelial fold and anterior chamber inflammation, which had good safety. TRAB drainage of aqueous humor from the anterior chamber to subconjunctival space and covering the drainage opening with scleral lamina can limit the excessive outflow of aqueous humor and reduce complications such as shallow anterior chamber and hyphema after the operation. One-time PHACO + IOL + TRAB operation can avoid transient ocular hypertension caused by the staged operation, prevent optic nerve damage caused by multiple intraocular operations and reduce complications.

CONCLUSION

From the above results, it can be seen that PHACO + IOL combined with TRAB has a good curative effect in the treatment of cataracts, which can improve the patients' vision and IOP, keep the functional integrity of corneal endothelial cells, and does not increase the occurrence of complications, the patients' satisfaction is high. The success of the operation depends on many factors, such as the damage degree of the trabecular meshwork, the extent, and duration of angle-closure, etc. Generally speaking, the shorter the closure time of atrial Angle adhesion, the better the prognosis of operation. Therefore, the selection of surgical timing is also very important, and the appropriate surgical timing is conducive to improving the success rate of operation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of The First People's Hospital of Fuyang District, Hangzhou. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BW was mainly responsible for the design of the research and the writing of the thesis. LT was mainly responsible for the implementation of the research project. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Sangwan VS, Gupta S, Das S. Cataract surgery in ocular surface diseases: clinical challenges and outcomes. *Curr Opin Ophthalmol.* (2018) 29:81–7. doi: 10.1097/ICU.0000000000000441
2. Fukuoka H, Afshari NA. The impact of age-related cataract on measures of frailty in an aging global population. *Curr Opin Ophthalmol.* (2017) 28:93–7. doi: 10.1097/ICU.0000000000000338
3. Self JE, Taylor R, Solebo AL, Biswas S, Parulekar M, Dev Borman A, et al. Cataract management in children: a review of the literature and current practice across five large UK centres. *Eye (Lond).* (2020) 34:2197–218. doi: 10.1038/s41433-020-1115-6
4. Avetisov KS, Ivanov MN, Yusef YN, Yusef SN, Aslamazova AE, Fokina ND. [Morphological and clinical aspects of anterior capsulotomy in femtosecond laser-assisted cataract surgery]. *Vestn Oftalmol.* (2017) 133:83–8. doi: 10.17116/oftalma2017133483-88
5. Evans J, Mwangi N, Burn H, Ramke J. Equity was rarely considered in Cochrane Eyes and Vision systematic reviews and primary studies on cataract. *J Clin Epidemiol.* (2020) 125:57–63. doi: 10.1016/j.jclinepi.2020.04.024
6. Agrawal S, Fledderjohann J, Ghosh S. Risk factors for self-reported cataract symptoms, diagnosis, and surgery uptake among older adults in India: Findings from the WHO SAGE data. *Glob Public Health.* (2021) 16:1771–85. doi: 10.1080/17441692.2020.1836246
7. Sarkisian SR Jr, Radcliffe N, Harasymowycz P, Vold S, Patrianakos T, Zhang A, et al. Visual outcomes of combined cataract surgery and minimally invasive glaucoma surgery. *J Cataract Refract Surg.* (2020) 46:1422–32. doi: 10.1097/j.jcrs.0000000000000317
8. Frolov MA, Frolov AM, Kazakova KA. [Combination treatment for cataract and glaucoma]. *Vestn Oftalmol.* (2017) 133:42–6. doi: 10.17116/oftalma2017133442-46
9. Han X, Fan Q, Hua Z, Qiu X, Qian D, Yang J. Analysis of corneal astigmatism and aberration in Chinese congenital cataract and developmental

cataract patients before cataract surgery. *BMC Ophthalmol.* (2021) 21:34. doi: 10.1186/s12886-020-01794-2
10. Tan S, Chen X, Cui C, Hou Y, Li W, You H. Biodegradation of saline phenolic wastewater in a biological contact oxidation reactor with immobilized cells of *Oceanimonas* sp. *Biotechnol Lett.* (2017) 39:91–6. doi: 10.1007/s10529-016-2226-9
11. Charles Crozafon P, Bouchet C, Zignani M, Griner R, Foster SD, Zou M, et al. Comparison of real-world treatment outcomes of femtosecond laser-assisted cataract surgery and phacoemulsification cataract surgery: A retrospective, observational study from an outpatient clinic in France. *Eur J Ophthalmol.* (2021) 31:1809–16. doi: 10.1177/1120672120925766
12. Foster GJL, Allen QB, Ayres BD, Devgan U, Hoffman RS, Khandelwal SS, et al. Phacoemulsification of the rock-hard dense nuclear cataract: options and recommendations. *J Cataract Refract Surg.* (2018) 44:905–16. doi: 10.1016/j.jcrs.2018.03.038
13. Maehara S, Matsumoto N, Takiyama N, Itoh Y, Kitamura Y, Yamashita K, et al. Surgical removal of cataract in an Asiatic black bear (*Ursus thibetanus*) by phacoemulsification and aspiration. *J Vet Med Sci.* (2020) 82:740–4. doi: 10.1292/jvms.19-0639
14. Qian Z, Huang J, Song B, Wei L, Fu L, Austin MW, et al. Cataract surgery (Phacoemulsification with Intraocular Lens Implantation) combined with endoscopic goniosynechialysis for advanced primary angle-closure glaucoma. *Ophthalmol Glaucoma.* (2021) 4:365–72. doi: 10.1016/j.ogla.2020.11.003
15. Han JV, Patel DV, Liu K, Kim BZ, Sherwin T, McGhee CNJ. Auckland cataract study IV: practical application of NZCRS cataract risk stratification to reduce phacoemulsification complications. *Clin Exp Ophthalmol.* (2020) 48:311–8. doi: 10.1111/ceo.13696
16. He L, Cui Y, Tang X, He S, Yao X, Huang Q, et al. Changes in visual function and quality of life in patients with senile cataract following phacoemulsification. *Ann Palliat Med.* (2020) 9:3802–9. doi: 10.21037/apm-20-1709
17. Kozera M, Konopińska J, Mariak Z, Rekas M. Effectiveness of iStent trabecular microbypass system combined with phacoemulsification versus phacoemulsification alone in patients with glaucoma and cataract depending on the initial intraocular pressure. *Ophthalmic Res.* (2021) 64:327–36. doi: 10.1159/000511456
18. Nyström A, Almarzouki N, Magnusson G, Zetterberg M. Phacoemulsification and primary implantation with bag-in-the-lens intraocular lens in children with unilateral and bilateral cataract. *Acta Ophthalmol.* (2018) 96:364–70. doi: 10.1111/aos.13626
19. Cairns JE. Trabeculectomy. Preliminary report of a new method. *Am J Ophthalmol.* (1968) 66:673–9. doi: 10.1016/0002-9394(68)91288-9
20. Hansapinyo L, Choy BNK, Lai JSM, Tham CC. Phacoemulsification versus phacotrabeculectomy in primary angle-closure glaucoma with cataract: long-term clinical outcomes. *J Glaucoma.* (2020) 29:15–23. doi: 10.1097/IJG.0000000000001397
21. Rao A, Padhy D, Das G, Sarangi S. Viscoless manual small incision cataract surgery with trabeculectomy. *Semin Ophthalmol.* (2018) 33:552–9. doi: 10.1080/08820538.2017.1339092
22. Elwehidy AS, Bayoumi NHL, Badawi AE, Hagras SM, Kamel R. Combined phacoemulsification-viscosynechialysis-trabeculotomy vs phacotrabeculectomy in uncontrolled primary angle-closure glaucoma with cataract. *J Cataract Refract Surg.* (2019) 45:1738–45. doi: 10.1016/j.jcrs.2019.07.031
23. Anbar M, Ammar H. Effect of different incision sites of phacoemulsification on trabeculectomy bleb function: prospective case-control study. *BMC Ophthalmol.* (2017) 17:103. doi: 10.1186/s12886-017-0500-9
24. Wang Y, Liang ZQ, Zhang Y, Hennein L, Han Y, Wu HJ. Efficacy and safety of phacoemulsification plus goniosynechialysis and trabectome in patients with primary angle-closure glaucoma. *Sci Rep.* (2021) 11:13921. doi: 10.1038/s41598-021-92972-9
25. Choi SO, Jeon HS, Hyon JY, Oh YJ, Wee WR, Chung TY, et al. Recovery of corneal endothelial cells from periphery after injury. *PLoS ONE.* (2015) 10:e0138076. doi: 10.1371/journal.pone.0138076

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang and Tang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 21 February 2022
doi: 10.3389/fsurg.2022.848234

Study on the Application Effect of Fast Track Surgery Care Combined With Continuous Care After Discharge in Patients With Laparoscopic Cholecystectomy

*Jian Yu, Xiao Lin and Hong Chen**

Operating Room, The First People's Hospital of Lianyungang, Jiangsu, China

Purpose: To explore the application effect of fast track surgery (FTS) care combined with continuous care after discharge in patients with laparoscopic cholecystectomy (LC).

Methods: Two hundred patients treated with LC in our hospital from May 2020 to September 2021 were selected and divided into the routine group receiving routine care ($n = 100$) and the combined group receiving FTS care combined with continuous care after discharge ($n = 100$) according to their care methods. We observed the care effect, surgical stress levels [epinephrine, cortisol, Hamilton anxiety scale (HAMA)], postoperative recovery (time to first exhaust, time to first meal, time to first getting out of bed, time to hospitalization), complications, SF-36 scores after discharge, and care satisfaction in both groups.

Results: The total efficiency of care in the combined group was better than that in the routine group ($P < 0.05$). At 1 d after surgery, the levels of epinephrine and cortisol in both groups were significantly higher than those at 1 h before surgery, and the HAMA scores were significantly lower than those at 1 h before surgery, and the combined group was lower than the routine group ($P < 0.05$). The time to first exhaustion, time to first meal, time to first getting out of bed, and time to hospitalization were shorter in the combined group than in the routine group ($P < 0.05$). The overall complication rate in the combined group was lower than that in the routine group ($P < 0.05$). The each item of SF-36 scores after discharge were higher in the combined group than in the routine group ($P < 0.05$). The total satisfaction with care was higher in the combined group than in the routine group ($P < 0.05$).

Conclusion: The implementation of FTS care combined with continuous care after discharge in LC patients is ideal, which can significantly reduce the level of surgical stress, accelerate the recovery process, and reduce the occurrence of complications, and improve the postoperative quality of life of patients significantly, and with high satisfaction, which is worthy of application.

Keywords: laparoscopic cholecystectomy, fast track surgery care, continuous care after discharge, surgical stress levels, Hamilton anxiety scale

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Wenjie Song,
Fourth Military Medical University, China
Li Zhang,
University of South China, China

****Correspondence:***
Hong Chen
Chenhong2021smile@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *04 January 2022*
Accepted: *27 January 2022*
Published: *21 February 2022*

Citation:
Yu J, Lin X and Chen H (2022) Study on the Application Effect of Fast Track Surgery Care Combined With Continuous Care After Discharge in Patients With Laparoscopic Cholecystectomy. Front. Surg. 9:848234. doi: 10.3389/fsurg.2022.848234

INTRODUCTION

With the improvement of material living standard and the change of diet structure, the prevalence of gallbladder disease in China is increasing year by year. The disease mainly presents with symptoms such as epigastric pain and abnormal liver function (1). At the beginning of its onset, the patient's symptoms are often insignificant, but as the disease progresses, it may cause shock and threaten the patient's life and health (2). For the intervention of gallbladder disease, the clinical treatment of surgical resection of lesions can benefit every patient, but the perioperative stress associated with surgery inevitably affects the patient's recovery and is closely related to postoperative complications (3, 4). How to effectively control surgery-related stress and reduce postoperative complications to accelerate patient recovery has become a hot topic of current research. Laparoscopic surgery is a minimally invasive technique in which a specially designed catheter is inserted into the patient's peritoneal cavity and passed through the laparoscope to expand the view of the operative area and thus remove the lesion more completely (5). Its application to focal resection in gallbladder disease has been shown to significantly reduce intraoperative blood loss and reduce surgical stress (6, 7). At the same time, the fast track surgery (FTS) care concept suggests that the blocking of stress in surgical patients should include preoperative care of the patient's physical and mental health, care to reduce the stress of therapeutic measures, and care to block afferent nerve conduction stress signals (8, 9). Once the concept was introduced, it was quickly adopted as a new model of perioperative care in many countries in Europe and the United States. In this study, FTS care was applied to patients undergoing laparoscopic cholecystectomy (LC), and it is not known whether the combination of the two has a superimposed effect on accelerating the patients' postoperative recovery. In addition, it has been suggested that the lack of continuity and compactness of clinical care for patients by health care professionals under the conventional care model makes it difficult for patients to obtain adequate professional care after discharge, which is not conducive to the advantages of LC treatment (10). Based on the above, in order to improve the quality of care services in our hospital, enhance the outcome of LC surgical treatment and improve the prognosis of patients, in recent years, our department has seamlessly connected FTS care with continuous care after discharge and observed the effect of its application to LC patients.

MATERIALS AND METHODS

Research Object

Two hundred patients treated with LC in our hospital from May 2020 to September 2021 were selected. Inclusion criteria: Meeting the indications for LC, i.e., symptomatic gallbladder stones, symptomatic chronic cholecystitis, symptomatic and surgically indicated gallbladder augmentation disease (11); Those who were cognitively normal and could cooperate with the relevant questionnaire assessment; Those who had signed the informed consent form. Exclusion criteria: Those treated with combined choledochoscopy or duodenoscopy; Those with intraoperative conversion to open surgery; Those with gallbladder stones combined with biliary stones; Those with illiteracy or combined cognitive impairment or cerebrovascular pathology; Those with combined diabetes mellitus or severe cardiopulmonary disease; Those with combined malignancy; Those with contraindications to LC, such as acute cholecystitis with severe complications, obstructive jaundice, gallbladder augmentation disease suspected to be cancerous, peritonitis, etc. (12); Those with combined bleeding disorders or coagulation disorders. They were divided into the routine group receiving routine care ($n = 100$) and the combined group receiving FTS care combined with continuous care after discharge ($n = 100$) according to the method of care. Comparing the general conditions such as age and primary illness between the two groups was not statistically significant and could be used for comparative studies ($P > 0.05$) (**Table 1**).

TABLE 1 | Comparison of general conditions of two groups (n, $\bar{x}\pm s$, %).

Itmes	Routine group ($n = 100$)	Combined group ($n = 100$)	t/χ^2 value	P-value
Age (years old)	40.93 ± 5.28	42.05 ± 5.16	1.517	0.131
BMI (kg/m^2)	24.32 ± 2.04	24.65 ± 2.11	1.124	0.262
Gender (cases)			0.188	0.664
Male	62 (62.00)	59 (59.00)		
Female	38 (38.00)	41 (41.00)		
Primary disease (cases)			0.239	0.887
Gallbladder stones	55 (55.00)	57 (57.00)		
Gallbladder polyps	27 (27.00)	24 (24.00)		
Others	18 (18.00)	19 (19.00)		

Research Methods

The routine group received routine care: (1) preoperative medical staff informed fasting for 6 h, no drinking for 2 h, surgical and anesthetic precautions, and postoperative functional exercises methods; (2) preoperative routine placement of gastric tube (removed after anal venting) and urinary catheter (removed 3 ∼ 5 days after surgery); (3) preoperative evening clean enema; (4) half an hour before surgery, intramuscular injection of atropine 0.5 mg + midazolam 3 mg in the ward; (5) intraoperative routine general anesthesia care; (6) postoperative drainage tubes were routinely left in place and removed for 24 ∼ 48 h; (7) pain pumps were not routinely used, and opioids were used for pain relief when necessary; (8) eating and watering after the anus was exhausted after surgery; (9) patients got out of bed when voluntary; (10) fluid control was 2,500 ∼ 3,000 ml on the postoperative day.

The combined group received FTS care combined with continuous care after discharge care. FTS care: (1) preoperative medical staff informed fasting for 6 h, no drinking for 2 h, adopting diversified forms of health education (information, pictures, electro-educational films, etc.) to popularize knowledge, precautions and key points of cooperation in disease, treatment,

rehabilitation and postoperative lifestyle, patiently answering patients' doubts, psychological guidance at the right time, preoperatively informing them that they have made adequate preparation for surgery to enhance their sense of security, and postoperatively working together with patients' families to enhance patients' confidence and self-control in fighting disease with suggestion and demonstration therapy; (2) preoperative gastrostomy tube and urinary catheter were not routinely placed, or left in place after anesthesia and removed after awakening; (3) preoperative intestinal preparation such as mechanical enema was not allowed; (4) atropine 0.5 mg + midazol 3 mg was injected intramuscularly before induction of anesthesia; (5) on the basis of routine general anesthesia care, the necessary warming measures were taken; (6) ostoperative drainage tube was not routinely left in place or removed 12 ∼ 24 h after surgery; (7) postoperative pain pump was continuously pumped intravenously with long-acting local anesthetics and non-opioid analgesics was oraled for pain relief; (8) eating by mouth early after surgery, drinking water 6 h after surgery, transition to semi-liquid food 24 ∼ 36 h after surgery; (9) postoperative 0 ∼ 6 h bed activity, 6 ∼ 24 h out of bed activity; (10) fluid control within 1,500 ml on the postoperative day.

Continuous care after discharge care: Before discharge, patients were given discharge instructions and introduction to the content of continuous care, and health knowledge manuals and postoperative assessment forms were issued, mainly including postoperative complications, mental, diet, sleep, exhaustion, urination, and defecation and precautions. A contact book was established and daily telephone follow-ups were made to assess patients' recovery and provide rehabilitation guidance, answering patients' questions, encouraging scientific exercise, and suggesting early return to work for those who recovered well.

Observation Index

Care Effect

After care, if the patients' clinical symptoms disappeared and their conditions gradually recovered, it was regarded as efficient; if the patients' symptoms were obviously relieved and their conditions improved, it was regarded as effective; not meeting the above criteria was regarded as ineffective. Total effective number = total - ineffective number.

Surgical Stress Levels

The physiological stress levels and psychological stress levels of the two groups were compared 1 h before and 1 d after surgery.The former was assessed by enzyme-linked immunoassay (kit purchased from Shanghai Jianlai Biotechnology Co., Ltd.) for the detection of epinephrine and cortisol levels in fasting venous blood; the latter was assessed by the Hamilton anxiety scale (HAMA), which consisted of 14 items, with each item assigned a score of 0–4 and a total score of ≥7 being the presence of anxiety symptoms.

Postoperative Recovery

The time of first exhaust, first meal, first getting out of bed and hospitalization in both groups were recorded.

Complications

The number of complications such as incisional pain, infection, bile leak, and bleeding (including intra-abdominal bleeding and bleeding from the puncture incision) during care was counted in both groups.

SF-36 score

At the first follow-up visit after discharge, the SF-36 was used to assess the quality of life in both groups. It consisted of 8 dimensions, that was, physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), mental health (MH), health transition (HT). Each dimension accounted for 100 points, and the score was proportional to the quality of life.

Care Satisfaction

At the first follow-up visit after discharge, the hospital's homemade Patient Satisfaction Questionnaire was used for assessment. It consisted of five entries, each of which was assigned a value of 1 ∼ 3 points, with a total score of 12 ∼ 15 as satisfied, 8 ∼ 11 as average, and 5 ∼ 7 as unsatisfied.

Statistical Methods

SPSS 22.0 software was applied, and the measurement data were expressed as mean ± standard deviation and compared by *t*-test. Count data were expressed as ratio, and the χ^2 test was used for comparison. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of Care Effect Between the Two Groups

After care, the total efficiency of care in the combined group was better than that in the routine group ($\chi^2 = 4.916$, $P = 0.027$) (**Figure 1**).

Comparison of Surgical Stress Levels Between the Two Groups

At 1 d after surgery, the levels of epinephrine and cortisol in both groups were significantly higher than those at 1 h before surgery, and the HAMA scores were significantly lower than those at 1 h before surgery, and the combined group was lower than the routine group ($P < 0.05$) (**Figure 2**).

Comparison of Postoperative Recovery Between the Two Groups

The time to first exhaustion, time to first meal, time to first getting out of bed, and time to hospitalization were shorter in the combined group than in the routine group ($P < 0.05$) (**Figure 3**).

Comparison of Complication Rates Between the Two Groups

The overall complication rate in the combined group was lower than that in the routine group ($\chi^2 = 4.421$, $P = 0.036$) (**Figure 4**).

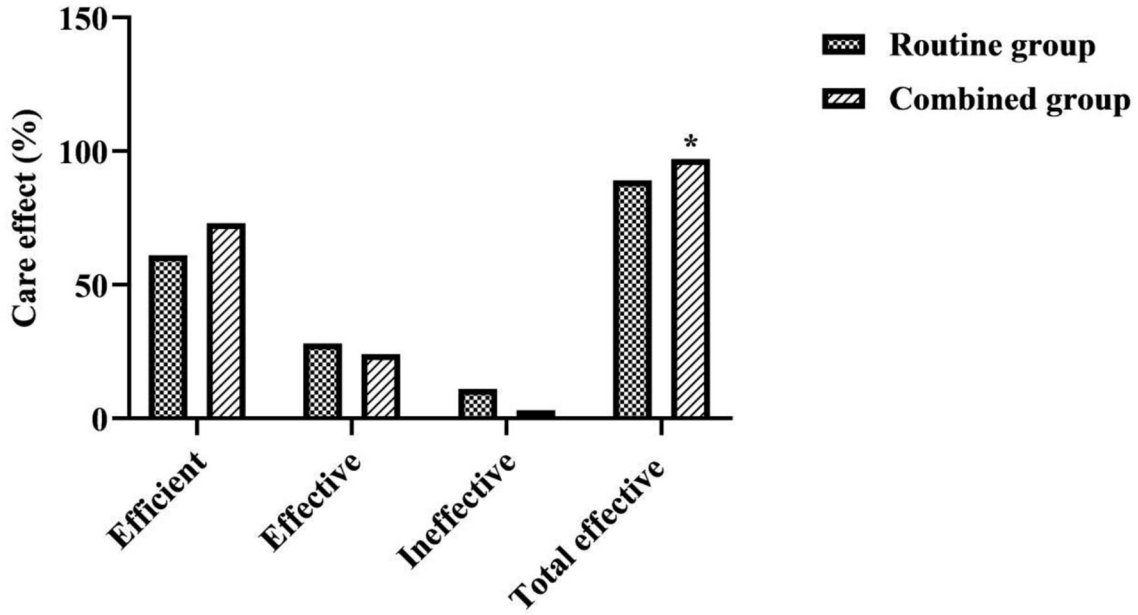


FIGURE 1 | Comparison of care effect between the two groups. *was a comparison with the same item in the routine group, $P < 0.05$.

Comparison of SF-36 Scores Between the Two Groups

The each item of SF-36 scores after discharge were higher in the combined group than in the routine group ($P < 0.05$) (**Figure 5**).

Comparison of Care Satisfaction Between the Two Groups

The total satisfaction with care was higher in the combined group than in the routine group ($\chi^2 = 8.416$, $P = 0.015$ (**Figure 6**).

DISCUSSION

Gallbladder disease is one of the common diseases that threaten human health. In China, the incidence of gallbladder stones is 10–15% and the incidence of cholecystitis is 28%. The main clinical method of treatment is surgical excision. At present, the LC technique in China is relatively mature, and its damage to abdominal muscles, fascia, nerves and blood vessels is small, and patients can have no obvious external trauma after surgery, leaving only one to four small incisions, which facilitates their postoperative recovery (13, 14). However, the somatic trauma, physiological stress, metabolic changes, and the resulting painful stimuli and anxiety caused by surgery can affect several systems of patients, including neurological, endocrine, and circulatory (15, 16). This interferes with the outcome of surgical treatment for LC patients and delays their postoperative physical and psychological recovery.

Care interventions are an important part of clinical care. In this study, FTS care combined with continuous care after discharge was applied to LC patients, and the results showed that the total efficiency of care in the combined group was better than that in the routine group ($P < 0.05$). At 1 d after surgery, the levels of epinephrine and cortisol in both groups were significantly higher than those at 1 h before surgery, and the HAMA scores were significantly lower than those at 1 h before surgery, and the combined group was lower than the routine group ($P < 0.05$). The time to first exhaustion, time to first meal, time to first getting out of bed, and time to hospitalization were shorter in the combined group than in the routine group ($P < 0.05$). The overall complication rate in the combined group was lower than that in the routine group ($P < 0.05$). Those suggests that providing comprehensive, optimized, and compact care care to LC perioperative patients is very beneficial to ensure successful surgery, reduce surgical stress, and accelerate patient recovery.

In the conventional care model: LC patients need to undergo a longer period of preoperative fasting and no drinking, which can lead to irritability, thirst, hunger, dehydration, hypoglycemia, and hypovolemia, increasing body consumption and affecting postoperative tissue repair and wound healing (17). Routine preoperative indwelling of gastric and urinary catheters can cause discomfort and limited early postoperative activities, and increase the risk of respiratory and urinary tract infections (18). Preoperative bowel preparation such as receiving mechanical enemas predisposes patients to preoperative dehydration, increasing the risk of hypotension during anesthesia, and can also cause intestinal edema, increasing the chance of postoperative intestinal paralysis and abdominal infection (19). During intraoperative care, the patient's stressful response to hypothermia can impair coagulation mechanisms, the cardiovascular system, and leukocyte function (20, 21). Retained drains can cause pain, limited mobility, or retrograde infection

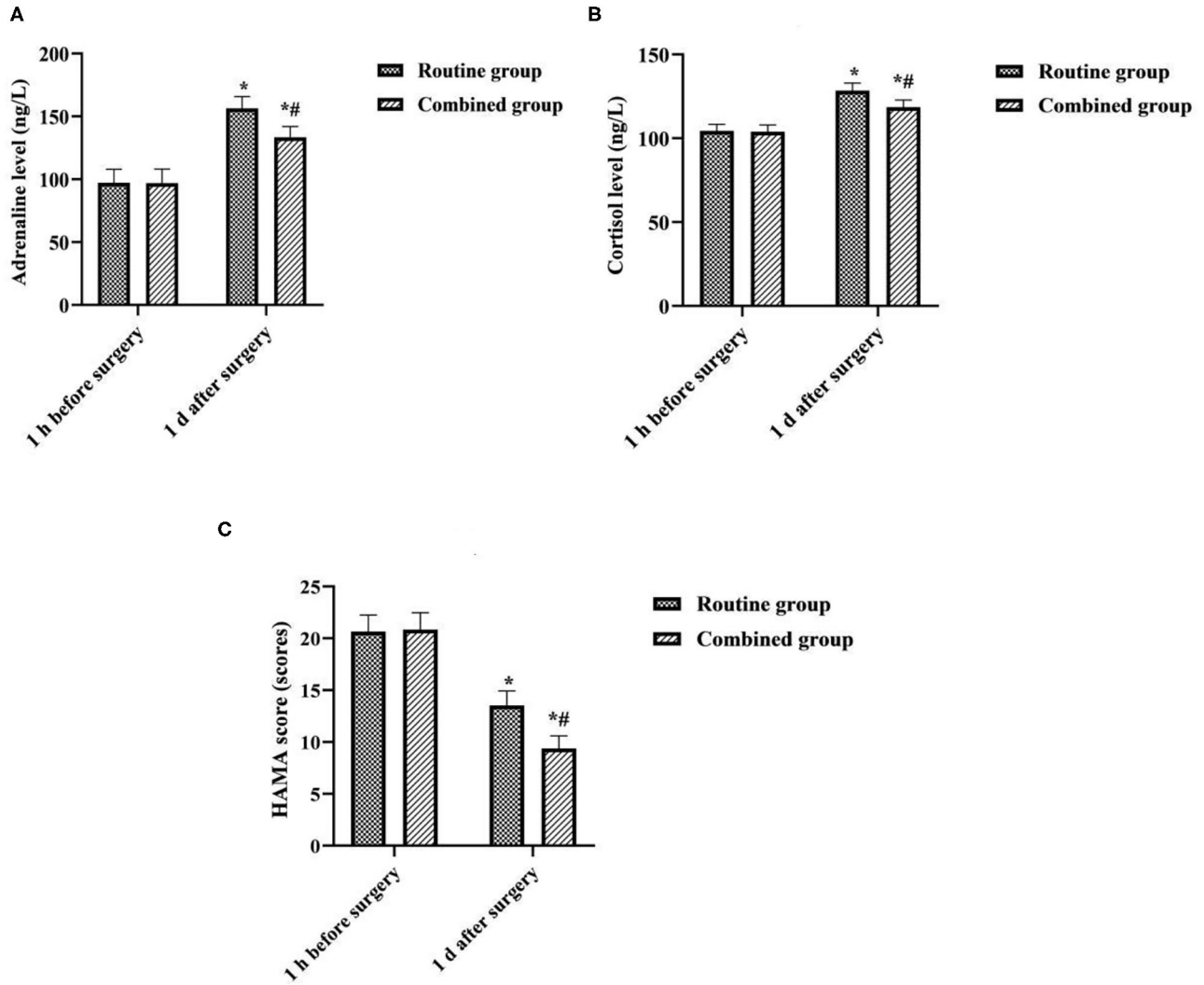


FIGURE 2 | Comparison of surgical stress levels between the two groups. *was compared with the same group 1 h before surgery, $P < 0.05$; # was compared with the routine group 1 d after surgery, $P < 0.05$. **(A)** Adrenaline level. **(B)** Cortisol level. **(C)** HAMA score.

in patients. The use of opioid analgesics and prolonged bed rest can affect the recovery of postoperative gastrointestinal function (22). Longer postoperative fasting can lead to malnutrition in patients and affect wound healing (23). In terms of fluid control, due to prolonged fasting and abstinence from food and drink, in order to maintain water and electrolyte balance, patients are often clinically over-infused, triggering pulmonary edema or intestinal edema, aggravating postoperative intestinal paralysis and affecting intestinal motility (24). In addition, surgery, as a major negative life event, can lead to a series of physiological and psychological behavioral reactions such as tension and fear, which in turn can lead to adverse emotions such as anxiety, affecting the surgical outcome and exacerbating the damage caused by surgical stress on the organism, which is detrimental to the patient's postoperative recovery (25).

In contrast, in the FTS care model: the short duration of patient fasting and drinking helps to relieve patients' preoperative thirst and hunger, avoid the development of postoperative insulin resistance, and reduce the postoperative stress response, helping to maintain a good metabolic status after surgery (26, 27). Not routinely placing gastric tubes, urinary catheters and drainage tubes helps to avoid uncomfortable irritation, stress and related complications caused by medical measures. The necessary intraoperative insulation measures can reduce the stress damage caused by hypothermia to the organism. In terms of postoperative analgesia, the combination of pain pumps and opioid analgesics has been shown to be effective in relieving pain stress caused by surgical trauma and creating conditions for the patient to get out of bed early (28). Early postoperative trans oral feeding helps to promote intestinal peristalsis, maintain intestinal mucosal function,

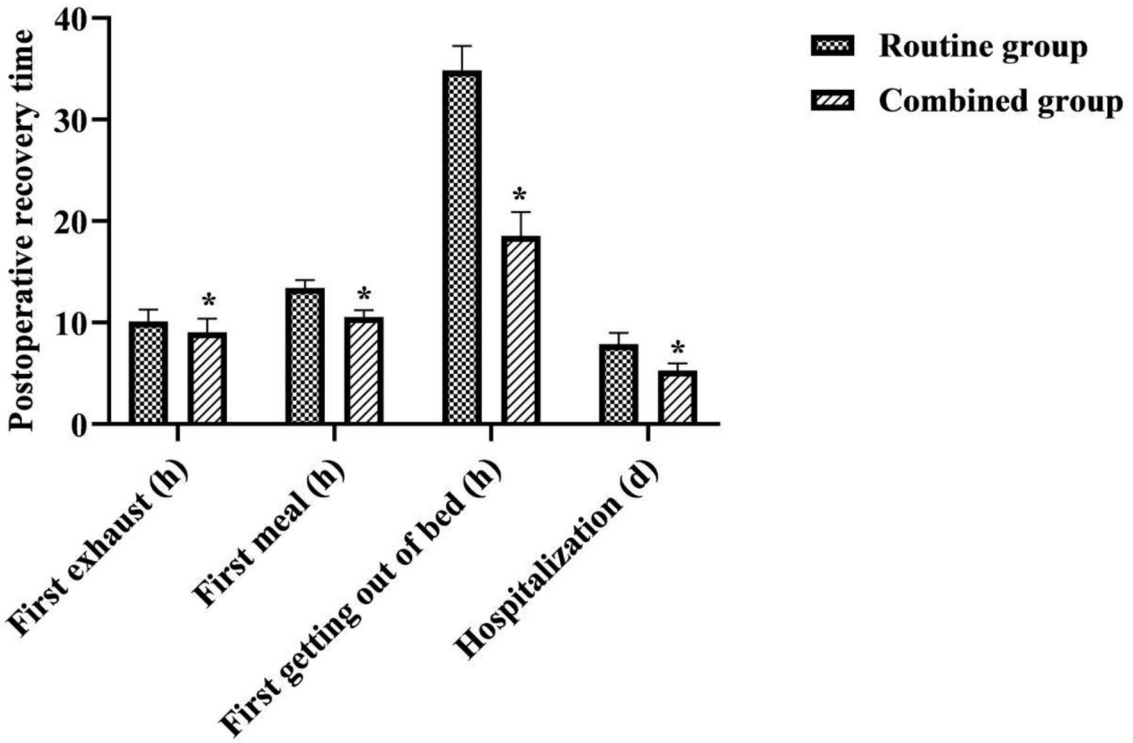


FIGURE 3 | Comparison of postoperative recovery between the two groups. *was a comparison with the same item in the routine group, $P < 0.05$.

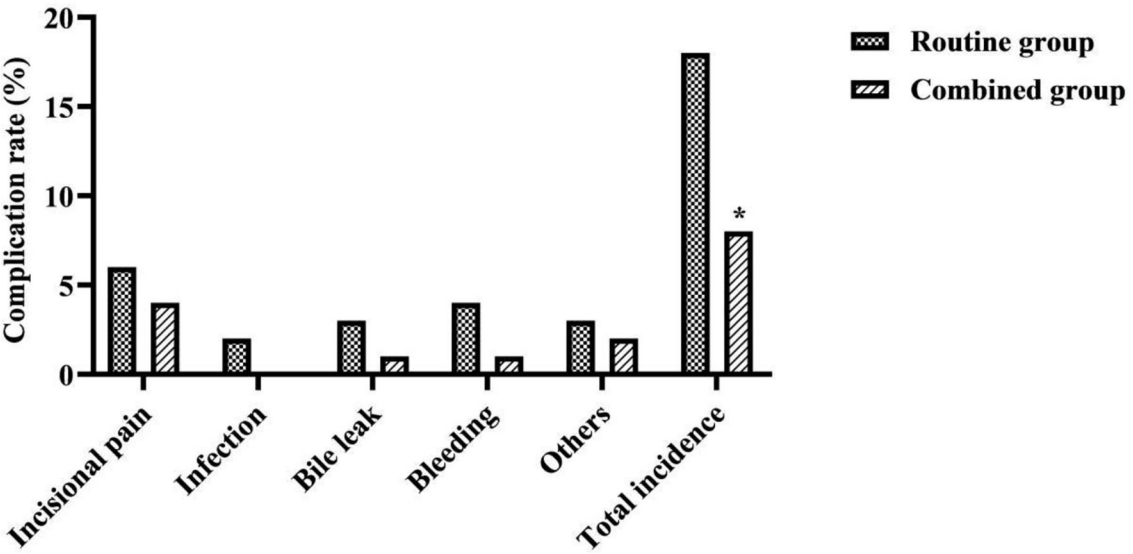


FIGURE 4 | Comparison of complication rates between the two groups. *was a comparison with the same item in the routine group, $P < 0.05$.

shorten postoperative anal venting time, and to a certain extent reduce the amount of postoperative fluids, which in turn helps to prevent hypoxemia and pulmonary edema and promote recovery of gastrointestinal function. Postoperative getting out of bed early promotes the recovery of gastrointestinal, bladder and respiratory system functions, which in turn helps to reduce the occurrence of abdominal distention, urinary retention, pulmonary complications and deep vein thrombosis. In addition, a variety of preoperative health education and psychological care can effectively reduce patients' doubts, tension and anxiety,

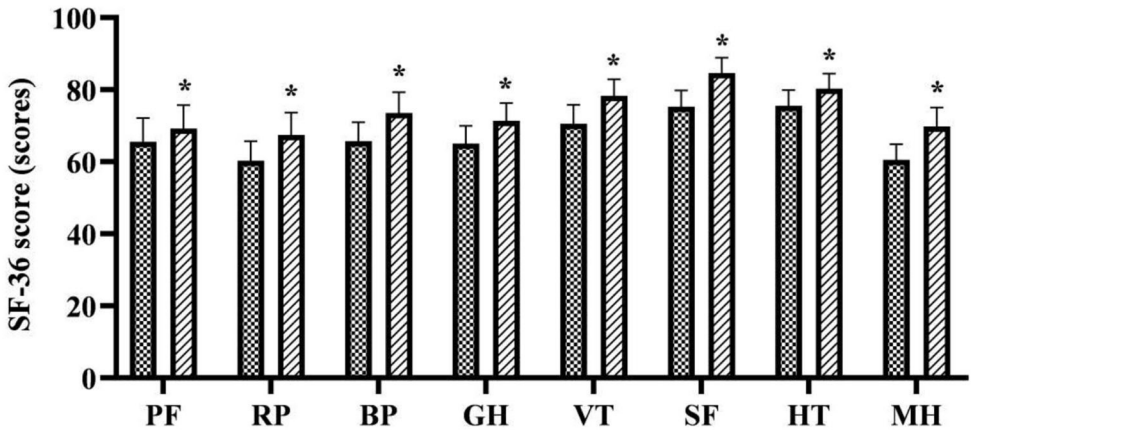


FIGURE 5 | Comparison of SF-36 scores between the two groups. *was a comparison with the same item in the routine group, $P < 0.05$.

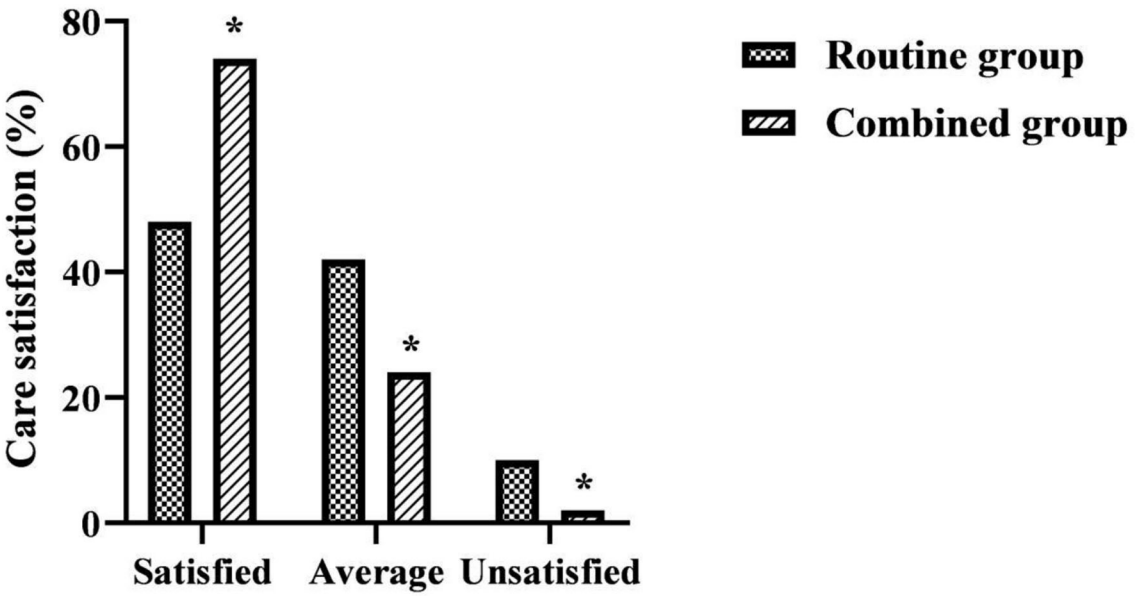


FIGURE 6 | Comparison of care satisfaction between the two groups. *was a comparison with the same item in the routine group, $P < 0.05$.

and can effectively relieve patients' postoperative pain. The above care measures will ultimately help to reduce physical and psychological stress and postoperative complications, as well as increase patients' confidence and compliance with treatment, and therefore will be beneficial in accelerating their recovery process.

Surgery, as an invasive treatment measure, inevitably leads to a series of pathological and physiological changes in the body while achieving therapeutic results, resulting in varying degrees of reduced quality of life for patients (29). In the results of this study, the each item of SF-36 scores after discharge were higher in the combined group than in the routine group ($P < 0.05$). The total satisfaction with care was higher in the combined group than in the routine group ($P < 0.05$). This suggests that the use of FTS care combined with continuous care after discharge for LC patients contributes to their quality of life and satisfaction. As a minimally invasive treatment, patients can be discharged from the hospital to continue treatment at

home in a short time after LC. However, under the routine care model, it is difficult for patients to receive additional medical support after discharge from the hospital. The implementation of continuous care after discharge in this study is a model of care that provides continuous targeted rehabilitation guidance for a period of time after the patient is discharged from the hospital. Its daily communication with patients in the form of telephone follow-up, medical and nursing staff can keep abreast of patients' recovery, and can encourage patients to exercise and exercise, supervise their healthy diet and ease their psychological problems through the telephone. This will help the patient to face the post-operative rehabilitation with a positive attitude, which will eventually help the patient to return to normal life or even early return to work, etc. as soon as possible. While meeting the care needs of patients in the rehabilitation stage, it also enhances communication between nurses and patients and promotes care-patient friendship, which is therefore very beneficial to improving patients' quality of life and satisfaction with care effect after discharge.

CONCLUSION

The implementation of FTS care combined with continuous care after discharge in LC patients is ideal, which can significantly reduce the level of surgical stress, accelerate the recovery process and reduce the occurrence of complications, and improve the postoperative quality of life of patients significantly and with high satisfaction, which is worthy of application.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First People's Hospital of Lianyungang. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

REFERENCES

1. Mu P, Yue P, Li T, Bai B, Lin Y, Zhang J, et al. Comparison of endoscopic naso-gallbladder drainage and percutaneous transhepatic gallbladder drainage in acute suppurative cholecystitis: study protocol clinical trial (SPIRIT Compliant). *Med*. (2020) 99:e19116. doi: 10.1097/MD.0000000000019116
2. olguín-Ruacho D, Cervantes-Sánchez CR. Quality and patient satisfaction after ambulatory laparoscopic management of non-severe and uncomplicated gallbladder pathology. *Cir Cir*. (2019) 87:656–61. doi: 10.24875/CIRU.19000833
3. Jian W, Song YZ, Xiang QF, Tian HY, Xie ZZ, Yang JB, et al. Application of transparent cap-assisted choledochoscopy in endoscopic gallbladder-preserving surgery. *Surg Laparosc Endosc Percutan Tech*. (2020) 30:317–21. doi: 10.1097/SLE.0000000000000786
4. Lim JH, Lee WJ, Choi SH, Kang CM. Cholecystectomy using the Revo-i robotic surgical system from Korea: the first clinical study. *Updates Surg*. (2021) 73:1029–35. doi: 10.1007/s13304-020-00877-5
5. Shi L, Guo H, Zheng Z, Liu J, Jiang Y, Su Y. Laparoscopic Surgery vs. Open surgery for colorectal cancer: impacts on natural killer cells. *Cancer Control*. (2020) 27:1073274820906811. doi: 10.1177/1073274820906811
6. Tavassoli A, Noorshafiee S. Laparoscopic cholecystectomy with two mini cosmetic incisions. *Updates Surg*. (2018) 70:73–6. doi: 10.1007/s13304-017-0504-2
7. Kauffman JD, Nguyen ATH, Litz CN, Farach SM, DeRosa JC, Gonzalez R, et al. Laparoscopic-guided vs. transincisional rectus sheath block for pediatric single-incision laparoscopic cholecystectomy: a randomized controlled trial. *J Pediatr Surg*. (2020) 55:1436–43. doi: 10.1016/j.jpedsurg.2020.03.002
8. Gralla O, Haas F, Knoll N, Hadzidiakos D, Tullmann M, Romer A, et al. Fast-track surgery in laparoscopic radical prostatectomy: basic principles. *World J Urol*. (2007) 25:185–91. doi: 10.1007/s00345-006-0139-2
9. Zhang C, Xiao J. Application of fast-track surgery combined with a clinical care pathway in the rehabilitation of patients undergoing total hip arthroplasty. *J Int Med Res*. (2020) 48:300060519889718. doi: 10.1177/0300060519889718
10. Akhtar MS, Khan N, Qayyum A, Khan SZ. Cost difference of enhanced recovery after surgery pathway vs. conventional care in elective laparoscopic cholecystectomy. *J Ayub Med Coll Abbottabad*. (2020) 32:470–75.
11. Hüscher CG, Lirici MM, Di Paola M, Crafa F, Napolitano C, Mereu A, et al. Laparoscopic cholecystectomy by ultrasonic dis-section without cystic duct and artery ligature. *Surg Endosc*. (2003) 17:442–51. doi: 10.1007/s00464-002-9068-3
12. Bakr AA, Khalil ME, Esmat GE. Acute cholecystitis is an indication for laparoscopic cholecystectomy: a prospective study. *JSLS*. (1997) 1:119–23.
13. Qu JW, Xin C, Wang GY, Yuan ZQ, Li KW. Feasibility and safety of single-incision laparoscopic cholecystectomy vs. conventional laparoscopic cholecystectomy in an ambulatory setting. *Hepatobiliary Pancreat Dis Int*. (2019) 18:273–77. doi: 10.1016/j.hbpd.2019.04.008
14. Lu J, Wang JF, Guo CL, Yin Q, Cheng W, Qian B. Intravenously injected lidocaine or magnesium improves the quality of early recovery after laparoscopic cholecystectomy: a randomised controlled trial. *Eur J Anaesthesiol*. (2021) 38:S1–8. doi: 10.1097/EJA.0000000000001348
15. Ouyang R, Ren H, Liu W, Yuan X, Lei E. Remifentanil inhibits the traumatic stress response in emergent trauma surgery. *J Clin Lab Anal*. (2019) 33:e22971. doi: 10.1002/jcla.22971
16. Crozier J, Williams A, Chan STF, Thompson G. Randomized trial of laparoscopic cholecystectomy procedure-specific consent form. *ANZ J Surg*. (2018) 88:E55–9. doi: 10.1111/ans.13888
17. Dock-Nascimento DB, Aguilar-Nascimento JE, Linetzky Waitzberg D. Ingestion of glutamine and maltodextrin 2 h preoperatively improves insulin sensitivity after surgery: a randomized, double blind, controlled trial. *Rev Col Bras Cir*. (2012) 39:449–55. doi: 10.1590/s0100-69912012000600002
18. Kriege M, Heid F, Alflen C, Schmidtmann I, Dette F, Noppens R, et al. The orogastric tube guide® as a novel strategy for gastric tube insertion: a prospective, randomized controlled clinical trial. *Minerva Anestesiol*. (2020) 86416–422. doi: 10.23736/S0375-9393.19.14076-X
19. Ertas IE, Ince O, Emirdar V, Gultekin E, Biler A, Kurt S. Influence of preoperative enema application on the return of gastrointestinal function

in elective cesarean sections: a randomized controlled trial. *J Matern Fetal Neonatal Med*. (2021) 34:1822–1826. doi: 10.1080/14767058.2019.1651264
20. Quine EJ, Murray L, Trapani T, Cooper DJ. Thromboelastography to assess coagulopathy in traumatic brain injury patients undergoing therapeutic hypothermia. *Ther Hypothermia Temp Manag*. (2021) 11:53–7. doi: 10.1089/ther.2020.0025
21. Kim HJ, Kim NC, Park CW. The effects of warming methods on temperature, cardiac function and cytokines in plateletpheresis donors. *Vox Sang*. (2008) 95:45–51. doi: 10.1111/j.1423-0410.2008.01046.x
22. Boscan P, Van Hoogmoed LM, Farver TB, Snyder JR. Evaluation of the effects of the opioid agonist morphine on gastrointestinal tract function in horses. *Am J Vet Res*. (2006) 67:992–7. doi: 10.2460/ajvr.67.6.992
23. Gao S, Zheng Y, Liu X, Tian Z, Zhao Y. Effect of early fasting and total parenteral nutrition support on the healing of incision and nutritional status in patients after sacrectomy. *Orthop Traumatol Surg Res*. (2018) 104:539–44. doi: 10.1016/j.otsr.2018.02.006
24. Li H, Li Y, He W, Wang Z. Efficacy and safety of early rapid infusion of icy normal saline in patients after cardiopulmonary resuscitation. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue*. (2014) 26:710–3. doi: 10.3760/cma.j.issn
25. Eijlers R, Dierckx B, Staals LM, Berghmans JM, van der Schroeff MP, Strabbing EM, et al. Virtual reality exposure before elective day care surgery to reduce anxiety and pain in children: a randomised controlled trial. *Eur J Anaesthesiol*. (2019) 36:728–37. doi: 10.1097/EJA.0000000000001059
26. Faria MS, de Aguilar-Nascimento JE, Pimenta OS, Alvarenga LC Jr, Dock-Nascimento DB, Slhessarenko N. Preoperative fasting of 2 h minimizes insulin resistance and organic response to trauma after video-cholecystectomy: a randomized, controlled, clinical trial. *World J Surg*. (2009) 33:1158–64. doi: 10.1007/s00268-009-0010-x
27. Zelić M, Štimac D, Mendrila D, TokmadŽić VS, Fišić E, Uravić M, et al. Preoperative oral feeding reduces stress response after laparoscopic cholecystectomy. *Hepatogastroenterol*. (2013) 60:1602–6.
28. Rakowski JA, Holloway RW, Ahmad S, Jeppson CN, James JA, Ghurani GB, et al. A prospective randomized trial of intravenous ketorolac vs. acetaminophen administered with opioid patient-controlled analgesia in gynecologic surgery. *Gynecol Oncol*. (2019) 155:468–72. doi: 10.1016/j.ygyno.2019.09.019
29. Chang YL, Tsai YF, Hsu CL, Chao YK, Hsu CC, Lin KC. The effectiveness of a nurse-led exercise and health education informatics program on exercise capacity and quality of life among cancer survivors after esophagectomy: a randomized controlled trial. *Int J Nurs Stud*. (2020) 101:103418. doi: 10.1016/j.ijnurstu.2019.103418

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Yu, Lin and Chen. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 21 February 2022
doi: 10.3389/fsurg.2022.848312

Etiology Analysis and Diagnosis and Treatment Strategy of Traumatic Brain Injury Complicated With Hyponatremia

Jianhua Zhang[1], *Wensheng Dong*[1], *Xianghong Dou*[2], *Jinjin Wang*[1], *Peng Yin*[1] *and Hui Shi*[1]*

[1] *Department of Neurosurgery, The Affiliated Lianyungang Second People's Hospital of Bengbu Medical College, Lianyungang, China,* [2] *Department of Neurology, Donghai County People's Hospital, Lianyungang, China*

Objective: To explore the etiology and diagnosis and treatment strategy of traumatic brain injury complicated with hyponatremia.

Methods: 90 patients with traumatic brain injury admitted to our hospital from December 2019 to December 2020 were retrospectively analyzed and divided into hyponatremic group (50 patients) and non-hyponatremic group (40 patients) according to the patients' concomitant hyponatremia, and the clinical data of the two groups were collected and compared. In addition, patients in the hyponatremia group were divided into a control group and an experimental group of 25 patients each according to their order of admission, with the control group receiving conventional treatment and the experimental group using continuous renal replacement therapy (CRRT). Hemodynamic indices, mortality and serum neuron-specific enolase (NSE) indices before and after treatment were compared between the control and experimental groups. The Glasgow coma scale (GCS) was used to assess the degree of coma before and after the treatment in the two groups, and the patients' disease status was assessed using the Acute Physiological and Chronic Health Evaluation Scoring System (APACHE II).

Results: The etiology of traumatic brain injury complicated with hyponatremia is related to the degree of brain injury, ventricular hemorrhage, cerebral edema, and skull base fracture ($P < 0.05$). After the treatment, the hemodynamic indexes, APACHE II scores, death rate, and NSE levels of the experimental group were significantly lower than those of the control group ($P < 0.001$); The experimental group yielded remarkably higher GAC scores as compared to the control group ($P < 0.001$).

Conclusion: The degree of brain injury, ventricular hemorrhage, cerebral edema, and skull base fracture were considered to be the main factors for traumatic brain injury complicated with hyponatremia. Continuous renal replacement therapy can effectively improve the clinical indicators of the patients with a promising curative effect, which merits promotion and application.

Keywords: traumatic head injury, hyponatremia, cause analysis, diagnosis and treatment strategy, APACHE II

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Yang Liu,
The First Medical Center of Chinese PLA General Hospital, China
Liang Hui,
Hainan General Hospital, China

***Correspondence:**
Hui Shi
lygshihui@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *04 January 2022*
Accepted: *24 January 2022*
Published: *21 February 2022*

Citation:
Zhang J, Dong W, Dou X, Wang J, Yin P and Shi H (2022) Etiology Analysis and Diagnosis and Treatment Strategy of Traumatic Brain Injury Complicated With Hyponatremia. Front. Surg. 9:848312. doi: 10.3389/fsurg.2022.848312

BACKGROUND

Traumatic brain injury, as a common disease in neurosurgery, refers to the organic damage to the brain tissue caused by severe head trauma (1, 2), with a rather high disability rate and fatality rate. Clinical manifestations include symptoms such as disturbance of consciousness, dizziness, and headache, the delayed treatment for which may give rise to complications such as permanent dysfunction, amnesia, and epilepsy, jeopardizing patients' life safety and hindering the quality of life (3–5). Hyponatremia, defined as serum sodium below 135 mmol/L, is a common complication after traumatic brain injury and often manifests as cerebral salt-wasting syndrome and inappropriate antidiuretic hormone secretion syndrome, which can lead to serious adverse consequences if not treated promptly (6). After traumatic brain injury, the release of anterior pituitary gland adrenocorticotropic hormone increases due to the stress response, which has a certain impact on sodium excretion, and the application of a large amount of dehydrating drugs after traumatic injury can also lead to low sodium, which may cause impaired nerve cell function, resulting in neurological dysfunction and even disability or death in severe cases (7, 8). In addition, patients with traumatic brain injury are frequently complicated with hyponatremia, which may trigger neurological dysfunction or even death and disability in severe cases due to damages to the patients' nerve cells. It has been found clinically that the understanding of the causes of traumatic brain injury complicated by hyponatremia serves to a better prognosis of patients and drives down mortality (9–11). In addition, the clinical treatment of this disease is mainly gastrointestinal sodium supplementation, which has obvious limitations and poor efficacy (12), so it is also urgent to explore more ideal treatment methods. Continuous renal replacement therapy (CRRT) refers to a group of therapeutic techniques for extracorporeal blood purification, which are now widely used in the treatment of critically ill patients with various non-renal diseases (13). It has the advantages of continuous, slow, isotonic and high-volume solute exchange, hemodynamic stability, removal of medium-molecular substances such as inflammatory mediators, and continuous and stable control of electrolyte and acid-base balance (14). To explore the etiology and diagnosis and treatment strategy of traumatic brain injury complicated with hyponatremia, the clinical data of 90 patients with traumatic brain injury admitted to our hospital from 2019 to 2020 were retrospectively analyzed to dissect the etiology, and of the 90 cases included, 50 cases diagnosed with hyponatremia were identified as research objects. The report is as follows:

MATERIALS AND METHODS

General Information

The clinical data of 90 patients with traumatic brain injury admitted to our hospital from December 2019 to December 2020 were retrospectively analyzed to dissect the etiology. Of the 90 cases included, the patients were divided into a hyponatremic group (50 cases) and a non-hyponatremic group (40 cases) according to their concomitant hyponatremia. Clinical data such as gender, age, body mass index (BMI), vasodilator drug application, place of residence, were collected and compared between the hyponatremic group and the non-hyponatremic group. In addition, patients in the hyponatremia group were divided into a control group and an experimental group of 25 patients each according to their order of admission, with the control group receiving conventional treatment and the experimental group using continuous renal replacement therapy.

Inclusion Criteria

① Patients met the diagnostic criteria (15) for traumatic brain injury; ② Acute hyponatremia occurred within 7 days of onset, and the serum sodium concentration was <125 mmol/L; ③ This study was approved by the hospital ethics committee, and the patients and their families signed the informed consent form after being fully informed of the purpose and process of the study.

Exclusion Criteria

① With coagulation dysfunction; ② Pregnant and lactating women; ③ Patients with a history of metabolic diseases; ④ Patients with hyponatremia caused by primary diseases such as chronic renal failure and nephrotic syndrome.

Methods

The control group received conventional treatment. The patient's central venous pressure was closely monitored. After sodium supplementation and intravenous drip of 3% hypertonic fluid, the vascular volume state was evaluated through the patient's clinical indicators, with the fluid intake stabilized at 900 mL each time. The patients were also given an intravenous infusion of 20 mg furosemide injection (manufacturer: Changbaishan Pharmaceutical Co., Ltd.; NMPA Approval Number H22024699; specification 2 ml: 20 mg), 1 time per day. On this basis, patients were supplemented with hypertonic saline, with the rate of serum sodium increase at 9 mmol/L every 24 h to avoid the occurrence of central pontine myelinolysis.

The experimental group was treated with continuous renal replacement therapy. A double-lumen catheter was inserted into the femoral vein to construct temporary vascular access, and a hemofiltration machine (manufacturer: Guangzhou Guolun Technology Co., Ltd.; model: Fresenius-5008S) was used to implement continuous venous hemodiafiltration treatment. During the treatment, the patient's blood Na^+ concentration was closely monitored for 8 h each time, and the sodium ion concentration of the replacement solution was adjusted according to the actual situation of the patient's blood Na^+ concentration. On this basis, sodium supplementation was performed according to the patient's blood Na^+ concentration. After 24 h, the therapy was continued if the patient's blood Na^+ concentration was still inadequate, and would be terminated when the patient's 72 h blood Na^+ concentration was maintained at 140 mmol/L−145 mmol/ L.

All the above treatments were completed in our hospital, and the detailed process was shown in **Figure 1**.

Observational Indexes

According to the diagnosis, 90 patients were divided into the non-hyponatremia group and hyponatremia group. Past medical history, degree of traumatic brain injury, mannitol use, clinical

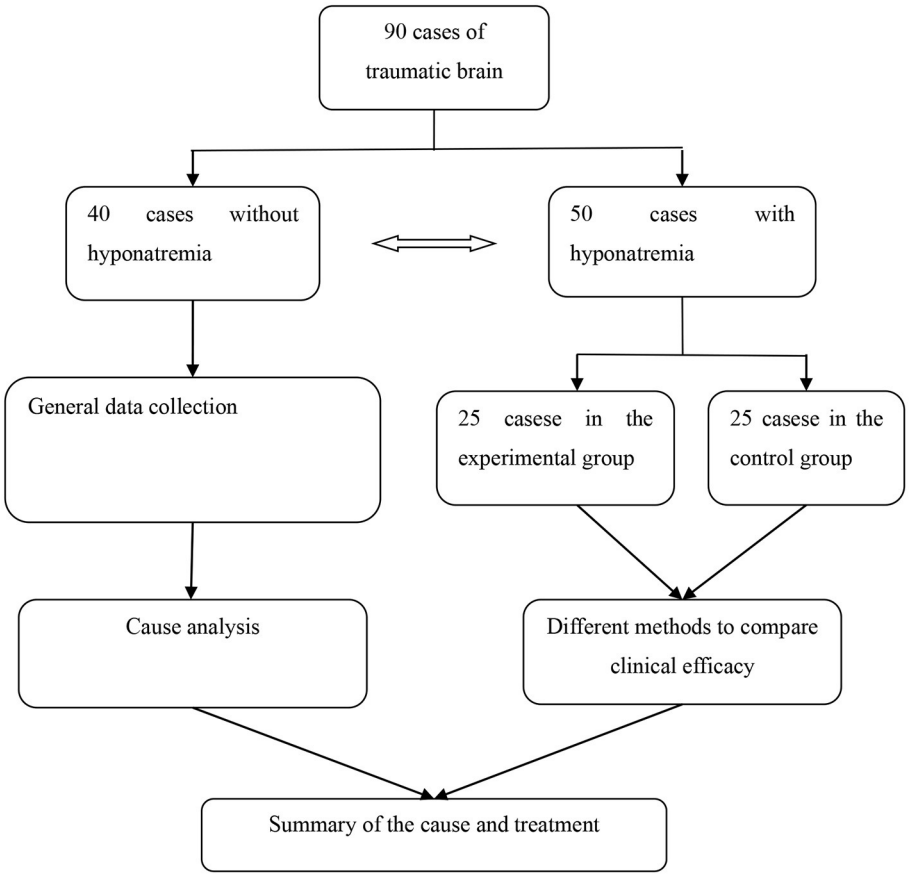


FIGURE 1 | Research flow chart.

manifestations (concussion, ventricular hemorrhage, cerebral edema, and skull base fracture) were collected from both groups to analyze the etiology of hyponatremia complicated by traumatic brain injury.

An ECG monitor (manufacturer: Changhai Berry Electronic Technology Co., Ltd.; model: JHY-40) was used to observe and compare the heart rate (HR) and mean arterial pressure (MAP) in hemodynamics before and after the treatment between the two groups.

The "Glasgow Coma Scale (GCS)" (16) was used to evaluate the coma degree of the two groups of patients before and after the treatment. The GCS includes three scoring systems, including best eye opening (maximum 4 points), best verbal response (maximum 5 points) and best motor response (maximum 6 points), with a total score of 3 to 15 points. The lower the score, the more severe the coma of the patients.

The "acute physiology and chronic health evaluation scoring system (APACHE) II Score Scale" (17) was used to evaluate the patient's condition before and after the treatment. The scale includes components of acute physiology, chronic health status and age, the total score of the scale is 71 points. The higher the score, the more severe the patients' condition.

The death rate of the two groups of patients after the treatment were observed and recorded.

The early morning fasting cubital venous blood of the two groups of patients was collected to separate the serum by centrifugation. The supernatant was collected and stored at −80°C. The serum Neuron-specific enolase (NSE) level in the sample was detected according to the enzyme-linked immunosorbent assay (ELISA) kit instructions. The operation strictly followed the kit instructions and operating procedures for standardized inspections.

Statistical Processing

SPSS 20.0 software was used to analyze the data in this study, and GraphPad Prism 7(GraphPad Software, San Diego, USA) was used to plot the graphics. The research included count data and measurement data. Count data were expressed by n(%) and analyzed by χ^2 test, and the measurement data were expressed by (Mean, SD), analyzed by t-test and normal distribution. $P < 0.05$ indicated statistical significance.

TABLE 1 | Comparison of general information of the two groups of patients [(mean, SD), n (%)].

	Hyponatremia group (n = 50)	Non-hyponatremia group (n = 40)	χ^2 or t value	P value
Gender				
Male	27 (54.00)	21 (52.50)	0.020	0.887
Female	23 (46.00)	19 (47.50)		
Average age (years)	49.27 ± 2.31	49.31 ± 2.27	0.082	0.935
BMI (kg/m^2)	21.55 ± 3.42	21.49 ± 3.31	0.084	0.933
Application of vasodilator drugs				
Yes	17 (34.00)	20 (50.00)	2.349	0.125
No	33 (66.00)	20 (50.00)		
Place of residence				
Urban	30 (60.00)	25 (62.50)	0.058	0.809
Rural	20 (40.00)	15 (37.50)		

TABLE 2 | Etiology analysis of the patients with hyponatremia [n (%)].

	Hyponatremia group (n = 50)	Non-hyponatremia group (n = 40)	χ^2 value	P value
Past medical history			0.080	0.777
Diabetes	26 (52.00)	22 (55.00)		
Hypetension	24 (48.00)	18 (45.00)		
Degree of brain injury				
Mild	5 (10.00)	13 (32.50)	7.031	0.008
Moderate	17 (34.00)	22 (55.00)	3.991	0.046
Severe	28 (56.00)	5 (12.50)	18.107	<0.001
Use of mannitol			0.172	0.679
Yes	45 (90.00)	37 92.50()		
No	5 (10.00)	3 (7.50)		
Concussion			0.057	0.811
Yes	20 (40.00)	17 (42.50)		
No	30 (60.00)	23 (57.50)		
Ventricular hemorrhage			19.306	<0.001
Yes	37 (74.00)	11 (27.50)		
No	13 (26.00)	29 (72.50)		
Brain edema			6.889	0.009
Yes	35 (70.00)	17 (42.50)		
No	15 (30.00)	23 (57.50)		
Skull base fracture			6.255	0.012
Yes	32 (64.00)	15 (37.50)		
No	18 (36.00)	25 (62.50)		

RESULTS

Comparison of General Information

There were no significant differences in gender, average age, BMI, application of vasodilator drugs, and place of residence between the two groups of patients ($P > 0.05$). See **Table 1** for details.

Analysis of the Etiology of Hyponatremia in Patients With Traumatic Brain Injury

The etiology of patients with complicated hyponatremia had no correlation with past medical history, mannitol application, and concussion ($P > 0.05$), while it was correlated with the degree of craniocerebral injury, intraventricular hemorrhage, cerebral edema, and skull base fracture ($P < 0.05$). See **Table 2** for details.

Comparison of Hemodynamic Indexes Between the Control Group and the Experimental Group Before and After Treatment

After treatment, HR and MAP in both groups decreased significantly compared with those before treatment, and the levels of each index in the experimental group were significantly lower than those in the control group ($P < 0.05$) (**Table 3**).

Comparison of GCS Scores Between the Control Group and the Experimental Group

After treatment, the GCS scores in both groups increased significantly compared to the pre-treatment, strong evidence of significantly higher GCS scores in the experimental group was found, in comparison with those of the control group ($P < 0.05$), as shown in **Figure 2**.

Comparison of APACHE II Scores Between the Control Group and the Experimental Group

Lower APACHE II scores were observed in the experimental group in contrast to the control group after the treatment ($P < 0.05$) (**Figure 3**).

Comparison of Mortality Rate Between Control Group and Experimental Group

There was one case of death in the experimental group and nine cases of death in the control group. The experimental group was recorded with fewer death cases when compared with the control group ($P < 0.05$), as shown in **Figure 4**.

Comparison of NSE Levels Between the Control Group and the Experimental Group

Results in **Figure 5** presented lower NSE levels in the experimental group than the control group ($P < 0.05$).

TABLE 3 | Comparison of hemodynamic indexes between the two groups (mean, SD).

Groups	HR (time/min)		MAP (mmHg)	
	Before treatment	After treatment	Before treatment	After treatment
Experimental group ($n = 25$)	95.37 ± 3.55	75.01 ± 2.13	110.27 ± 22.12	81.55 ± 10.51
Control group ($n = 25$)	94.88 ± 3.69	85.99 ± 3.51	110.12 ± 22.45	98.89 ± 16.35
t value	0.478	13.372	0.024	4.461
P value	0.635	<0.001	0.981	<0.001

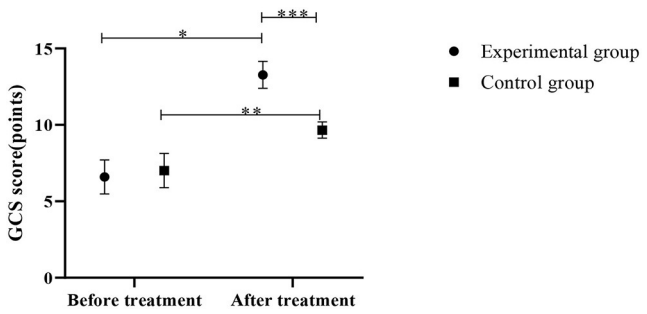


FIGURE 2 | Comparison of GCS scores between the control group and the experimental group (Mean, SD). The abscissa represents before and after the treatment, and the ordinate represents GCS score, points; the GCS scores of patients in the experimental group before and after the treatment were (6.59 ± 1.11) points and (13.27 ± 0.88) points respectively; the GCS scores of the control group before and after the treatment were (7.01 ± 1.12) points and (9.66 ± 0.53) points respectively; *Indicates that there is a significant difference in the GCS scores of the experimental group before and after the treatment ($t = 23.579$, $P < 0.001$); **Indicates that there is a significant difference in the GCS scores of the control group before and after the treatment ($t = 10.693$, $P < 0.001$); ***Indicates that there is a significant difference in the GCS scores of the two groups of patients after the treatment ($t = 17.571$, $P < 0.001$).

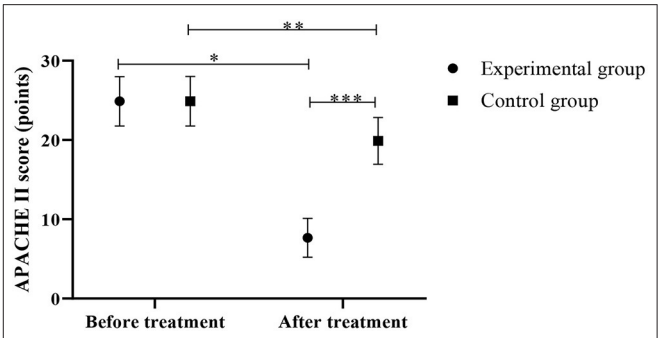


FIGURE 3 | Comparison of APACHE II scores between the control group and the experimental group (Mean, SD). The abscissa represents before and after the treatment, and the ordinate represents APACHE II score, points; the APACHE II scores of patients in the experimental group before and after the treatment were (24.88 ± 3.11) points and (7.65 ± 2.45) points respectively; the APACHE II scores of the control group before and after the treatment were (24.89 ± 3.12) points and (19.88 ± 2.95) points respectively; *Indicates that there is a significant difference in the APACHE II scores of the experimental group before and after the treatment ($t = 21.759$, $P < 0.001$); **Indicates that there is a significant difference in the APACHE II scores of the control group before and after the treatment ($t = 5.834$, $P < 0.001$); ***Indicates that there is a significant difference in the APACHE II scores of the two groups of patients after the treatment ($t = 15.946$, $P < 0.001$).

DISCUSSION

Brain injury is mainly caused by trauma, with hyponatremia as the most influential factor in the prognosis of the disease (18–20). Currently, most scholars believe that the pathogenesis of traumatic brain injury complicated by hyponatremia is related to abnormal secretion of antidiuretic hormone and cerebral salt wasting syndrome (21, 22). Specifically, brain injury predisposes to brain salt depletion syndrome, leading to increased renal sodium excretion and low sodium reabsorption rates, ultimately leading to excessive sodium secretion and hyponatremia (23). In addition, brain injury also stimulates antidiuretic hormone secretion, which strengthens the renal tubule reabsorption capacity, resulting in a significant decline in blood sodium and then hyponatremia. The complications of hyponatremia in traumatic brain injury may induce symptoms such as irritability, nausea, and lethargy, or even death in severe cases if patients fail to receive effective treatment (24, 25). It has been found clinically that the understanding of the etiology of traumatic brain injury complicated by hyponatremia serves to a better prognosis of patients. In this study, it was found that the cause of traumatic brain injury complicated by hyponatremia was related to the degree of brain injury, ventricular hemorrhage, cerebral edema, and skull base fracture ($P < 0.05$), which may be attributed to the following factors (26, 27): ① Severe brain injury inhibits the activity of renal sympathetic nerves, thereby increasing the glomerular filtration and causing the reduction of sodium reabsorption in the renal tubules; ② Abnormal secretion of the antidiuretic hormone leads to hyponatremia as symptoms such as intraventricular hemorrhage and cerebral edema trigger blood circulation disorder, hypothalamus damage, and increased intracranial pressure; ③ Cerebrospinal fluid leakage after skull base fracture impairs the patient's hypothalamic function, resulting in hyponatremia. Clinically, most patients with brain injury are complicated with hyponatremia, which aggravates the condition and increases the mortality rate if effective treatment measures are absent. Therefore, in clinical treatment, after diagnosis of cerebral salt wasting syndrome, sodium supplementation was timely provided to maintain a balanced state of electrolytes in the patient's body. However, the treatment approach is conservative and has limitations (28, 29). CRRT can effectively remove solute and water to restore the electrolyte

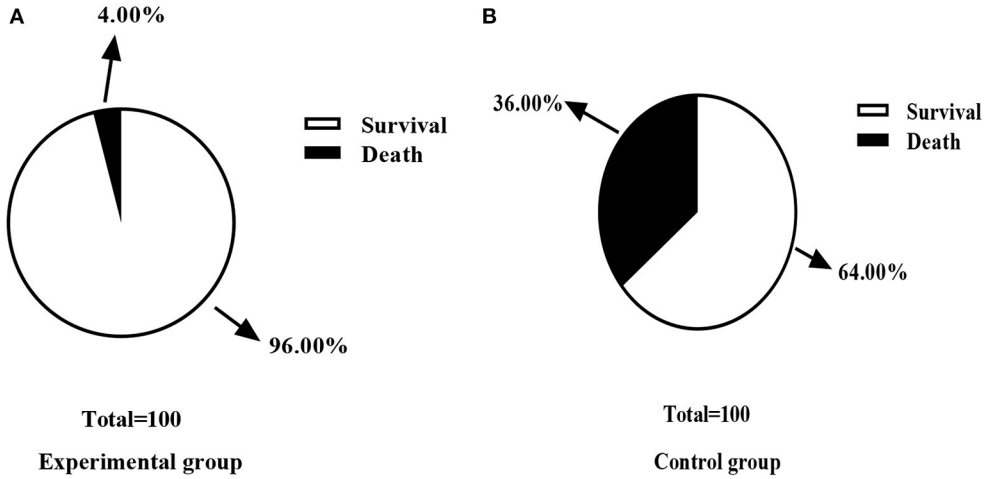


FIGURE 4 | Comparison of mortality rate between control group and experimental group [n (%)]. **(A)** This figure is the death rate of the experimental group; **(B)** is the death rate of the control group; In the experimental group, one case of death (4.00%) and 24 cases of survival (96.00%) were recorded. In the control group, nine cases of death (36.00%) and 16 cases (64.00%) of survival were recorded; There was a significant difference in the death rate between the two groups of patients after the treatment ($\chi^2 = 8.000$, $P < 0.05$).

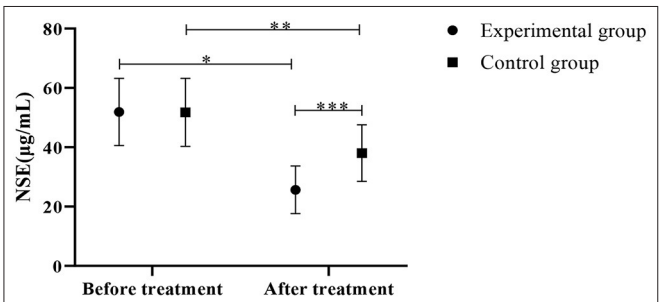


FIGURE 5 | Comparison of NSE levels between the control group and the experimental group (Mean, SD). The abscissa indicates before and after the treatment, and the ordinate indicates the NSE level, μg/mL; The NSE levels of patients in the experimental group before and after the treatment were (51.88 ± 11.33) μg/mL and (25.65 ± 8.02) μg/mL respectively; The NSE levels of patients in the control group before and after the treatment were (51.75 ± 11.45) μg/mL and (38.02 ± 9.52) μg/mL respectively; *Indicates that there is a significant difference in the NSE level of the experimental group before and after the treatment ($t = 9.448$, $P < 0.001$); **Indicates that there is a significant difference in NSE level before and after the treatment in the control group ($t = 4.610$, $P < 0.001$); ***Indicates that there is a significant difference in the NSE levels of the two groups of patients after the treatment ($t = 4.969$, $P < 0.001$).

balance. Furthermore, timely adjustment of the replacement fluid Na^+ according to the patient's blood Na^+ concentration avoids the imbalance of blood Na^+ correction speed and reduces the occurrence of excessive blood pressure osmotic fluctuations. In addition to the correction of hyponatremia, continuous renal replacement therapy effectively relieves cerebral edema, removes nitrogen metabolites, reduces osmotic pressure, and maintains the patient's internal environment in a stable state (30). The results of this experiment showed a significantly lower death rate and a lower NSE level of the experimental group after the treatment than the control group ($P < 0.05$), indicating that the therapy can improve the patient's clinical indicators to reduce mortality. In addition, the present study also found that the GCS score after treatment was higher in the experimental group than in the control group ($P < 0.05$), and the results of James E (31) et al. stated that "the GCS score after treatment was (14.1 ± 0.73) in the treatment group, which was significantly higher than that of (8.9 ± 0.52) in the control group ($P < 0.05$)", which is generally consistent with the results of this study. It fully indicates that CRRT produced significant clinical effects in improving patients' conditions compared with conventional treatment.

In conclusion, the degree of brain injury, ventricular hemorrhage, cerebral edema, and skull base fracture were considered the main factors for traumatic brain injury complicated with hyponatremia. CRRT can effectively improve the clinical indicators of the patients with a promising curative effect, which merits promotion and application.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Lianyungang Second People's Hospital of Bengbu Medical College. The patients/participants

provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JZ is responsible for writing the article. WD is responsible for the design of the study. XD is responsible for the collection of case data. JW and PY are responsible for the recording of the results and statistics. HS is the instructor of the entire study. All authors contributed to the article and approved the submitted version.

FUNDING

This research is supported by the Lianyungang Municipal Health Commission (202120).

REFERENCES

1. Harbert A, Northam W, Elton S, Quinsey C. Targeted head CT reduction for pediatric patients with hydrocephalus and traumatic brain injury: academic center institutional experience as an example of opportunities for further improvement. *Childs Nerv Syst.* (2020) 36:583–9. doi: 10.1007/s00381-019-04376-w
2. Schur S, Martel P, Marcoux J. Optimal Bone Flap Size for Decompressive Craniectomy for Refractory Increased Intracranial Pressure in Traumatic Brain Injury: Taking the Patient's Head Size into Account. *World Neurosurgery*. (2020). 139E430-E436. doi: 10.1016/j.wneu.2020.01.232
3. Bree D, Mackenzie K, Stratton J, Levy D. Enhanced post-traumatic headache-like behaviors and diminished contribution of peripheral CGRP in female rats following a mild closed head injury. *Cephalalgia.* (2020) 40:748–60. doi: 10.1177/0333102420907597
4. Guilhaume-Correa F, Cansler SM, Shalosky EM, Goodman MD, Evanson NK. Greater neurodegeneration and behavioral deficits after single closed head traumatic brain injury in adolescent versus adult male mice. *J Neur Res.* (2020) 98:557–70. doi: 10.1002/jnr.24535
5. Khanuja T, Unni HN. Intracranial pressure-based validation and analysis of traumatic brain injury using a new three-dimensional finite element human head model. *Proc Inst Mech Eng H.* (2020) 234:3–15. doi: 10.1177/0954411919881526
6. Baek SH, Jo YH, Ahn S, Medina-Liabres K, Oh YK, Lee JB, et al. Risk of overcorrection in rapid intermittent bolus vs slow continuous infusion therapies of hypertonic saline for patients with symptomatic hyponatremia: The SALSA randomized clinical trial. *JAMA Intern Med.* (2021) 181:81–92. doi: 10.1001/jamainternmed.2020.5519
7. Hoffmann DB, Popescu C, Komrakova M, Welte L, Saul D, Lehmann W, et al. Chronic hyponatremia in patients with proximal femoral fractures after low energy trauma: A retrospective study in a level-1 trauma center. *Bone Rep.* (2019) 12:100234. doi: 10.1016/j.bonr.2019.100234
8. Jäckle K, Klockner F, Hoffmann DB, Roch PJ, Reinhold M, Lehmann W, et al. Influence of hyponatremia on spinal bone quality and fractures due to low-energy trauma. *Medicina (Kaunas).* (2021) 57:1224. doi: 10.3390/medicina57111224
9. Singh S, Das KK, Deora H, Jaiswal AK, Behari S. Traumatic partial posterior cord brachial plexus injury in a patient with aberrant innervation of the long head of the triceps by the axillary nerve: Implications in nerve transfer surgery. *Asian J Neurosurg.* (2020) 15:391–3. doi: 10.4103/ajns.AJNS_160_19
10. Gillespie CS, Mcleavy CM, Islim AI, Prescott S, McMahon CJ. Rationalising neurosurgical head injury referrals: development and validation of the Liverpool Head Injury Tomography Score (Liverpool HITS) for mild TBI. *Br J Neurosurg.* (2020) 34:127–34. doi: 10.1080/02688697.2019.1710825
11. Anderson TN, Hinson HE, Dewey EN, Rick EA, Schreiber MA, Rowell SE. Early tranexamic acid administration after traumatic brain injury is associated with reduced syndecan-1 and angiopoietin-2 in patients with traumatic intracranial hemorrhage. *J Head Trauma Rehabil.* (2020) 35:317–23. doi: 10.1097/HTR.0000000000000619
12. Phillips N, Dalziel SR, Borland ML, Dalton S, Lyttle MD, Bressan S, et al. Imaging and admission practices in paediatric head injury across emergency departments in Australia and New Zealand: A PREDICT study. *Emerg Med Australas.* (2020) 32:240–9. doi: 10.1111/1742-6723.13396
13. Hoff BM, Maker JH, Dager WE, Heintz BH. Antibiotic dosing for critically Ill adult patients receiving intermittent hemodialysis, prolonged intermittent renal replacement therapy, and continuous renal replacement therapy: an update. *Ann Pharmacother.* (2020) 54:43–55. doi: 10.1177/1060028019865873
14. Alharthy A, Faqihi F, Memish ZA, Balhamar A, Nasim N, Shahzad A, et al. Continuous renal replacement therapy with the addition of CytoSorb cartridge in critically ill patients with COVID-19 plus acute kidney injury: A case-series. *Artif Organs.* (2021) 45:E101–12. doi: 10.1111/aor.13864
15. Araki T, Yokota H, Morita A. Pediatric traumatic brain injury: characteristic features, diagnosis, and management. *Neurol Med Chir (Tokyo).* (2017) 57:82–93. doi: 10.2176/nmc.ra.2016-0191
16. Wang J, Zhou W, Yin X. Improvement of hyponatremia is associated with lower mortality risk in patients with acute decompensated heart failure: a meta-analysis of cohort studies. *Heart Fail Rev.* (2019) 24:209–17. doi: 10.1007/s10741-018-9753-5
17. Rinaldi S, Santoni M, Leoni G, Fiordoliva I, Marcantognini G, Meletani T, et al. The prognostic and predictive role of hyponatremia in patients with advanced non-small cell lung cancer (NSCLC) with bone metastases[J]. *Support Care Cancer.* (2019) 27:1255–61. doi: 10.1007/s00520-018-4489-2
18. Chen Z, Jia Q, Liu C. Association of hyponatremia and risk of short- and long-term mortality in patients with stroke: a systematic review and meta-analysis. *J Stroke Cerebrovasc Dis.* (2019) 28:1674–83. doi: 10.1016/j.jstrokecerebrovasdis.2019.02.021
19. Sato Y, Yoshihisa A, Oikawa M, Nagai T, Yoshikawa T, Saito Y, et al. Hyponatremia at discharge is associated with adverse prognosis in acute heart failure syndromes with preserved ejection fraction: a report from the JASPER registry. *Eur Heart J Acute Cardiovasc Care.* (2019) 8:623–33. doi: 10.1177/2048872618822459
20. Holland-Bill L, Christiansen CF, Ulrichsen SP, Ring T, Lunde Jørgensen JO, Sørensen HT. Preadmission diuretic use and mortality in patients hospitalized with hyponatremia: a propensity score-matched cohort study. *Am J Ther.* (2019) 26:e79–91. doi: 10.1097/MJT.0000000000000544
21. Woodfine JD, Sood MM, MacMillan TE, Cavalcanti RB, van Walraven C. Derivation and validation of a novel risk score to predict overcorrection of severe hyponatremia: the severe hyponatremia overcorrection risk (SHOR) score. *Clin J Am Soc Nephrol.* (2019) 14:975–82. doi: 10.2215/CJN.12251018
22. Portales-Castillo I, Sterns RH. Allostasis and the clinical manifestations of mild to moderate chronic hyponatremia: no good adaptation goes unpunished. *Am J Kidney Dis.* (2019) 73:391–9. doi: 10.1053/j.ajkd.2018.10.004
23. Yoon HK, Lee HC, Kim YH, Lim YJ, Park HP. Predictive factors for delayed hyponatremia after endoscopic transsphenoidal surgery in patients with nonfunctioning pituitary tumors: a retrospective observational study. *World Neurosurg.* (2019) 122:e1457–64. doi: 10.1016/j.wneu.2018.11.085
24. Lassey SC, Napoe GS, Carusi D, Schantz-Dunn J, Robinson JN. Hyponatremia among parturients transferred to the hospital after prolonged labor during an attempted home birth. *Obstet Gynecol.* (2019) 134:106–8. doi: 10.1097/AOG.0000000000003306
25. Pomeranz D, Irwin C, Lipman GS. Large-volume hypertonic saline for empiric treatment of severe exercise-associated hyponatremia in an ultramarathon runner. *Curr Sports Med Rep.* (2019) 18:163–5. doi: 10.1249/JSR.0000000000000593
26. Xiao S, Liu Y, Li K, Lou B, Chen K, Chang Z. Successful treatment of an 86-year-old patient with severe hyponatremia leading to central and extrapontine myelinolysis: A case report. *Aging Med (Milton).* (2019) 2:56–9. doi: 10.1002/agm2.12056

27. Filippone EJ, Ruzieh M, Foy A. Thiazide-associated hyponatremia: clinical manifestations and pathophysiology. *Am J Kidney Dis.* (2020) 75:256–64. doi: 10.1053/j.ajkd.2019.07.011
28. Sarmiento K, Gioia GA, Kirkwood MW, Wade SL, Yeates KO, A. commentary for neuropsychologists on CDC's guideline on the diagnosis and management of mild traumatic brain injury among children. *Clin Neuropsychol.* (2020) 34:259–77. doi: 10.1080/13854046.2019.1660806
29. Fu P, Bai L, Cai Z, Li R, Yung KKL. Fine particulate matter aggravates intestinal and brain injury and affects bacterial community structure of intestine and feces in Alzheimer's disease transgenic mice. *Ecotoxicol Environ Saf.* (2020) 192:110325. doi: 10.1016/j.ecoenv.2020.110325
30. Ibrahim KA, Eleyan M, Abd El-Rahman HA, Khwanes SA, Mohamed RA. Quercetin attenuates the oxidative injury-mediated upregulation of apoptotic gene expression and catecholaminergic neurotransmitters of the fetal rats' brain following prenatal exposure to fenitrothion insecticide. *Neurotox Res.* (2020) 37:871–82. doi: 10.1007/s12640-020-00172-6
31. Sweeney JE, Johnson AM. Exploratory study of HRB signs, patterns, and right-left differences relating to spatial cognition following nonimpact mild traumatic brain injury. *Appl Neuropsychol Adult.* (2020) 27:532–9. doi: 10.1080/23279095.2019.1575220

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhang, Dong, Dou, Wang, Yin and Shi. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 21 February 2022
doi: 10.3389/fsurg.2022.844533

Application of Rapid Rehabilitation Surgical Nursing Combined With Continuous Nursing in Self-Care Ability, Medication Compliance and Quality of Life of Renal Transplant Patients

Linyan Song[1]*, *Qing Jin*[2], *Liying Zhu*[2], *Zhe Liu*[2] and *Wenjuan Cheng*[2]

[1] Nursing Department, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China, [2] Department of Urology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

OPEN ACCESS

Edited by:
Weiguo Li,
Harbin Institute of Technology, China

Reviewed by:
Wenjie Song,
Fourth Military Medical University, China
Li Zhang,
University of South China, China

***Correspondence:**
Linyan Song
songlinyan78@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *28 December 2021*
Accepted: *19 January 2022*
Published: *21 February 2022*

Citation:
Song L, Jin Q, Zhu L, Liu Z and Cheng W (2022) Application of Rapid Rehabilitation Surgical Nursing Combined With Continuous Nursing in Self-Care Ability, Medication Compliance and Quality of Life of Renal Transplant Patients. Front. Surg. 9:844533. doi: 10.3389/fsurg.2022.844533

Objective: To explore the effects of rapid rehabilitation surgery (FTS) nursing combined with continuous nursing on self-care ability, medication compliance and quality of life of patients after renal transplantation.

Methods: Sixty patients who received kidney transplantation in our hospital from January 2019 to January 2021 were randomly divided into the control group and the observation group with 30 patients in each group according to the random number table method. The control group was given FTS nursing, while the observation group was given continuous nursing on the basis of the control group. General data were collected and compared between the two groups. Postoperative indexes such as the time of first intake and the like of patients in the two groups were recorded. The patients' comfort, self-care ability, medication compliance and quality of life after renal transplantation were evaluated in the two groups. During the follow-up, the hospitalization of patients with complications was recorded.

Results: There was no significant difference in the first intake, blood glucose, creatinine, urea nitrogen, blood potassium or postoperative hospital stay between the two groups ($P > 0.05$). There was no significant difference in the postoperative physical, mental, psychological, social and environmental dimensions between the two groups ($P > 0.05$). The scores of cognitive symptom management, exercise and communication with doctors in the two groups in post-intervention were higher than those in pre-intervention, and the scores in the observation group in post-intervention were higher than those in the control group ($P < 0.05$). The medication compliance in the observation group (93.33%) was higher than that in the control group (70.00%) ($\chi^2 = 5.455$, $P = 0.020$). In post-intervention, the scores of quality of life of the observation group were higher than those of the control group ($P < 0.05$). The admission rate of complications in the observation group (10.00%) was lower than that in the control group (30.00%) ($\chi^2 = 3.750$, $P = 0.035$).

Conclusion: FTS nursing can help renal transplantation patients to obtain more stable postoperative blood pressure, renal function and other indicators and comfort. On this basis, combined with continuous nursing can improve patients' self-care ability and medication compliance, which is of great significance to improve the quality of life of patients.

Keywords: kidney transplantation, rapid rehabilitation surgical nursing, continuing nursing, self-protection ability, quality of life

INTRODUCTION

Kidney transplantation is an effective treatment for end-stage renal disease. In recent years, with the development of medical technology, the survival rate of grafts after kidney transplantation has obviously improved, which is conducive to prolonging the life span of patients and improving the quality of life (1). Good hemodialysis and peritoneal dialysis are the basis of kidney transplantation. Good perioperative preparation, safe anesthesia techniques and implementation of intraoperative heat preservation measures are the key to ensure the success of surgery, reduce postoperative complications, and promote the recovery of patients (2). Fast-track surgery (FTS) was first proposed by KehIet al. (3) of Denmark, and its main purpose is to optimize the perioperative treatment plan through a series of optimization measures with evidence-based medical evidence, so as to relieve the pressure of patient's physical and mental trauma, and thus achieve the purpose of rapid recovery and reduce the total mortality. After the concept of FTS was introduced into China, it was widely used in many surgical fields such as orthopedics, cardiothoracic surgery, breast surgery, gastrointestinal surgery, etc. Its advantages are gradually recognized by the medical profession. Its main contents include perioperative nutritional support and liquid management, emphasizing oxygen supply, early feeding and minimally invasive surgery (4). FTS nursing requirements, in actual clinical application, according to the patients' age, type of surgery, operation time, fluid loss during operation and other factors, formulate specific personalized nursing scheme for patients (5). After kidney transplantation, the use of a large number of immunosuppressants leads to the decline of the body's resistance. At the same time, complications such as rejection, delayed recovery of transplanted renal function and urinary fistula bring difficulties to the nursing and patient management of kidney transplantation. Conventional nursing is limited to the care of hospitalized patients. It is difficult for patients to obtain professional nursing guidance after they are discharged from hospital, and the patients' self-management ability and medication compliance are poor, making it difficult to meet the needs of kidney transplant recipients for life-long medical treatment. Therefore, it is very important to carry out health education, improve medication compliance and control the occurrence of postoperative complications after discharge. Continuous nursing can provide professional care for discharged patients, improve their self-management ability, find abnormalities as early as possible, and get timely and effective treatment (6, 7). In this study, FTS nursing combined with continuous nursing of renal transplant patients was used to explore the influence of two nursing methods on self-care ability, medication compliance and quality of life of renal transplant patients.

DATA AND METHODS

General Information

Sixty patients who received kidney transplantation in our hospital from January 2019 to January 2021 were randomly divided into the control group and the observation group with 30 patients in each group according to the random number table method. The control group was given FTS nursing, and the observation group was given continuous nursing on the basis of the control group.

Inclusion criteria

Age ≥18 years old; Those who meet the indications of kidney transplantation are treated; Chronic diseases, such as hypertension and diabetes, were stably controlled.

Exclusion criteria

Patients with multiple organ transplants; A second kidney transplantation; Patients with other serious diseases of organ foundation; Highly sensitive objects; Patients who failed to follow doctor's advice, withdrew from the study or had incomplete follow-up information. All patients and their families have obtained informed consent, and this study was approved by the hospital ethics committee.

Research Methods

Patients in the control group received FTS nursing: The nursing management team established was mainly composed of researchers and doctors, nurses and dieticians in their hospitals studying the direction of renal transplantation. Specific qualification requirements are as follows: Medical personnel with bachelor degree or above and relevant certificates; More than 5 years working experience in kidney transplantation diagnosis and treatment; Good communication and coordination skills. ① Training and functions of nursing team: intensive training on nutrition therapy guidelines and related knowledge of kidney diseases for participants for one week in the form of lectures, group discussions, scene drills, etc. The head nurse of the department is responsible for coordinating the cooperation between the team members, the attending physician

is responsible for the formulation of nutrition plan for patients, management and protection department is responsible for the formulation of nutrition plan, and the nutritionist is responsible for the modification. ② Personalized care plan: establish nutrition file for each patient, including general information of the patient (age, gender, educational level, marriage relationship, etc.), nutrition instruction list, biochemical test list, and physical test list. Body mass index (BMI) and total calories were calculated based on the patient's height and weight (carbohydrates accounted for 55–65% of the total daily calories, protein supply was 1.0–1.2g/kg per day, and fat supply accounted for about 25–35% of the total energy). Ensure the balance of water and electrolyte according to the biochemical test results, and adjust it according to patients' edema, blood pressure and electrolyte. ③ Preoperative education: patients determine the operation time according to the operation sequence, and use oral education and written materials to education patients before operation, explain the theory and technology of kidney transplantation, preoperative preparation, what problems will occur during operation, how to solve the problems of surgeons and nurses, how to cooperate with patients, and tell them to keep a good attitude and build confidence in overcoming disease. ④ Intraoperative preparation: Adius the room temperature to 26–28°C 1 h before the patient entered the operation room, and the room temperature was kept constant at 22–24°C until the end of the operation after the operation began, in order to reduce the heat loss of patients and provide a comfortable operation environment. In the operation and nursing operation, try to reduce the exposure of patients' bodies, reduce the overflow of flushing fluid during operation and keep the operating bed dry. The electronic heating infusion set was used to heat the infusion to 37°C, and the non-surgical area was covered with clothing or surgical towels with good thermal insulation performance to isolate it from the surrounding cold air, and to keep warm during the operation of the patient. Drugs with short half-life should be used as anesthetics to reduce the dosage of opioids. ⑤ Postoperative observation: closely observe the changes of patients' condition in order to maintain the volume balance and water-electrolyte balance of patients with polyuria; In order to prevent rejection, immunosuppressants were used in time and correctly. If complications such as delayed recovery of transplanted renal function occur after operation, the responsible team shall follow up in time and take effective treatment and nursing measures, and arrange hemodialysis treatment if necessary to promote the recovery of renal function. ⑥ Guidance at discharge: after the patient's condition is stable and reaches the discharge indications, give health education to the patients before discharge, know that the patient is taking medicine on time according to the doctor's advice, and check it regularly.

The observation group was additionally provided with continuous nursing on the basis of the control group. ① Follow-up after discharge: after the renal transplant patients are discharged from hospital, the responsible nurses are still responsible for continuous follow-up, tracking and guidance. Educate patients to pay attention to rest, combining rest with rest. Keep the living environment clean, quickly prevent colds and infection symptoms, and seek medical treatment. The necessity of long-term use of immunosuppressants was emphasized, and patients were urged to take medicine on time and pay attention to the complications of immunosuppressants. In diet, you should eat more foods rich in vitamins, take physiological doses of calcium for a long time, limit drinking water, and limit the intake of salt, protein and fat. ② Establish patient files: set up follow-up archives at the time of discharge, regular follow-up by phone and outpatient service, including the patient's vital signs, urine volume, rejection, diet, exercise status, drug use, etc., to master the patient taking immunosuppressive agents. ③ Self-management education: in the follow-up nursing, guide the patients' self-care ability, and take medicine on time and according doctor's orders. The therapeutic effect of drugs, possible adverse reactions of drugs and precautions were

TABLE 1 | Comparison of general information of patients between the two groups.

Group	Age (years)	Gender		BMI(kg/m^2)	Degree of education	
		Man	Woman		Junior secondary and below	Junior high school and above
Control group ($n = 30$)	32.59 ± 6.17	21	9	23.13 ± 1.35	10	20
Observation group ($n = 30$)	31.85 ± 5.63	23	7	22.76 ± 1.26	12	18
t/χ^2 value	0.485	0.341		1.097	0.287	
P value	0.629	0.559		0.277	0.592	

Group	Marital relations		Dialysis mode	
	Married	Be unmarried	Hemodialysis	Peritoneal dialysis
Control group ($n = 30$)	21	9	24	6
Observation group ($n = 30$)	23	7	27	3
χ^2 value	0.341		1.176	
P value	0.559		0.278	

explained to patients, so that they were psychologically prepared to observe whether accelerated rejection occurred. Strictly avoid accidents or missions, especially telling patients that increasing or decreasing the dose of immunosuppressants at will may cause serious consequences. At the same time, explain the purpose and requirements of each examinations are to the patient and emphasize the importance of regular review. ④ Personalized adjustment of nursing plan: when the patients returned to our hospital for reexamination and telephone follow-up, we could show the patients that the operation had achieved the expected goal with objective and real examination data, thus further strengthening the patients' confidence in treatment. Patients who failed to achieve the expected goals were analyzed and discussed with the patients and their families, and more detailed care intervention plan was formulated. ⑤ Psychological care: Pay attention to the patients' psychological status, conduct home care and give patients more social support. Ask the family members to pay attention to the emotional and social communication needs of patients. Hospitals regularly organize activities such as friendship and mutual assistance among patients, and provide more social support to patients through various channels.

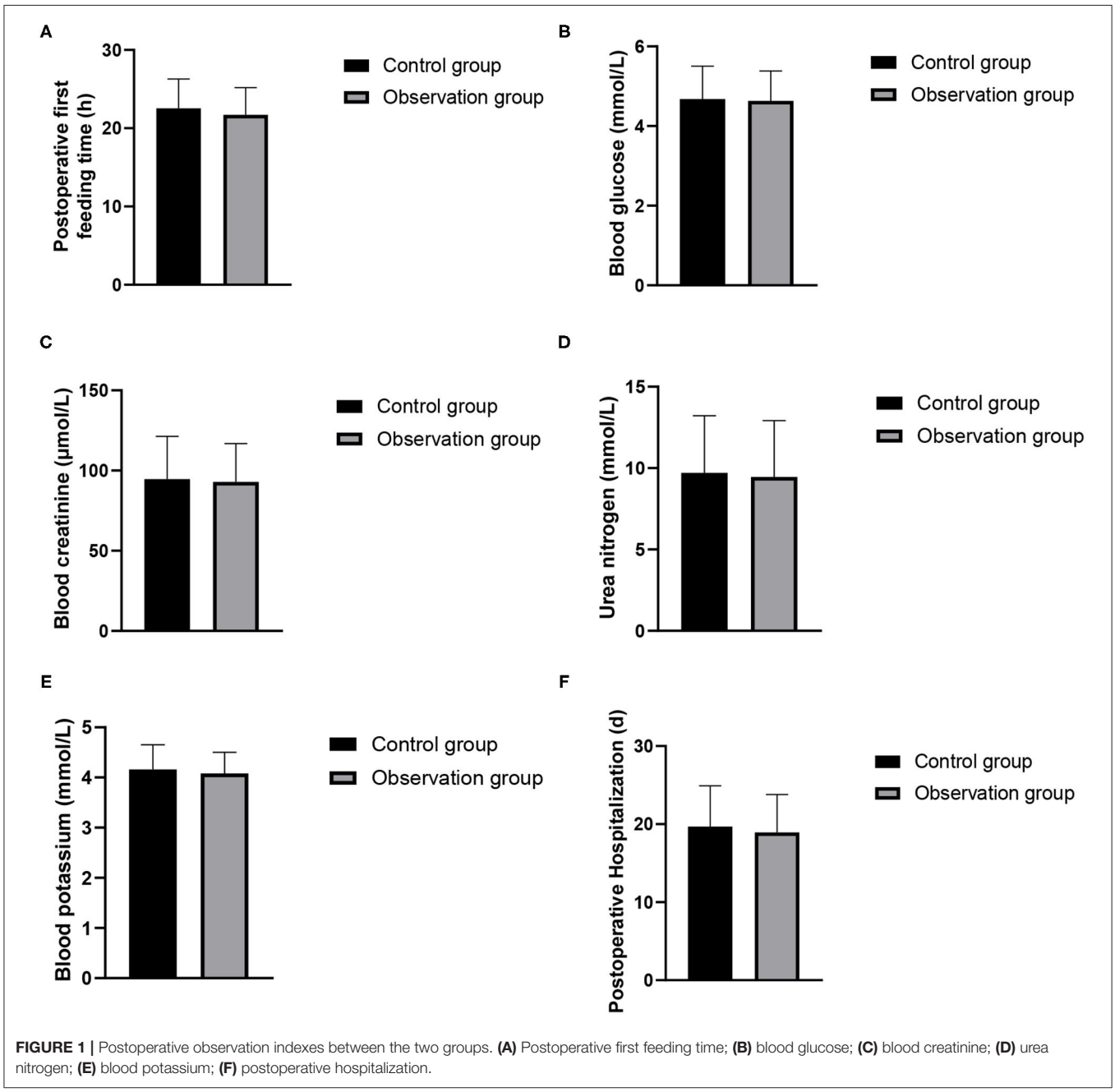


FIGURE 1 | Postoperative observation indexes between the two groups. **(A)** Postoperative first feeding time; **(B)** blood glucose; **(C)** blood creatinine; **(D)** urea nitrogen; **(E)** blood potassium; **(F)** postoperative hospitalization.

Observation Indicators

General data such as gender, age, BMI, educational level, marriage relationship, and dialysis method were collected and compared between the two groups. The postoperative indexes such as the time of first intake, postoperative blood glucose, serum creatinine, urea nitrogen, blood potassium, and postoperative hospital stay were recorded in the two groups. The comfort level of two groups after kidney transplantation was assessed using the Comfort Scale for Renal Transplant Recipients, which included four dimensions such as physiology, mental psychology, society and environment, with a total of 25 items. The items were scored according to the Likert 4-level scoring method with 1–4 points, the total score ranged from 25 to 100. A score of ≥62.5 indicates good comfort. A higher score indicated higher comfort, and the total score <62.5 indicated poorer comfort.

After a follow-up of six months, the self-care ability of the two groups was assessed using the self-management behavior scale, which included three dimensions (15 items), namely, cognitive symptom management practice, exercise, and communication with doctors, with a 5-level score of 1–5 points for each item, indicating complete non-compliance to complete compliance, 15–75 points, and the self-care ability of the patients was gradually enhanced with the improvement of the score. At the same time, according to the medication evaluation criteria, the medication compliance of two groups of patients was evaluated, which was divided into complete, partial and complete non-compliance. The self-rating scale for quality of life assessment was selected for assessment, including 4 dimensions of physical health, psychology/spirit, society/economy, and family. The score for each dimension was 0–30 points. A higher score indicated a better quality of life. Follow-up for 6 months, recording the hospitalization of patients due to complications.

Statistical Methods

SPSS 20.0 software was used for processing. The measurement data of the experimental data were expressed as mean ± standard deviation, the *t* test was used for pairwise comparison. The count data were expressed as (rate) and the comparison was performed using chi-square test. The test level was $\alpha = 0.05$, and $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of General Information of Patients Between the Two Groups

There was no significant difference in general information such as gender, age, BMI, educational level, marriage relationship, and dialysis method between the two groups ($P>0.05$). As show in **Table 1**.

Comparison of Postoperative Observation Indexes Between the Two Groups

There was no significant difference in the time of first intake, blood glucose, creatinine, urea nitrogen, blood potassium or postoperative hospital stay between the two groups ($P > 0.05$). As show in **Figure 1**.

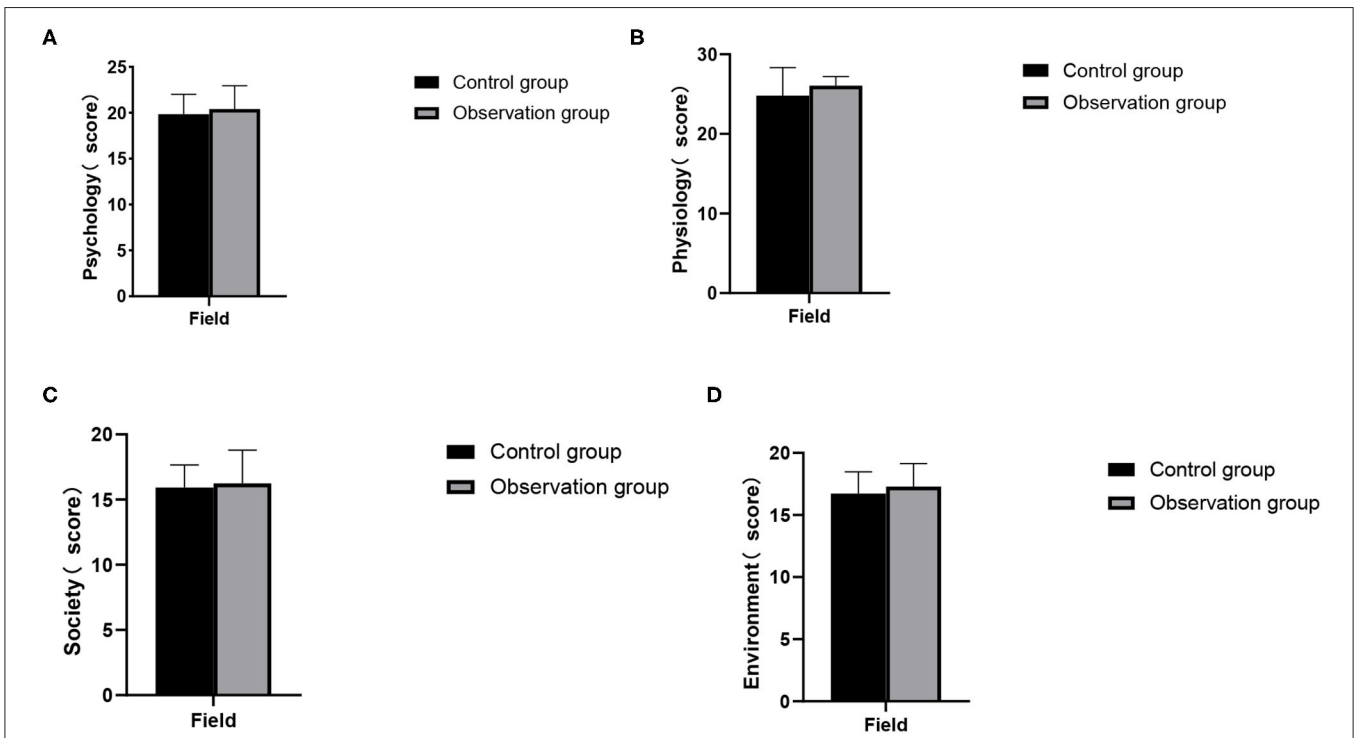


FIGURE 2 | Postoperative comfort indicators between the two groups. **(A)** Psychology; **(B)** physiology; **(C)** society; **(D)** environment.

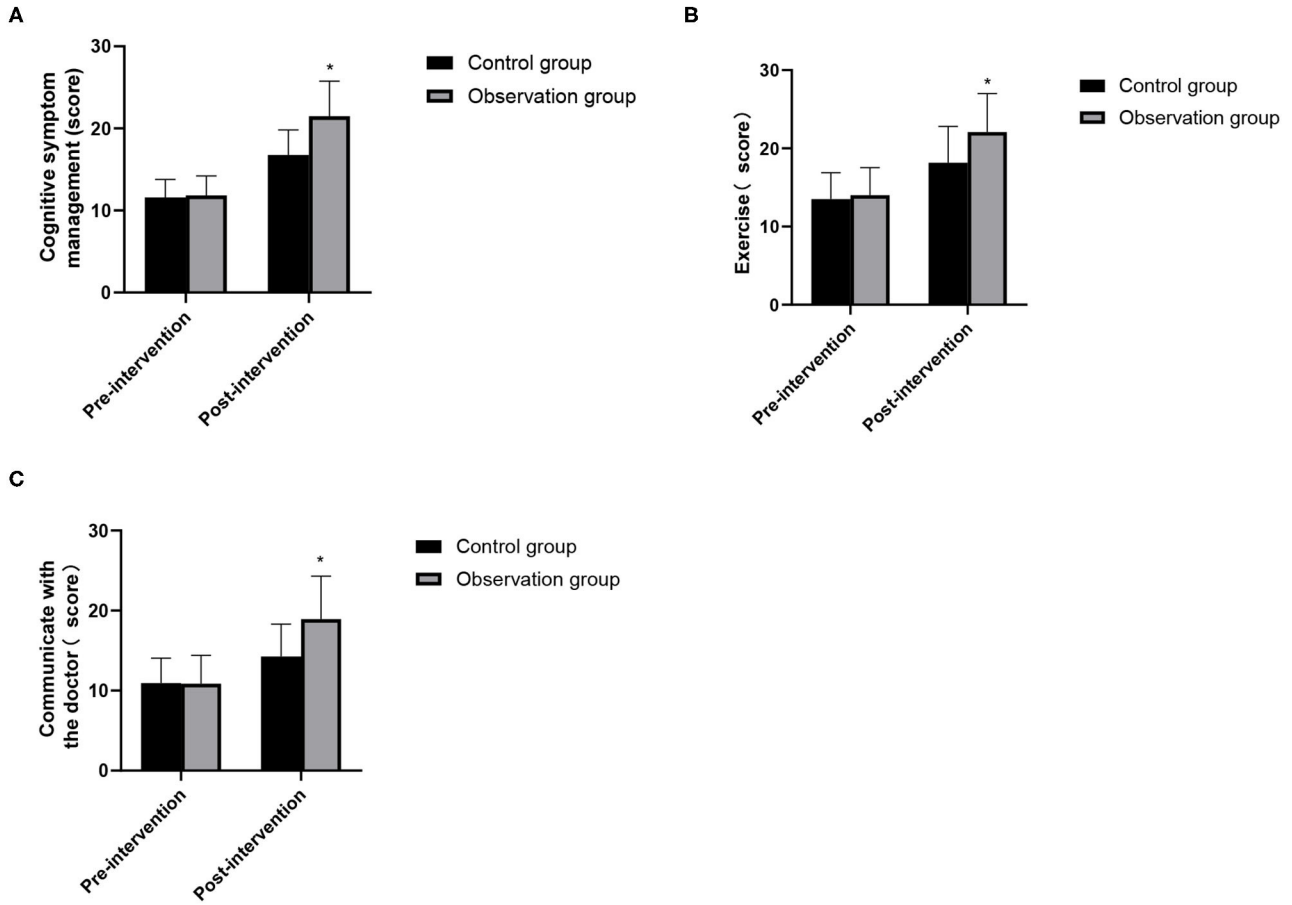


FIGURE 3 | Changes in self-care ability between the two groups. **(A)** Cognitive symptom management; **(B)** exercise; **(C)** communicate with the doctor. Compared with the control group, $^*P < 0.05$.

Comparison of Postoperative Comfort Indicators Between the Two Groups

There was no significant difference in the postoperative physical, mental, psychological, social and environmental dimensions between the two groups ($P > 0.05$). As show in **Figure 2**.

Comparison of Changes in Self-Care Ability Between the Two Groups

The scores of cognitive symptom management, exercise and communication with doctors in the two groups in pre-intervention were higher than those in pre-intervention, and the differences were statistically significant ($P < 0.05$). There was no significant difference between the two groups in pre-intervention ($P > 0.05$). In post-intervention, the scores of the observation group were higher than that of the control group and the differences were statistically significant ($P < 0.05$). As show in **Figure 3**.

Comparison of Medication Compliance Between the Two Groups

The medication compliance of the observation group (93.33%) was higher than that of the control group (70.00%), and the difference was statistically significant ($\chi^2 = 5.455$, $P = 0.020$). As show in **Figure 4**.

Comparison of Changes in Quality of Life Between the Two Groups

In pre-intervention, there was no significant difference in the scores of physical health, psychology/spirit, society/economy, family and other dimensions of quality of life between the two groups ($P > 0.05$). In post-intervention, the scores of quality of life of the observation group were higher than those of the control group, and the differences were statistically significant ($P < 0.05$). As show in **Figure 5**.

Hospitalization of Patients With Complications in Two Groups

The complication admission rate of the observation group (10.00%) was lower than that of the control group (30.00%), and the differences were statistically significant ($\chi^2 = 3.750$, $P = 0.035$). As show in **Figure 6**.

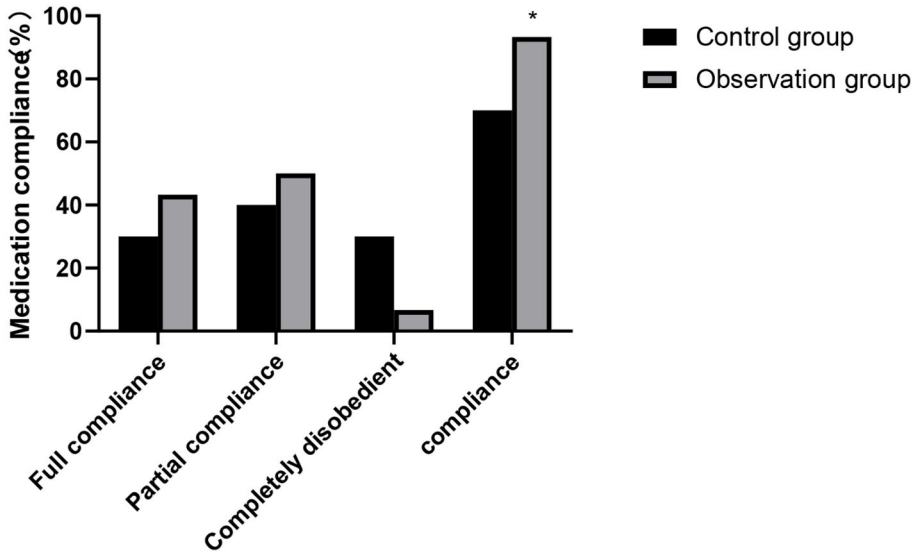


FIGURE 4 | Medication compliance between the two groups. Compared with the control group, $^*P < 0.05$.

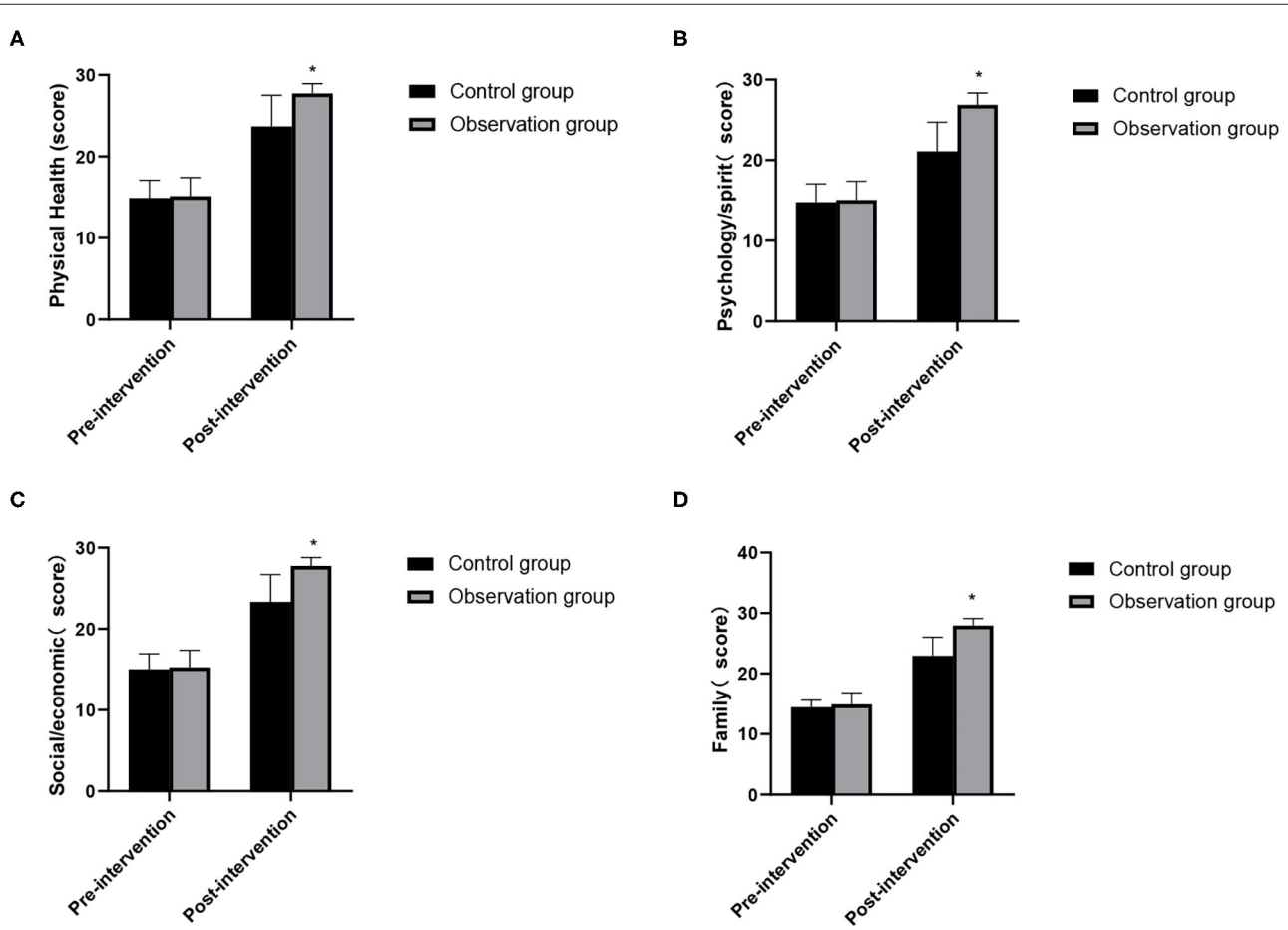


FIGURE 5 | Changes in quality of life between the two groups. **(A)** Physical health; **(B)** psychology/spirit; **(C)** social/economic; **(D)** family. Compared with the control group, $^*P < 0.05$.

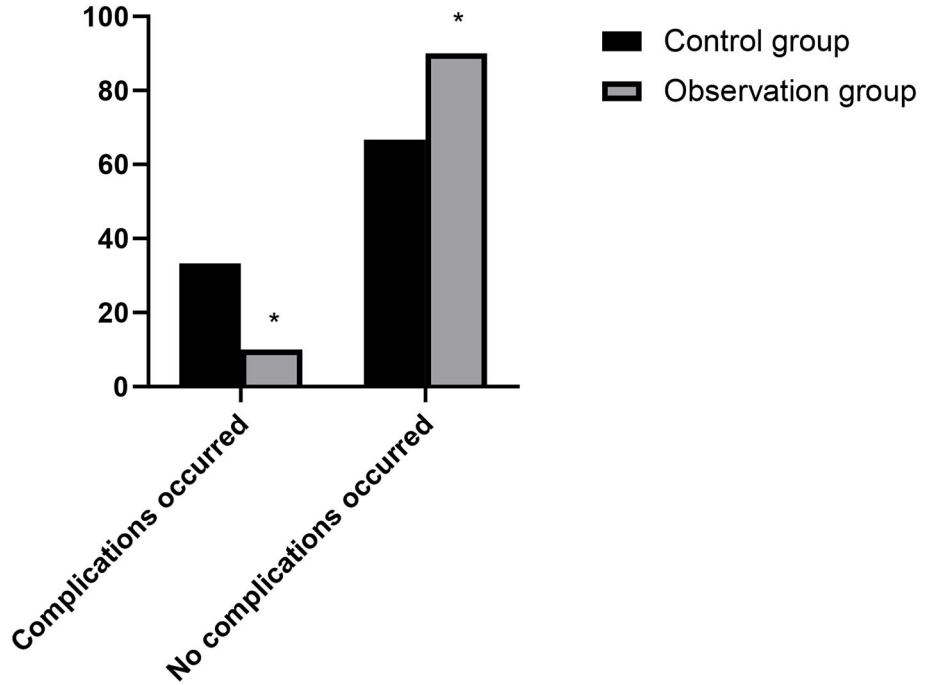


FIGURE 6 | Hospitalization of patients with complications in two groups. Compared with the control group, $^*P < 0.05$.

DISCUSSION

The treatment of kidney transplantation is a kind of intense psychological stress for patients, which indirectly has adverse effects on patients' physiological and psychological function by affecting neuroendocrine and immune system. Therefore, it is of great significance to provide personalized and high-quality nursing care during the perioperative period to improve patients' tolerance to surgery (8). FTS nursing aims at blocking or reduce surgical stress reaction, reduce postoperative complications, accelerating patients' recovery and reduce hospital stay by optimizing multi-mode perioperative path and taking effective measures verified by evidence-based medicine (9, 10). Nursing continuously promotes the transformation of hospitals from "simple treatment mode" to "integrated service" (prevention service, treatment service, nursing service, rehabilitation and health care service). It can not only meet the needs of patients for health education, but also strengthen the enthusiasm of patients for rehabilitation, which is crucial for kidney transplant patients to improve the quality of life and return to normal social life (11, 12).

In this study, the FST nursing mode was adopted to comprehensively train medical staff on the diagnosis and nursing problems that may occur before, during and after the operation, standardize the diagnosis and nursing procedures of kidney transplantation, and strengthen the care and respect for the patients' humanity during the operation, so that patients can get the highest level of medical treatment and care during the perioperative period. The results showed that there was no significant difference in the time of first intake, postoperative blood glucose, creatinine, urea nitrogen, blood potassium and postoperative hospital stay between the two groups, and the overall postoperative comfort was higher. FST nursing model carries out nutritional assessment and screening before operation to reduce the risk of operation. Nurses should establish a good psychological defense mechanism for patients, and conduct personalized psychological intervention to help patients reduce their negative psychology (13). At the same time, we should strengthen the patient's knowledge education about kidney transplantation and its complications, improve the psychological resilience level of kidney transplant patients, relieve their psychological pressure and improve their mental health (14). Maintaining normal body temperature during operation can reduce the pressure of operation, the risk of organ dysfunction and the discomfort of patients. Choose short-acting anesthetics to reduce the adverse reactions of anesthetics, so that patients can begin to recover faster after operation. The patients' condition after transplantation should be closely observed to ensure their safety so that they can receive better care (15, 16).

After kidney transplantation, it is necessary to maintain the normal function of the transplanted kidney for a long time, and the recipient needs to take immunosuppressive drugs for life. Among them, the patient's non-compliance with drug treatment plan is the main cause of rejection and death of the transplanted kidney (17). Therefore, how to improve medication compliance of renal transplant patients is an urgent problem to be solved. Continuous nursing can strengthen the medical staff's observation of patients' medication compliance, educate patients' medication, and guide their medication behavior, thus greatly improving patients' medication compliance and

understanding of medication plan (18). In this study, the sum of self-care ability scores such as cognitive symptom management, exercise and communication with doctors after continuous nursing intervention in two groups was higher than that in pre-intervention, and the scores in the observation group in post-intervention were higher than those in the control group. Medication compliance of the observation group was also better than that of the control group. It shows that active and continuous nursing could significantly improve patients' medication compliance and self-care ability, promote the survival and functional maintenance of transplanted kidney, and is also of great significance to improve patients' life quality (19).

Conventional nursing mainly relies on patients' voluntary reexamination. With the shortening of time, patients' attention is mostly focused on whether the indicators are normal or not, and the uneven compliance and self-care ability will affect the treatment effect and disease outcome (20). The results showed that the patients in the observation group had significantly higher quality of life scores than those in the control group after rapid rehabilitation surgery nursing combined with continuous nursing intervention. Patients in the observation group were also less likely to be readmitted for complications. It fully explained that FST nursing combined with continuous nursing strengthened the intervention measures for renal function protection, actively carried out rehabilitation exercise and psychological counseling nursing for patients after kidney transplantation, found early complications in time, and improved the long-term quality of life of patients.

FST nursing can help kidney transplant patients to obtain more stable postoperative renal function and other indicators and comfort. On this basis, combined with continuous nursing can improve the patient's self-care ability and medication compliance, which is of great significance to improve the quality of life of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LS is responsible for the revision of the paper and the guidance of the research. QJ is responsible for the design of the research. LZ is responsible for the inclusion of cases. ZL is responsible for the evaluation of the results. WC is responsible for the statistical analysis of the data. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Viklicky O, Novotny M, Hruba P. Future developments in kidney transplantation. *Curr Opin Organ Transplant.* (2020) 25:92–8. doi: 10.1097/MOT.0000000000000722
2. Tena B, Vendrell M. Perioperative considerations for kidney and pancreas-kidney transplantation. *Best Pract Res Clin Anaesthesiol.* (2020) 34:3–14. doi: 10.1016/j.bpa.2020.01.005
3. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg.* (2002) 183:630–41. doi: 10.1016/S0002-9610(02)00866-8
4. Golder HJ, Papalois V. Enhanced recovery after surgery: history, key advancements and developments in transplant surgery. *J Clin Med.* (2021) 10:1634. doi: 10.3390/jcm10081634
5. Zhu Q, Yang J, Zhang Y, Ni X, Wang P. Early mobilization intervention for patient rehabilitation after renal transplantation. *Am J Transl Res.* (2021) 13:7300–5.
6. Anyszek A, Wyzgał J, Czyzewski Ł. Long-term results of kidney transplantation: analysis of selected factors. *Transplant Proc.* (2020) 52:2305–9. doi: 10.1016/j.transproceed.2020.03.035
7. Samarehfekri A, Dehghan M, Arab M, Ebadzadeh MR. Effect of foot reflexology on pain, fatigue, and quality of sleep after kidney transplantation surgery: a parallel randomized controlled trial. *Evid Based Complement Alternat Med.* (2020) 1:5095071. doi: 10.1155/2020/5095071
8. Van Sandwijk MS, Ten Berge IJ, Majoie CB, Caan MW, De Sonneville LM, Van Gool WA, et al. Cognitive changes in chronic kidney disease and after transplantation. *Transplantation.* (2016) 100:734–42. doi: 10.1097/TP.0000000000000968
9. He D, Wang FZ, Zhang Z, Huang F, Chen JJ Li B. [Effect of low-frequency electrical acupoint stimulation on gastrointestinal motility function following radical gastrectomy in patients with gastric cancer]. *Zhen Ci Yan Jiu.* (2020) 45:51–6. doi: 10.13702/j.1000-0607.1901256
10. Liu Y. Application of fast track surgery in routine nursing for patient with colorectal cancer. *Saudi J Biol Sci.* (2017) 24:1939–42. doi: 10.1016/j.sjbs.2017.11.045
11. Ozdemir Koken Z, Karahan S, Tuncbilek Z, Senol Celik S. Nursing diagnoses and interventions in kidney transplant recipients: a retrospective study. *Transplant Proc.* (2019) 51:2321–3. doi: 10.1016/j.transproceed.2019.03.047
12. Rajkumar T, Mazid S, Vucak-Dzumhur M, Sykes TM, Elder GJ. Health-related quality of life following kidney and simultaneous pancreas kidney transplantation. *Nephrology (Carlton).* (2019) 24:975–82. doi: 10.1111/nep.13523
13. Jiang M, Liu S, Deng H, Liang X, Bo Z. The efficacy and safety of fast track surgery (FTS) in patients after hip fracture surgery: a meta-analysis. *J Orthop Surg Res.* (2021) 16:162. doi: 10.1186/s13018-021-02277-w
14. Jamieson NJ, Hanson CS, Josephson MA, Gordon EJ, Craig JC, Halleck F, et al. Motivations, challenges, and attitudes to self-management in kidney transplant recipients: a systematic review of qualitative studies. *Am J Kidney Dis.* (2016) 67:461–78. doi: 10.1053/j.ajkd.2015.07.030
15. Quint EE, Schopmeyer L, Banning LBD, Moers C, El Moumni M, Nieuwenhuijs-Moeke GJ, et al. Transitions in frailty state after kidney transplantation. *Langenbecks Arch Surg.* (2020) 405:843–50. doi: 10.1007/s00423-020-01936-6
16. Shen C, Chang S, Zhou K, Che G. [The present situation and prospect of day surgery and enhanced recovery after surgery in thoracic surgery]. *Zhongguo Fei Ai Za Zhi.* (2020) 23:800–5. doi: 10.3779/j.issn.1009-3419.2020.102.08

17. Scheel J, Schieber K, Reber S, Jank S, Eckardt KU, Grundmann F, et al. Psychological processing of a kidney transplantation, perceived quality of life, and immunosuppressant medication adherence. *Patient Prefer Adherence.* (2019) 13:775–82. doi: 10.2147/PPA.S194254
18. Scheel J, Reber S, Stoessel L, Waldmann E, Jank S, Eckardt KU, et al. Patient-reported non-adherence and immunosuppressant trough levels are associated with rejection after renal transplantation. *BMC Nephrol.* (2017) 18:107. doi: 10.1186/s12882-017-0517-6
19. Mitsui Y, Araki M, Maruyama Y, Yoshinaga K, Sadahira T, Wada K, et al. Quality of life and mental satisfaction improve slowly in preemptive kidney transplantation compared with nonpreemptive kidney transplantation. *Transplant Proc.* (2020) 52:740–7. doi: 10.1016/j.transproceed.2020.01.042
20. Andersen MH, Lønning K, Bjørnelv GM, Fagerström L. Nursing intensity and costs of nurse staffing demonstrated by the RAFAELA system: liver vs. *kidney transplant recipients J Nurs Manag.* (2016) 24:798–805. doi: 10.1111/jonm.12384

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Song, Jin, Zhu, Liu and Cheng. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

REVIEW
published: 22 February 2022
doi: 10.3389/fsurg.2022.847213

Therapeutic Potential of Menstrual Blood-Derived Stem Cell Transplantation for Intrauterine Adhesions

Yantao He[1†], *Yanhua Han*[1†] *and Yun Ye*[2*]

[1] *Department of Gynecology and Obstetrics, Zhongshan City People's Hospital, Zhongshan, China,* [2] *Centre for Reproductive Medicine, Zhongshan City People's Hospital, Zhongshan, China*

An increasing number of women experience intrauterine adhesion as a result of intrauterine operations, such as induced abortion, which can cause infertility, recurrent abortion and amenorrhea. Although some strategies have been applied clinically, such as hysteroscopy adhesiolysis of intrauterine adhesions, the results have not been promising. As regenerative medicine develops, research on menstrual blood-derived stem cell transplantation is increasing due to the properties of these cells, including self-renewal, differentiation, angiogenesis, anti-inflammation and immunomodulation. As a result, menstrual blood-derived stem cells may be an ideal cell source for the treatment of intrauterine adhesion. Excitingly, it has been reported that autologous menstrual blood stem cells could recovery injured endometrium and improve infertility in patients with refractory intrauterine adhesion. In this review, we discuss the possible potential of menstrual blood-derived stem cell transplantation for intrauterine adhesion, including the antifibrosis, angiogenesis, anti-inflammation and immunoregulation properties of the cells, which brings hopes for clinical therapy.

Keywords: intrauterine adhesion, Asherman syndrome, menstrual blood-derived stem cells, transplantation, angiogenesis

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Li Genlin,
University of South China, China
Lihong Chen,
The First Affiliated Hospital of Fujian Medical University, China

***Correspondence:**
Yun Ye
bigbig.g@126.com

[†]*These authors have contributed equally to this work*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *01 January 2022*
Accepted: *24 January 2022*
Published: *22 February 2022*

Citation:
He Y, Han Y and Ye Y (2022) Therapeutic Potential of Menstrual Blood-Derived Stem Cell Transplantation for Intrauterine Adhesions. Front. Surg. 9:847213. doi: 10.3389/fsurg.2022.847213

BACKGROUND

Intrauterine adhesion (IUA), also named as Asherman syndrome, refers to endometrial fibrosis caused by the damage of endometrium basal layer caused by repeated improper intrauterine operation and infection, which leads to partial or complete adhesion or even occlusion of uterus. IUA is characterized by symptoms such as recurrent miscarriage, fertile disorder, hypomenorrhea, amenorrhea and pregnancy complications (1). The pathogenesis of IUA is as follows: when the endometrium is repeatedly damaged, the basal layer of the endometrium cannot regenerate and is replaced by a large number of monolayer epithelium and fibrous tissue. Endometrium atrophy, rarefied, gland inactive, low response to hormone stimulation, blurred boundary between functional layer and basal layer, resulting in adhesion formation. IUA is mostly associated with trauma, infection, and genetic susceptibility, and contributes to secondary infertility in women (2). A main cause of IUA is curettage, such as post-abortion or miscarriage curettage, which may injure the endometrium. Additionally, tuberculosis and some infections are strong risk factors for IUA since the invasion of viruses and other microorganisms could induce fibrosis and inhibit the repair of the endometrium. Presently,

TABLE 1 | The therapeutic effects of autologous MenSCs on patients with IUA.

Patients, n	Age, years	Transplantation method	Isolated volume, ml	Transplantation numbers, million	Duration of menstruation before transplantation, day	Duration of menstruation after transplantation, day	Endometrial thickness before transplantation, mm	Endometrial thickness after transplantation, mm	Pregnancy rate, n (%)
12	22–40	*in situ*	1	10	2.4 ± 0.7	5.3 ± 0.6	3.9 ± 0.9	7.5 ± 0.6	5 (41.7)
7	20–40	*in situ*	0.5	1	Unclear	Unclear	3.9 ± 1.03	6.7 ± 0.8	3 (43)

hysteroscopy adhesiolysis combined with hormonal therapy is the main treatment for removing the visible IUA (3). At present, the traditional treatment has a good effect on mild and moderate IUA, but for patients with severe IUA, pregnancy complications often occur after hysteroscopic adhesiolysis, such as recurrent miscarriage, earlier delivery and abnormal placental development on account of injured endometrium (4). Several researchers have paid much attention to a new adult stem cell, which is able to regenerate endometrial tissue, although more studies are needed (5). Therefore, the application of stem cells from the endometrium, such as menstrual blood-derived stem cell (MenSCs), is a research hotspot for endometrial regeneration. At present, MenSCs have been used in the treatment of polycystic ovary syndrome, myocardial infarction, type I diabetes and other diseases.

The decrease or absence of the number of endometrial stem cells and local inflammatory environment are the fundamental reasons for the re-adhesion after IUA and separation. Given their pluripotency and low immunogenicity, MenSCs are believed to have therapeutic potential for IUA. Study showed that MenSCs could differentiate into endometrial cells when managed *in vitro* and reproduct endometrial tissue in mice with IUA *in vivo* (5, 6). Another study revealed that MenSCs transplantation combined with estrogen could improve endometrial abnormalities (7). MenSCs have a positive effect on antifibrosis, angiogenesis, and anti-inflammation in IUA. Moreover, another study revealed that reproductive endometrial tissue and vessel were found but fibrosis was decreasing in the uterus of IUA because of stem cell transplantation and exosome treatments, and researchers found that exosomal treatment contributed to recovery injured endometrial tissue caused by IUA (8). These studies demonstrate that MenSCs is a good candidate for the treatment of IUA. Autologous MenSCs have been transplanted to patients with refractory IUA for clinical therapy. The results revealed that patients with refractory IUA had thicker endometrium and prolonged menstrual duration managed by MenSCs transplantation, and some of them achieved clinical pregnancy (9). In that study, five out of 12 patients got pregnant, and in other words, there was a pregnancy rate of 41.7% (9). Another study also showed women with IUA had thicker significantly endometrium after autologous MenSCs transplantation (10). We summarized the efficacy of autologous MenSCs transplantation in patients with IUA in **Table 1** (9, 10). The researches on MenSCs transplantation for the models of IUA are not enough, and clinical trials also need more attention, which could bring hopes for patients with IUA.

Abbreviations: IUA, Intrauterine adhesion; MenSCs, Menstrual blood-derived stem cells; TGF-β, Transforming growth factor-β; PDGF-BB, Platelet-derived growth factor; EGF, Epidermal growth factor; VEGFR, Vascular endothelial growth factor Receptor; MCP1, Monocyte chemoattractant protein 1; GMCSF, Granulocyte macrophage colony stimulating factor; SDF-1, Stromal cell-derived factor-1; IGF-1, Insulin-like growth factor 1; CXCR4, CXC chemokine receptor 4; IL-10, Interleukin−10; NK cells, Nature killer cells; HIF-1α, Hypoxia inducible factor-1 alpha; NO, Nitric oxide; IGF, Insulin-like growth factor.

CHARACTERISTICS OF MENSCS

MenSCs obtained from the menstrual blood of women have attracted the attention of numerous researchers because of their many advantages (11, 12). MenSCs have beneficial properties, including ease of acquisition, non-invasive collection procedures, widespread expansion capacities, rapid amplification abilities, genomic stability and high proliferation rates without being tumorigenic or immunogenic (13). Some researchers have found that MenSCs are multipotent, with the potential to differentiate into germ cells, endometrial cells, and endothelial, osteogenic, adipocytic, cardiomyocytic, respiratory epithelial, neurocytic, cartilaginous, myocytic, hepatic, and pancreatic cell lines (14, 15). In addition, these cells can secrete cytokines to induce antifibrosis, angiogenesis, anti-inflammation and immunoregulation. MenSCs are thought to be isolated from menstrual blood instead of the endometrium, express some cell-surface markers such as CD166, CD105, CD90, CD73, CD49, CD44, CD29, CD9, and HLA-ABC and differentiate into chondrocytes, osteocytes, and adipocytes (16). Studies have shown that the positive expression rates of MenSCs in the third generation were CD29 [(99.13 ± 0.19) %], CD44 [(98.97 ± 0.34) %], CD73 [(99.8 ± 0.08) %] and CD105 [(99.17 ± 0.34)]%, and the positive expression rates were all above 95%, and the expression rate of CD90 was (72.43 ± 0.76) % (17). MenSCs can also express the embryonic stem cell markers Oct-4 and SSEA-3/4 and PDGFR-β (6, 18). Whether MenSCs express embryonic markers c-Kit (CD117) and SSEA-4 is under argument, and more studies are needed to explore whether these markers are expressed by MenSCs (16). MenSCs don't express HLA-DR, CD133, CD45, CD 34, and CD19 (19). The

relevant markers are summarized in **Figure 1**. In addition, in order to evaluate the influence of menstrual blood storage time before MenSCs isolation on their vitality, the collected menstrual blood samples were divided into four equal parts and stored at 4°C. MenSCs were then isolated at 6, 24, 48, and 72 h, respectively. The results showed that there were no significant differences between MenSCs isolated after these different storage periods. Therefore, menstrual blood samples can be stored at 4°C for at least 3 days before further processing (20).

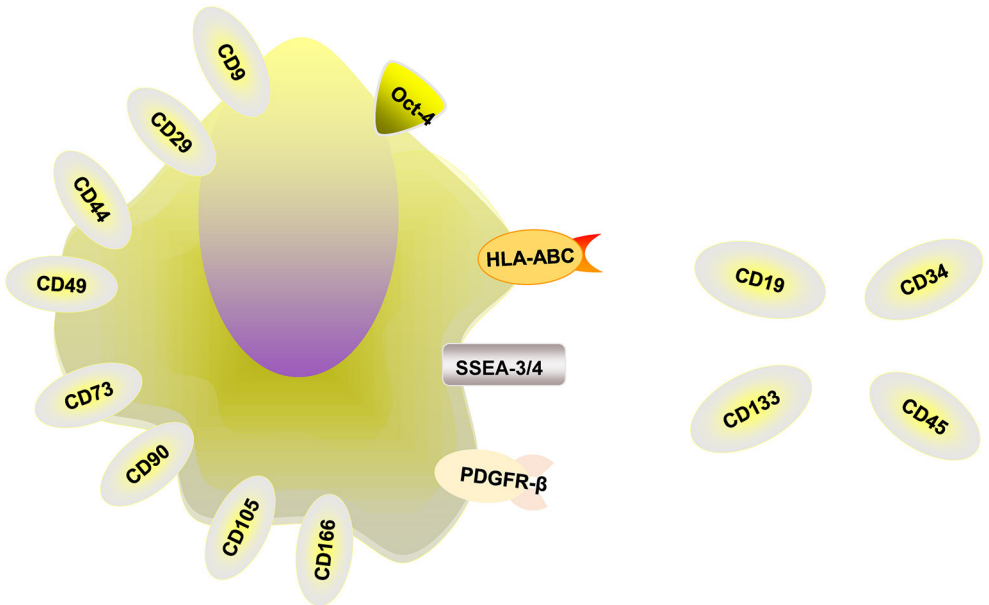


FIGURE 1 | The relevant markers of MenSCs. MenSCs express CD9, CD29, CD44, CD49, CD73, CD90, CD105, and CD166, HLA-ABC, Oct-4, and SSEA-3/4 and PDGFR-β and unexpress CD19, CD34, CD45, CD133, and HLA-DR.

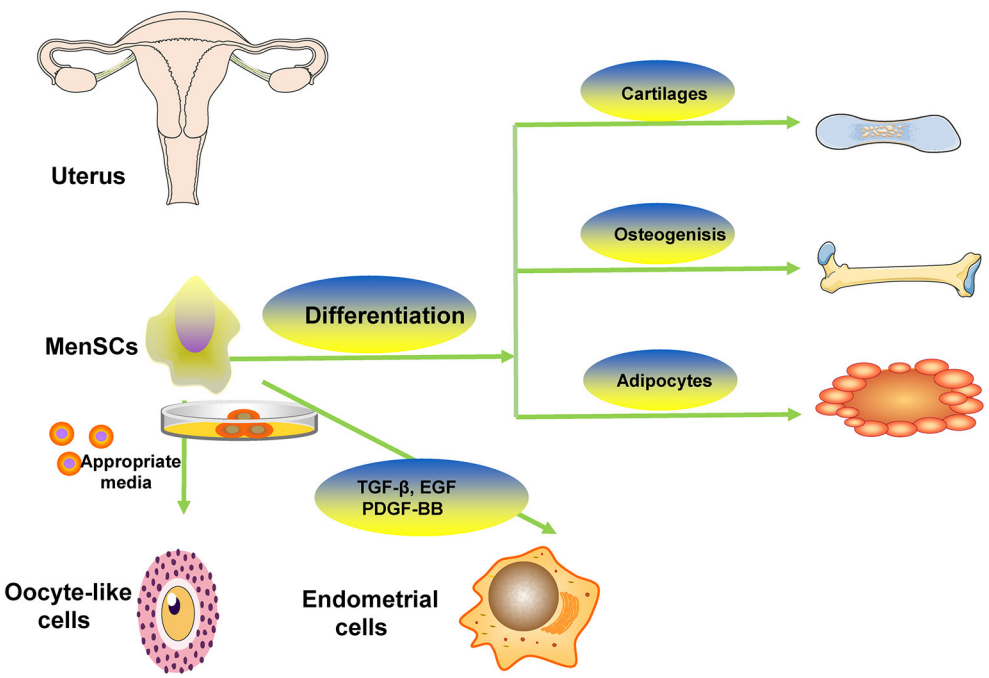


FIGURE 2 | The representative differentiation of MenSCs. MenSCs differentiate into cartilaginous, adipocytic, osteogenic, oocyte-like cells.

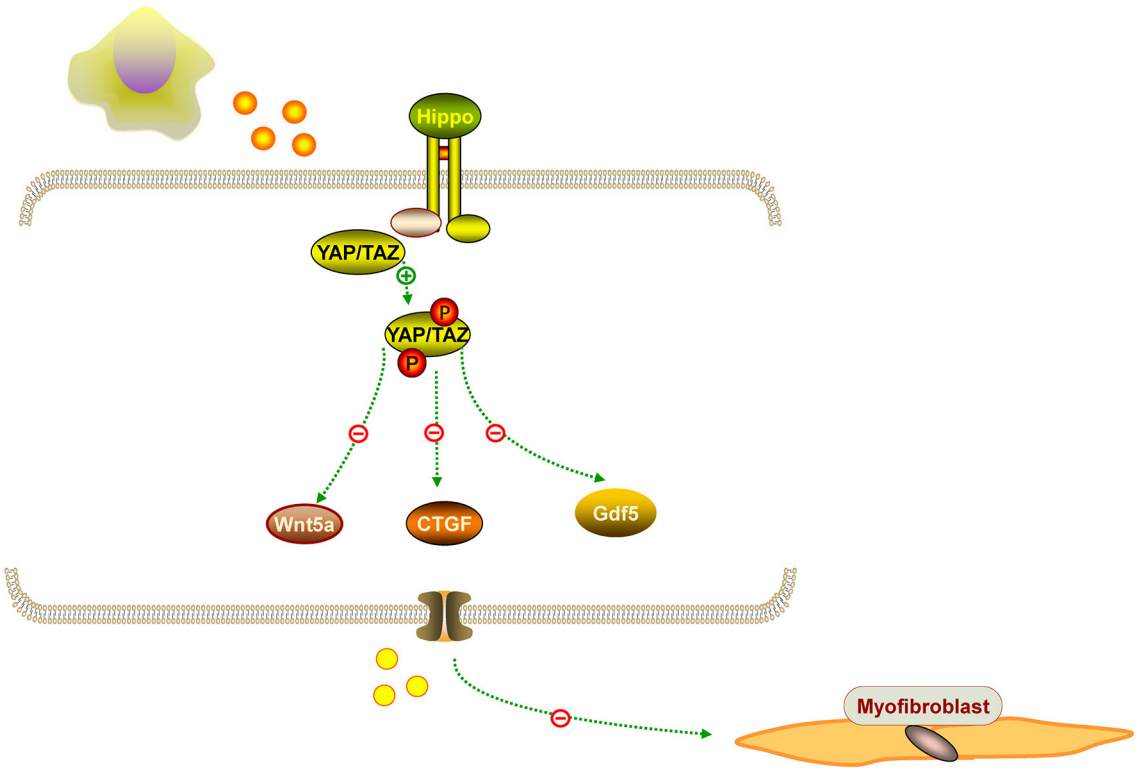


FIGURE 3 | The representation of the antifibrotic effect of MenSCs. MenSCs could suppressed endometrial myofibroblast differentiation by Hippo/TAZ pathway stimulation, and the pathway can downstream factors CTGF, Wnt5a, and Gdf5.

DIFFERENTIATION OF MENSCS

Some studies showed that MenSCs had capacity of differentiating into different cells such as adipocytic, osteogenic, cardiogenic, cartilaginous, cardiomyocytic, muscle, neurogenic, glial-like, endothelial, oocyte-like, granulosa, respiratory epithelial, myocytic, hepatic, and pancreatic tissues (14, 15, 20). The representative differentiation of MenSCs is showed in **Figure 2**. Study revealed that MenSCs were able to differentiate into ovarian tissue-like cells when managed *in vitro* and that MenSCs treatment could repair injured ovary in animal models with premature ovarian failure (21). Another study showed that MenSCs could differentiate into oocyte-like cells and express follicle stimulating hormone receptor and luteinizing hormone receptor, which were oocyte-like cell markers, induced by appropriate media (22). Study revealed that MenSCs could differentiate into endometrial cells *in vitro via* appropriate medium contained with 17β-estradiol valerate, transforming growth factor-β (TGF-β)-1, epidermal growth factor (EGF), platelet-derived growth factor (PDGF)-BB (23). Some researchers found that there were some morphological changes in managed MenSCs, and they expressed oocyte-related genes (LHR, FSHR, STRA8, PRDM, STELLA, GDF9, SCP3, DDX4, and ZP2) in the 2nd week of culture, suggesting the possibility of MenSCs differentiating into oocyte-like cells (24). To demonstrate the stem cell properties of MenSCs, studies have been conducted to test their pluripotency by culturing them with various types of differentiation media. The study found that MenSCs underwent adipogenic, osteogenic, cartilaginous, neural and cardiogenic differentiation, respectively, demonstrating their stem cell properties (20). The possible differentiation pathway is depicted in **Figure 2**.

ANTIFIBROTIC EFFECTS OF MENSCS

IUA is characterized by an increased fibrotic area, thinner endometrium, fewer glands, and fewer microvessels. Hysteroscopy adhesiolysis cannot completely alleviate fibrosis. Surprisingly, MenSCs have antifibrotic effects in some diseases. For example, MenSCs can ameliorate liver fibrosis *via* paracrine mediators (25). Another study demonstrated that exosomal from MenSCs had a positive effect on pulmonary fibrosis by activating NLRP3 inflammasome and regulating mtDNA damage and ROS, which bring hopes for patients with fibrotic lung disease (26). Based on the fibrosis pathology, alleviating endometrial fibrosis is important for IUA treatment. It is known that myofibroblasts contribute to fibrosis formation. Another study showed that MenSCs inhibited endometrial myofibroblast differentiation by activation of the Hippo/TAZ pathway (27). Similarly, Fan et al. confirmed that MenSCs could markedly accelerate endometrial damage repair in an IUA rat model by Hippo signaling pathway

stimulation, that the Hippo signaling pathway was the most significantly changed pathway, and that the expression of downstream factors CTGF, Wnt5a, and Gdf5 were significantly altered in the treatment groups (28). Researchers found that human amniotic epithelial cells upregulated MMP-8 expression to decrease collagen deposition in the uterine scar, and *in vitro* studies further confirmed an increase level of MMP-8 in hAECs cultured with hydrogen peroxide (28). We propose that MenSCs have antifibrotic effects on IUA, which needs further investigation. The representation of the antifibrotic effect of MenSCs is mentioned in **Figure 3**.

ANGIOGENESIS

Another function of MenSCs is their angiogenic effect. MenSCs show a strong angiogenic effect on endothelial cells both *in vitro* and *in vivo* (29). MenSCs were also able to induce angiogenesis *in vivo* (29). Zhang et al. found MenSCs-CM played an important role in angiogenesis in mice, which was associated with activation of AKT and ERK pathways, and overexpression of some factors such as VEGFR1, VEGFR2, eNOS, VEGFA, and TIE2 in HUVECs. These studies revealed MenSCs could revovery the injured endometrium and solve the fertile disorders in mice, which mainly depended on the angiogenesis induced by MenSCs (30). The angiogenesis of MenSCs in **Figure 4**.

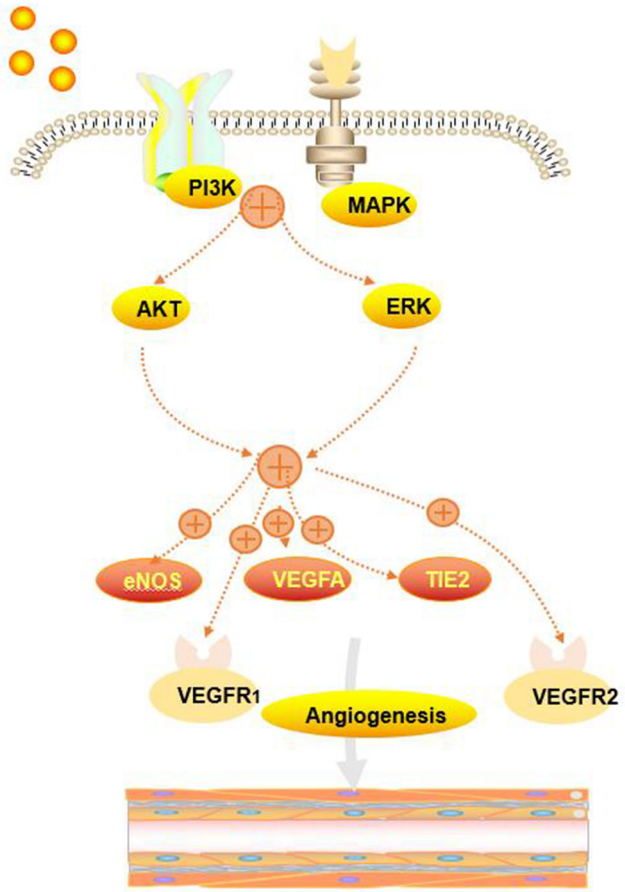


FIGURE 4 | The angiogenesis of MenSCs. MenSCs could activate AKT and ERK pathways and induce the overexpression of eNOS, VEGFA, VEGFR1, VEGFR2, and TIE2.

THE IMMUNOMODULATORY AND ANTI-INFLAMMATORY FUNCTION OF MENSCS

Menstrual blood stromal fibroblasts have the capacity of immunomodulatory and anti-inflammatory effects, which is similar with stem cells (6). MenSCs could suppress the apoptosis of MLE-12 cells *via* downregulating the expression of cytokines, such as GITR, GM-CSF, RANTES, MIP-1γ, eotaxin, MCP-5 and CCL1, which were involved with inflammatory reaction (31). In addition, *in vitro* studies demonstrated that MenSCs had a negative effect on macrophage bactericidal properties and the production of reactive oxygen intermediates, indicating that MenSCs effect the macrophage numbers, which provides a theoretical basis for clinical treatment in future (32). Moreover, MenSCs can have a negative effect on PI3K/Akt/mTOR/IKK signaling mediated by TLR4, leading to a decreasing of inflammatory cytokine, as p-NF-κBp65 could not be translocated into the nucleus (33). Another study showed that the maturation of human blood monocyte-derived dendritic cells was suppressed *via* interleukin−6 and interleukin−10(IL-10) secreted by MenSCs (34). The Immunomodulatory and anti-inflammatory function of MenSCs in **Figure 5**.

Studies have found that in a mouse model of ulcerative colitis, MenSCs reduced the infiltration of inflammatory cells, such as natural killer cells and macrophages, decreased the content of inflammatory factors such as tumor necrosis factor-α and IL-2, and increased the levels of inflammatory cytokines. IL-10 and IL-4 content (35). Researchers observed IL-10 and CXC chemokine receptor 4 (CXCR4) overexpress and numbers of regulatory B cells was increasing, suggesting that MenSCs have immunomodulatory properties (36). Some studies confirmed that nature killer cells (NK cells) were proliferating induced managed by MenSCs, but they were not when managed by IFN-γ/IL-1β-pretreated MenSCs (37). The researches on immunomodulation and anti-inflammation of MenSCs need more attention and efforts.

PARACRINE EFFECTS OF MENSCS

MenSCs secrete various chemokines that are crucial for the treatment of some diseases. One study confirmed that MenSCs had a positive effect on models of limb ischemia, by secreting some cytokines such MMP-3, MMP-10, IL-4 and hypoxia inducible factor-1 alpha (HIF-1α) (38). In addition, MenSCs secrete cytokines such as TGF-β2, EGF, PDGF and nitric oxide (NO) to enhance myocardial salvage and regeneration (39). Cuenca et al. confirmed that MenSCs could improve cutaneous regeneration by secreting cytokines, including MMP-3, MMP-10, PDGF, and angiopoietin (40). MenSCs express cytokines,

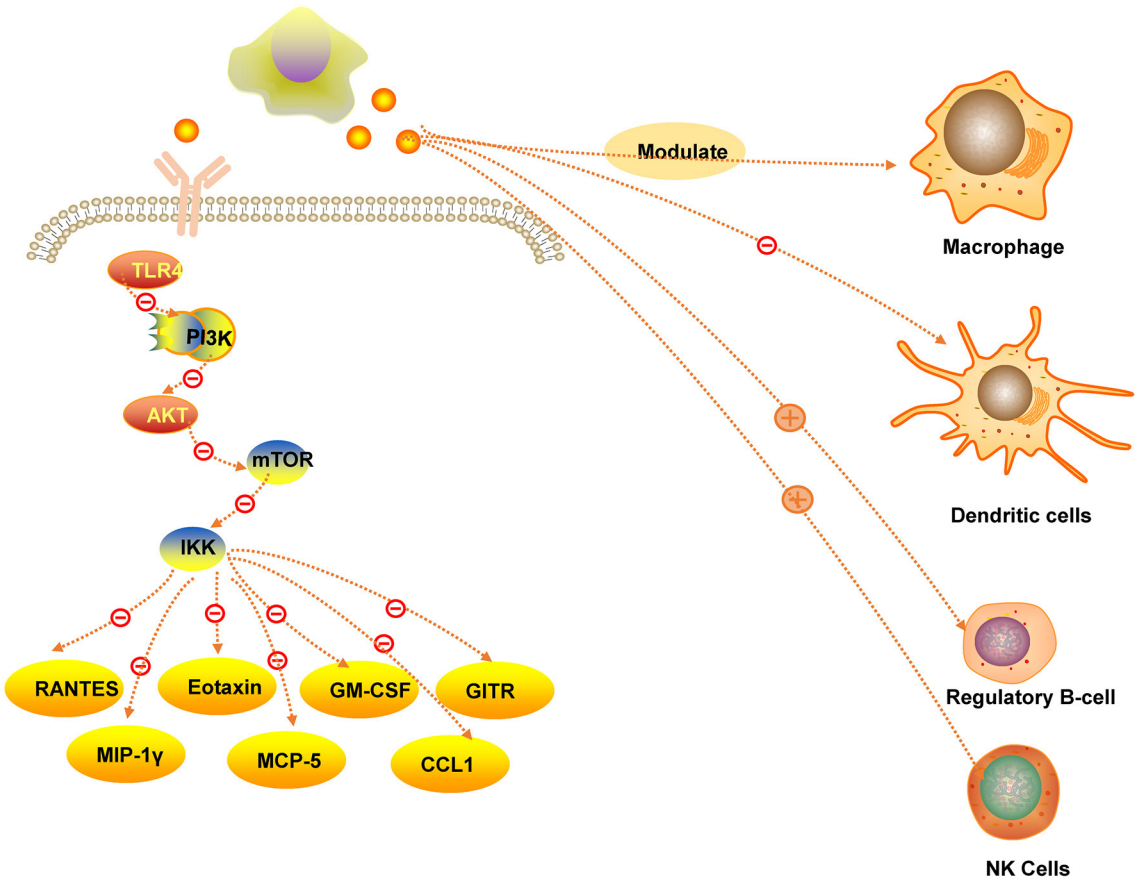


FIGURE 5 | The immunomodulatory and anti-inflammatory function of MenSCs.

including IL-8, IL-6, IGFBP-6, angiopoietin-2, ICAM-1, Axl and angiogenin to improve liver function and inhibit liver cell apoptosis (41). MenSCs also secrete TGF-β1 and rhTGF-β1 to play antitumor roles in cervical cancer, suggesting that MenSCs therapy is promising for the treatment of cervical cancer (42). MenSCs also secreted TSP-1, IGF-1 and stromal cell-derived factor-1(SDF-1) in a rat model of IUA. Another study showed that MenSCs have a positive effect on a rat model of IUA by secreting insulin-like growth factor (IGF)-1, thrombospondin-1 and SDF-1 (43).

SAFETY OF MENSCS TRANSPLANTATION

MenSCs have properties of self-rewal and differentiation. Some researchers have conducted studies to determine whether MenSCs are likely to form tumors. One study demonstrated that MenSCs transplantation is safe for endometrial treatment for IUA (44). Some researchers believe that MenSCs have no risk of tumor formation and that MenSCs could have potential therapeutic effects on diseases through paracrine effects and immunomodulation (20). MenSCs has the advantages of convenient collection, non-invasiveness, no pain, multiple collection and no ethical disputes. Compared with bone marrow mesenchymal stem cells, MenSCs has higher proliferation ability, which is conducive to obtaining sufficient number of cells clinically in a short time. Some researchers evaluated the biosafety of MenSCs transplantation in animal model of IUA, especially paying attention to toxicity and tumorigenicity, the results suggesting that MenSCs transplantation is safe for rat model of IUA (9). One meta-analysis systematically reviewed also suggested that MenSCs transplantation is safe for IUA treatment by prolonging menstruation duration and recovering endometrial thickness (45). However, research on the safety of MenSCs transplantation is not enough, and whether graft-vs.-host disease, adverse reactions or malignant transformation will occur after transplantation remains to be observed for a long time. More researches on safety of stem cell transplantation are needed to achieve the goals of MenSCs transplantation for clinical treatment.

CONCLUSION

MenSCs are easily obtained and can self-renew without forming tumors. Based on the multiple biological characteristics of MenSCs, including antifibrosis, angiogenesis, anti-inflammation and immunoregulation properties, MenSCs transplantation

seems to be a promising therapy for some diseases. However, most studies have been conducted on animals, and clinical trials are scarce. There are some difficulties for clinical transplantation. The perfect method of obtaining MenSCs effectively needs deep consideration. In addition to MenSCs, bone marrow mesenchymal stem cells, adipose mesenchymal stem cells, human umbilical cord blood mesenchymal stem cells and other stem cells from different sources also play a key role in endometrial regeneration and reconstruction. The best time, method and dosage of stem cell transplantation also need a large sample of clinical data to further verify the safety and effectiveness of MenSCs. Whether the disease could recur after stem cell transplantation. The molecular mechanisms of the cells' angiogenesis, antifibrosis, anti-inflammation and immunoregulation properties need to be explore deeply. In addition, standard methods of sample collection should be optimized, and age-related effects should be investigated. In summary, further preclinical research is essential to achieve the goal of MenSCs transplantation in the clinic.

AUTHOR CONTRIBUTIONS

YHe was responsible for writing the first draft of the manuscript. YHa contributed to the data acquisition of the article and revising it critically for important intellectual content. YY was responsible for critical review of the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Dreisler E, Kjer JJ. Asherman's syndrome: current perspectives on diagnosis and management. *Int J Womens Health.* (2019) 11:191–8. doi: 10.2147/IJWH.S165474
2. Santamaria X, Isaacson K, Simón C. Asherman's syndrome: it may not be all our fault. *Hum Reprod.* (2018) 33:1374–80. doi: 10.1093/humrep/dey232
3. Salazar CA, Isaacson K, Morris S. A comprehensive review of Asherman's syndrome: causes, symptoms and treatment options. *Curr Opin Obstet Gynecol.* (2017) 29:249–56. doi: 10.1097/GCO.0000000000000378
4. Deans R, Vancaillie T, Ledger W, Liu J, Abbott JA. Live birth rate and obstetric complications following the hysteroscopic management of intrauterine adhesions including Asherman syndrome. *Hum Reprod.* (2018) 33:1847–53. doi: 10.1093/humrep/dey237
5. Cervelló I, Santamaría X, Miyazaki K, Maruyama T, Simón C. Cell therapy and tissue engineering from and toward the uterus. *Semin Reprod Med.* (2015) 33:366–72. doi: 10.1055/s-0035-1559581
6. Gargett CE, Schwab KE, Deane JA. Endometrial stem/progenitor cells: the first 10 years. *Hum Reprod Update.* (2016) 22:137–63. doi: 10.1093/humupd/dmv051
7. Wang X, Bao H, Liu X, Wang C, Hao C. Effects of endometrial stem cell transplantation combined with estrogen in the repair of endometrial injury. *Oncol Lett.* (2018) 16:1115–22. doi: 10.3892/ol.2018.8702
8. Saribas GS, Ozogul C, Tiryaki M, Alpaslan Pinarli F, Hamdemir Kilic S. Effects of uterus derived mesenchymal stem cells and their exosomes on asherman's syndrome. *Acta Histochem.* (2020) 122:151465. doi: 10.1016/j.acthis.2019.151465
9. Ma H, Liu M, Li Y, Wang W, Yang K, Lu L, et al. Intrauterine transplantation of autologous menstrual blood stem cells increases endometrial thickness and pregnancy potential in patients with refractory intrauterine adhesion. *J Obstet Gynaecol Res.* (2020) 46:2347–55. doi: 10.1111/jog.14449
10. Tan J, Li P, Wang Q, Li Y, Li X, Zhao D, et al. Autologous menstrual blood-derived stromal cells transplantation for severe Asherman's syndrome. *Hum Reprod.* (2016) 31:2723–9. doi: 10.1093/humrep/dew235
11. Meng X, Ichim TE, Zhong J, Rogers A, Yin Z, Jackson J, et al. Endometrial regenerative cells: a novel stem cell population. *J Transl Med.* (2007) 5:57. doi: 10.1186/1479-5876-5-57
12. Rossignoli F, Caselli A, Grisendi G, Piccinno S, Burns JS, Murgia A, et al. Isolation, characterization, and transduction of endometrial decidual tissue multipotent mesenchymal stromal/stem cells from menstrual blood. *Biomed Res Int.* (2013) 2013:901821. doi: 10.1155/2013/901821
13. Domnina A, Novikova P, Obidina J, Fridlyanskaya I, Alekseenko L, Kozhukharova I, et al. Human mesenchymal stem cells in spheroids improve fertility in model animals with damaged endometrium. *Stem Cell Res Ther.* (2018) 9:50. doi: 10.1186/s13287-018-0801-9
14. Lai D, Wang F, Yao X, Zhang Q, Wu X, Xiang C. Human endometrial mesenchymal stem cells restore ovarian function through improving the renewal of germline stem cells in a mouse model of premature ovarian failure. *J Transl Med.* (2015) 13:155. doi: 10.1186/s12967-015-0516-y
15. Patel AN, Park E, Kuzman M, Benetti F, Silva FJ, Allickson JG. Multipotent menstrual blood stromal stem cells: isolation, characterization, and differentiation. *Cell Transplant.* (2008) 17:303–11. doi: 10.3727/096368908784153922
16. Chen L, Qu J, Xiang C. The multi-functional roles of menstrual blood-derived stem cells in regenerative medicine. *Stem Cell Res Ther.* (2019) 10:1. doi: 10.1186/s13287-018-1105-9
17. Calloni R, Cordero EA, Henriques JA, Bonatto D. Reviewing and updating the major molecular markers for stem cells. *Stem Cells Dev.* (2013) 22:1455–76. doi: 10.1089/scd.2012.0637
18. Chen J, Du X, Chen Q, Xiang C. Effects of donors' age and passage number on the biological characteristics of menstrual blood-derived stem cells. *Int J Clin Exp Pathol.* (2015) 8:14584–95.
19. Chen L, Qu J, Cheng T, Chen X, Xiang C. Menstrual blood-derived stem cells: toward therapeutic mechanisms, novel strategies, and future perspectives in the treatment of diseases. *Stem Cell Res Ther.* (2019) 10:406. doi: 10.1186/s13287-019-1503-7
20. Liu Y, Niu R, Yang F, Yan Y, Liang S, Sun Y, et al. Biological characteristics of human menstrual blood-derived endometrial stem cells. *J Cell Mol Med.* (2018) 22:1627–39. doi: 10.1111/jcmm.13437
21. Liu T, Huang Y, Zhang J, Qin W, Chi H, Chen J, et al. Transplantation of human menstrual blood stem cells to treat premature ovarian failure in mouse model. *Stem Cells Dev.* (2014) 23:1548–57. doi: 10.1089/scd.2013.0371
22. Lai D, Guo Y, Zhang Q, Chen Y, Xiang C. Differentiation of human menstrual blood-derived endometrial mesenchymal stem cells into oocyte-like cells. *Acta Biochim Biophys Sin (Shanghai).* (2016) 48:998–1005. doi: 10.1093/abbs/gmw090
23. Zheng SX, Wang J, Wang XL, Ali A, Wu LM, Liu YS. Feasibility analysis of treating severe intrauterine adhesions by transplanting menstrual blood-derived stem cells. *Int J Mol Med.* (2018) 41:2201–12. doi: 10.3892/ijmm.2018.3415
24. Sheikholeslami A, Kalhor N, Sheykhhasan M, Jannatifar R, Sahraei SS. Evaluating differentiation potential of the human menstrual blood-derived stem cells from infertile women into oocyte-like cells. *Reprod Biol.* (2021) 21:100477. doi: 10.1016/j.repbio.2020.100477
25. Chen L, Zhang C, Chen L, Wang X, Xiang B, Wu X, et al. Human menstrual blood-derived stem cells ameliorate liver fibrosis in mice by targeting hepatic stellate cells via paracrine mediators. *Stem Cells Transl Med.* (2017) 6:272–84. doi: 10.5966/sctm.2015-0265
26. Sun L, Zhu M, Feng W, Lin Y, Yin J, Jin J, et al. Exosomal miRNA Let-7 from menstrual blood-derived endometrial stem cells alleviates pulmonary fibrosis through regulating mitochondrial DNA damage. *Oxid Med Cell Longev.* (2019) 2019:4506303. doi: 10.1155/2019/4506303
27. Zhu H, Pan Y, Jiang Y, Li J, Zhang Y, Zhang S. Activation of the Hippo/TAZ pathway is required for menstrual stem cells to suppress myofibroblast and

inhibit transforming growth factor β signaling in human endometrial stromal cells. *Hum Reprod.* (2019) 34:635–45. doi: 10.1093/humrep/dez001
28. Fan Y, Sun J, Zhang Q, Lai D. Transplantation of human amniotic epithelial cells promotes morphological and functional regeneration in a rat uterine scar model. *Stem Cell Res Ther.* (2021) 12:207. doi: 10.1186/s13287-021-02260-6
29. Alcayaga-Miranda F, Cuenca J, Luz-Crawford P, Aguila-Díaz C, Fernandez A, Figueroa FE, et al. Characterization of menstrual stem cells: angiogenic effect, migration and hematopoietic stem cell support in comparison with bone marrow mesenchymal stem cells. *Stem Cell Res Ther.* (2015) 6:32. doi: 10.1186/s13287-015-0013-5
30. Zhang Y, Lin X, Dai Y, Hu X, Zhu H, Jiang Y, et al. Endometrial stem cells repair injured endometrium and induce angiogenesis via AKT and ERK pathways. *Reproduction.* (2016) 152:389–402. doi: 10.1530/REP-16-0286
31. Chen X, Wu Y, Wang Y, Chen L, Zheng W, Zhou S, et al. Human menstrual blood-derived stem cells mitigate bleomycin-induced pulmonary fibrosis through anti-apoptosis and anti-inflammatory effects. *Stem Cell Res Ther.* (2020) 11:477. doi: 10.1186/s13287-020-01926-x
32. Martínez-Aguilar R, Romero-Pinedo S, Ruiz-Magaña MJ, Olivares EG, Ruiz-Ruiz C, Abadía-Molina AC. Menstrual blood-derived stromal cells modulate functional properties of mouse and human macrophages. *Sci Rep.* (2020) 10:21389. doi: 10.1038/s41598-020-78423-x
33. Chen D, Zeng R, Teng G, Cai C, Pan T, Tu H, et al. Menstrual blood-derived mesenchymal stem cells attenuate inflammation and improve the mortality of acute liver failure combining with A2AR agonist in mice. *J Gastroenterol Hepatol.* (2021) 36:2619–27. doi: 10.1111/jgh.15493
34. Bozorgmehr M, Moazzeni SM, Salehnia M, Sheikhian A, Nikoo S, Zarnani AH. Menstrual blood-derived stromal stem cells inhibit optimal generation and maturation of human monocyte-derived dendritic cells. *Immunol Lett.* (2014) 162:239–46. doi: 10.1016/j.imlet.2014.10.005
35. Xu X, Wang Y, Zhang B, Lan X, Lu S, Sun P, et al. Treatment of experimental colitis by endometrial regenerative cells through regulation of B lymphocytes in mice. *Stem Cell Res Ther.* (2018) 9:146. doi: 10.1186/s13287-018-0874-5
36. Li X, Lan X, Zhao Y, Wang G, Shi G, Li H, et al. SDF-1/CXCR4 axis enhances the immunomodulation of human endometrial regenerative cells in alleviating experimental colitis. *Stem Cell Res Ther.* (2019) 10:204. doi: 10.1186/s13287-019-1298-6
37. Shokri MR, Bozorgmehr M, Ghanavatinejad A, Falak R, Aleahmad M, Kazemnejad S, et al. Human menstrual blood-derived stromal/stem cells modulate functional features of natural killer cells. *Sci Rep.* (2019) 9:10007. doi: 10.1038/s41598-019-46316-3
38. Murphy MP, Wang H, Patel AN, Kambhampati S, Angle N, Chan K, et al. Allogeneic endometrial regenerative cells: an "Off the shelf solution" for critical limb ischemia? *J Transl Med.* (2008) 6:45. doi: 10.1186/1479-5876-6-45
39. Jiang Z, Hu X, Yu H, Xu Y, Wang L, Chen H, et al. Human endometrial stem cells confer enhanced myocardial salvage and regeneration by paracrine mechanisms. *J Cell Mol Med.* (2013) 17:1247–60. doi: 10.1111/jcmm.12100
40. Cuenca J, Le-Gatt A, Castillo V, Belletti J, Díaz M, Kurte G M, et al. The reparative abilities of menstrual stem cells modulate the wound matrix signals and improve cutaneous regeneration. *Front Physiol.* (2018) 9:464. doi: 10.3389/fphys.2018.00464
41. Chen L, Xiang B, Wang X, Xiang C. Exosomes derived from human menstrual blood-derived stem cells alleviate fulminant hepatic failure. *Stem Cell Res Ther.* (2017) 8:9. doi: 10.1186/s13287-016-0453-6
42. Liu QY, Ruan F, Li JY, Wei L, Hu P, Chen HW, et al. Human menstrual blood-derived stem cells inhibit the proliferation of HeLa cells via TGF-β1-mediated JNK/P21 signaling pathways. *Stem Cells Int.* (2019) 2019:9280298. doi: 10.1155/2019/9280298
43. Zhang S, Li P, Yuan Z, Tan J. Platelet-rich plasma improves therapeutic effects of menstrual blood-derived stromal cells in rat model of intrauterine adhesion. *Stem Cell Res Ther.* (2019) 10:61. doi: 10.1186/s13287-019-1155-7
44. Chang QY, Zhang SW, Li PP, Yuan ZW, Tan JC. Safety of menstrual blood-derived stromal cell transplantation in treatment of intrauterine adhesion. *World J Stem Cells.* (2020) 12:368–80. doi: 10.4252/wjsc.v12.i5.368
45. Zhao Y, Luo Q, Zhang X, Qin Y, Hao J, Kong D, et al. Clinical efficacy and safety of stem cell-based therapy in treating Asherman syndrome: a system review and meta-analysis. *Stem Cells Int.* (2020) 2020:8820538. doi: 10.1155/2020/8820538

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 He, Han and Ye. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 22 February 2022
doi: 10.3389/fsurg.2022.844984

Comparison of Different Blood Transfusion Methods in Patients Undergoing Cesarean Section

Fei Guo[†], *Heshan Tang*[†] *and Xiaoqiang Wei**

Department of Blood Transfusion, The First Affiliated Hospital of Naval Military Medical University, Shanghai, China

Purpose: To compare the effect of allogeneic transfusion and acute normovolemic hemodilution (ANH) autologous transfusion in patients undergoing cesarean section.

Methods: Patients who underwent cesarean section and received blood transfusion therapy from February 2019 to July 2021 in our hospital were observed and divided into the allogeneic group (n = 55) who received allogeneic transfusion therapy and the autologous group (n = 55) who received ANH autologous transfusion therapy according to the mode of transfusion. Observations included vital signs [heart rate (HR), mean arterial pressure (MAP), stroke volume variation (SVV)], blood routine [red blood cells (RBC), platelets (PLT), hematocrit (HCT), hemoglobin (Hb)], T-cell subsets ($CD4^+$, $CD8^+$, $CD4^+/CD8^+$), immunoglobulins (IgA, IgM, IgG), inflammatory factors [C-reactive protein (CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-6], and adverse effects were counted in both groups.

Results: There was no statistical significance in the intra-group and inter-group comparisons of HR, MAP, and SVV between the two groups before transfusion and transfusion for 10 min ($P > 0.05$). 5d after operation, the RBC, PLT, HCT, and Hb of the allogeneic group were lower than those before operation, and the autologous group was higher than that of the allogeneic group ($P < 0.05$). 5d after operation, the CRP, TNF-α, and IL-6 of the allogeneic group were higher than those before operation, and the autologous group was lower than that of the allogeneic group ($P < 0.05$). 5d after operation, the $CD4^+$, $CD4^+/CD8^+$ of the allogeneic group were lower than before operation, and the $CD8^+$ was higher than before operation. The $CD4^+$ and $CD4^+/CD8^+$ of the autologous group were higher than that of the allogeneic group, and $CD8^+$ was lower than that of the allogeneic group ($P < 0.05$). 5d after operation, the IgA, IgG, and IgM of the allogeneic group were lower than those before operation, and the autologous group was higher than that of the allogeneic group ($P < 0.05$). During blood transfusion, there was no significant difference in the adverse reaction rate between the two groups ($P > 0.05$).

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Wenjun Gu,
Shanghai Jiao Tong University School of Medicine, China
Lihu Xie,
University of South China, China

***Correspondence:**
Xiaoqiang Wei
Weixiaoqiang1998@smmu.edu.cn

[†]*These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *29 December 2021*
Accepted: *24 January 2022*
Published: *22 February 2022*

Citation:
Guo F, Tang H and Wei X (2022) Comparison of Different Blood Transfusion Methods in Patients Undergoing Cesarean Section. Front. Surg. 9:844984. doi: 10.3389/fsurg.2022.844984

Conclusion: Both allogeneic transfusion and ANH autologous transfusion have little effect on the vital signs of patients undergoing cesarean section, but ANH autologous transfusion is more helpful to the stability of blood routine, T-cell subsets, immunoglobulin, and inflammation levels after surgery, which is a safe and effective way of blood transfusion.

Keywords: cesarean section, allogeneic transfusion, acute normovolemic hemodilution, autologous transfusion, application effect

INTRODUCTION

Cesarean section is an important midwifery procedure in the field of obstetrics. It is suitable for cases where the fetus cannot be delivered from the vagina normally, such as cephalopelvic error, birth canal abnormalities, fetal distress, fetal position error, umbilical cord prolapse, history of cesarean section, multiple births, etc. (1, 2). Placenta praevia and placental abruption are common complications of cesarean section, which can exacerbate the incidence of perinatal hemorrhage in cesarean section, and the incidence is much higher than that of natural delivery, therefore, in obstetric surgery, the blood transfusion rate of cesarean section 0.77% is higher than natural delivery 0.23% (3, 4). Preoperative blood preparation is an important preoperative preparation for cesarean section. It can effectively reduce the risk of disseminated intravascular coagulation (DIC), shock and even death in patients with cesarean section bleeding. Therefore, it is beneficial to improve the uterine retention rate and survival rate of pregnant women. For patients with large blood loss during cesarean section, urgent blood transfusion is often required in clinic, currently, allogeneic blood transfusion is mainly used, but it is associated with postoperative infection, immunosuppression and a poor prognosis (5). Acute normovolemic hemodilutio (ANH) autologous transfusion is an autologous blood transfusion method in which autologous blood is drawn preoperatively and supplemented with an equal volume of crystal or colloidal fluid, and the patient's blood loss is combined during the operation to return the autologous blood (6).

The acute normovolemic hemodilutio (ANH) autologous transfusion is a form of autotransfusion in which autologous blood is drawn preoperatively and replenished with an equal volume of crystalloid or colloidal fluid, and then returned autologous blood intraoperatively according to the amount of blood lost by the patient (6). It can effectively reduce the hematocrit (HCT), reduce the loss of blood elements during bleeding, improve the body's tolerance after hemodilution, and shorten the time of ischemia and hypoxia in patients through blood dilution, which is a blood conservation technique that can reduce the risk of anesthesia and surgery and provide fresh

TABLE 1 | Comparison of patients' general conditions (n, $M \pm SD$, %).

Indexs	Allogeneic group ($n = 55$)	Autologous group ($n = 55$)	t/χ^2 value	P value
Age (years old)	28.02 ± 3.11	28.76 ± 2.98	1.274	0.205
Gestational week (weeks)	36.54 ± 0.59	36.62 ± 0.61	0.699	0.486
Body mass index (kg/cm^2)	26.85 ± 3.24	27.03 ± 3.26	0.290	0.772
Operative time (h)	1.57 ± 0.83	1.61 ± 0.79	0.259	0.796
Blood loss (mL)	953.25 ± 26.01	956.24 ± 25.47	0.609	0.544
Number of outputs (times)			0.147	0.702
1	24 (43.64)	26 (47.27)		
≥2	31 (56.36)	29 (52.73)		
History of cesarean section (cases)			0.042	0.838
No	37 (67.27)	38 (69.09)		
Yes	18 (32.73)	17 (30.91)		
ASA classification (cases)			0.146	0.702
II	28 (50.91)	30 (54.55)		
III	27 (49.09)	25 (45.45)		
Maternity status (cases)			0.326	0.955
Placenta previa	38 (69.09)	39 (70.91)		
Placental abruption	5 (9.09)	4 (7.27)		
Placental implantation	3 (5.46)	4 (7.27)		
Others	9 (16.36)	8 (14.55)		

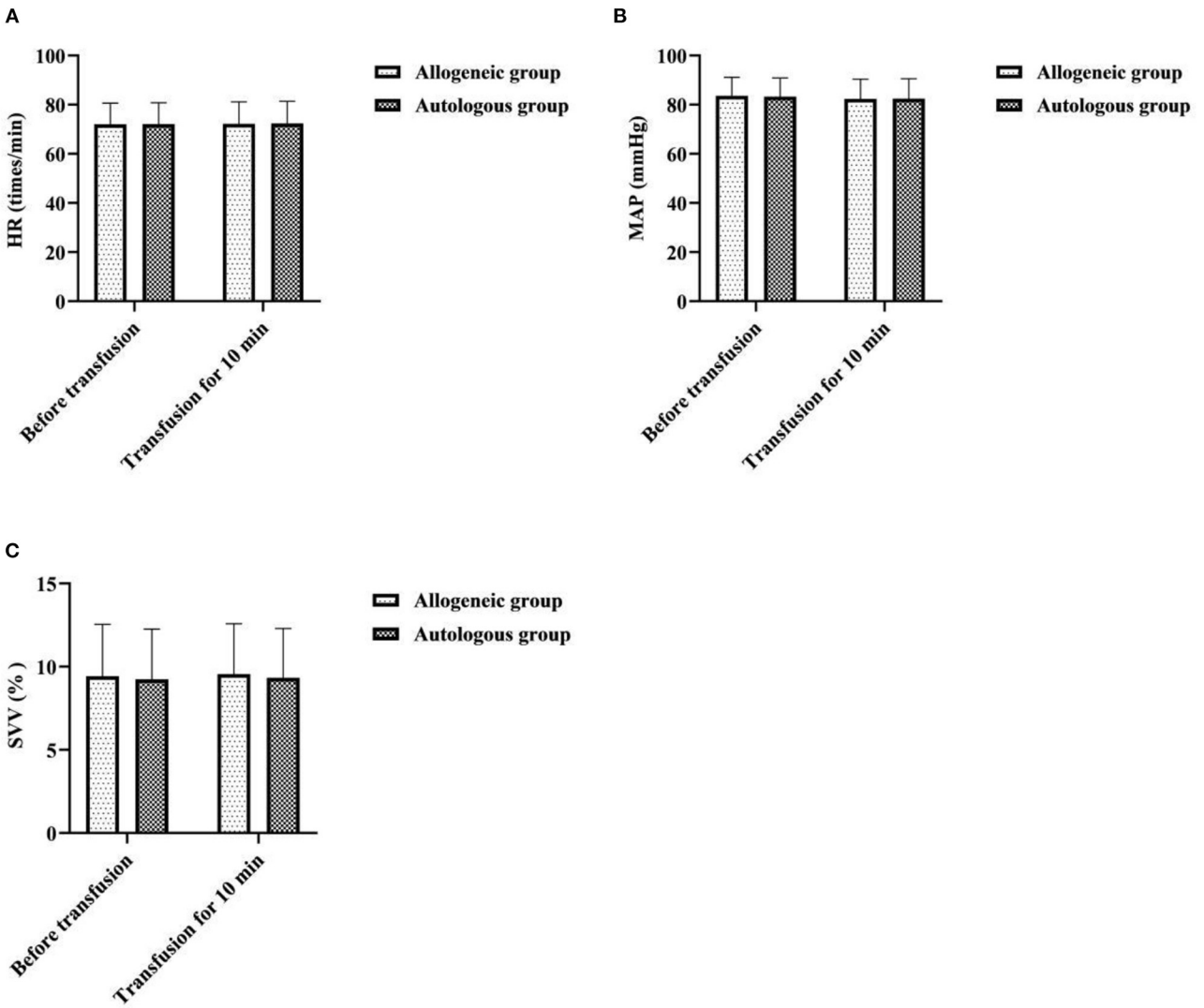


FIGURE 1 | Effect of different blood transfusion methods on patients' vital signs. **(A)** HR, **(B)** MAP, and **(C)** SVV.

whole blood to the patient (7). It has been widely used in major surgeries such as orthopedics, oncology and neurosurgery, but there are very few applications and related reports in the field of obstetrics (8, 9). This study compares the application effect of allogeneic transfusion and ANH autologous transfusion in patients undergoing cesarean section, aiming to explore the effectiveness and safety of ANH autologous transfusion in patients undergoing cesarean section.

MATERIALS AND METHODS

Research Object

Patients who underwent cesarean section and received blood transfusion from February 2019 to July 2021 in our hospital were used as observation subjects. Inclusion criteria: age 20–35 years old; proposed cesarean section; American Society of Anesthesiologists (ASA) classification II–III (10); normal liver and kidney function, normal cardiopulmonary function; normal four items before transfusion; normal coagulation function; preoperative platelet (PLT) $> 100\times10^9$/L, HCT $> 33\%$, hemoglobin (Hb) > 110 g/L (11); patients or her family had signed the informed consent. Exclusion criteria: people undergoing allogeneic and autologous transfusion at the same time; people who had a history of heart disease or tumor disease; people who had a history of neurological or psychiatric disease; people with immune system diseases; people with systemic acute and chronic infections; People with cognitive and communication impairments. They were divided into the allogeneic group ($n = 55$) receiving allogeneic transfusion therapy and the autologous group ($n = 55$) receiving ANH autologous transfusion therapy according to the mode of blood transfusion. There was no significant difference between the two groups in terms of age, gestational weeks and other general conditions,

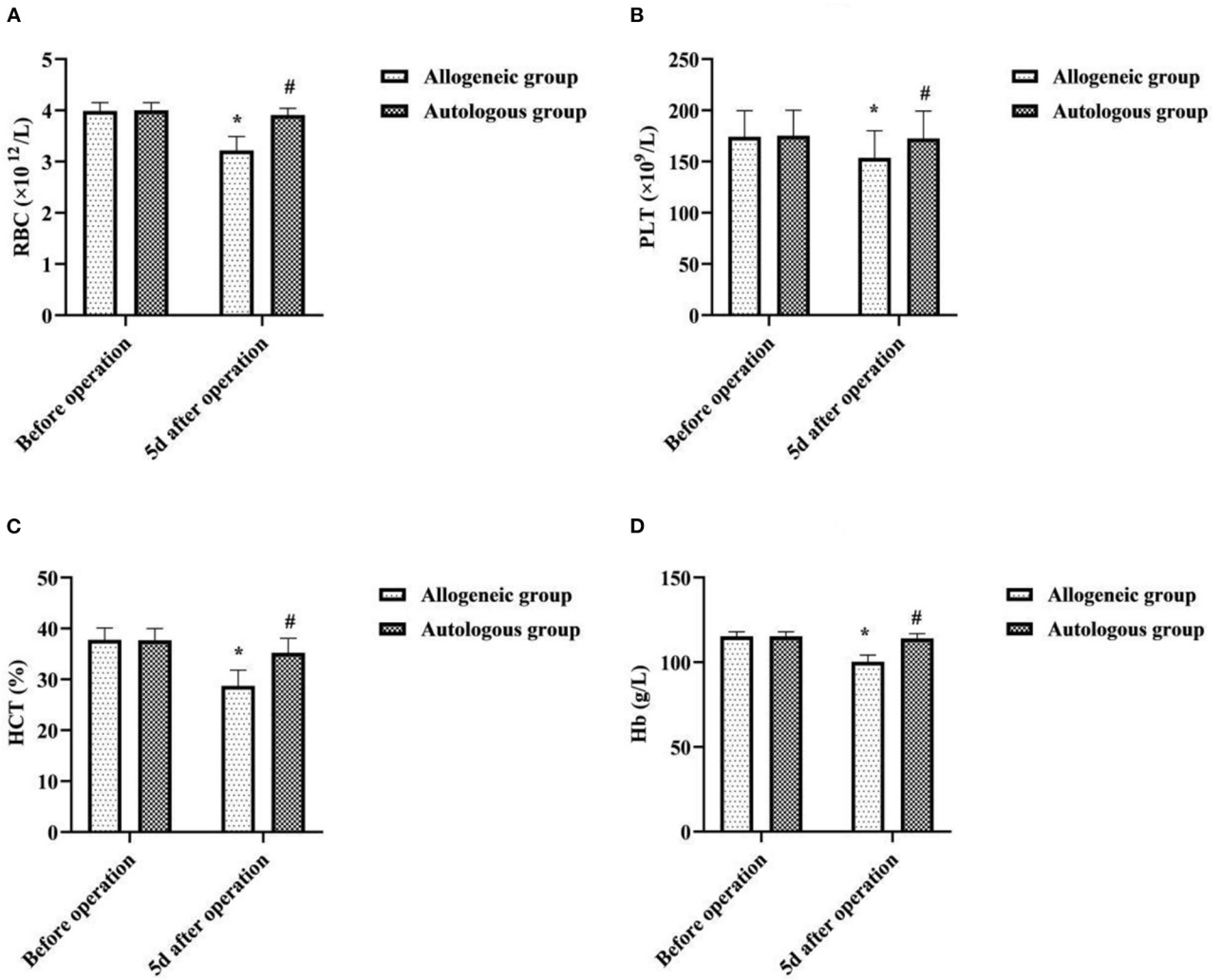


FIGURE 2 | Effect of different blood transfusion methods on patients' blood routine. **(A)** RBC, **(B)** PLT, **(C)** HCT, and **(D)** Hb. Compared with the same group before operation, $^{*}P < 0.05$; compared with allogeneic group 5d after operation, $^{\#}P < 0.05$.

which were comparable, which were comparable ($P > 0.05$) (**Table 1**).

Research Methods

Patients in both groups underwent cesarean section and general anesthesia was induced intraoperatively. On this basis, the allogeneic group received allogeneic transfusion therapy, i.e., when HCT < 24% or Hb < 80 g/L, stock blood was taken for transfusion perfusion according to the amount of blood lost by the patient. The autologous group received ANH autologous transfusion therapy, i.e., radial artery and right internal jugular vein puncture placement were performed after induction of anesthesia and before the start of surgery. Preoperatively, according to the patient's intraoperative bleeding prediction, the CZK-IB microcomputer liquid sampling controller (purchased from Zhengzhou Feilong Medical Equipment Co., Ltd.) was used to collect 300–420 mL of autologous blood through the radial artery and stored in a blood storage bag and treated with light shielding and freshness. An equal volume of 6% hydroxyethyl starch (HES) 130/0.4 (purchased from Shandong Hualu Pharmaceutical Co., Ltd., approval number H37022757) was then infused *via* the internal jugular vein. autologous blood was transfused at the end of the main intraoperative step or when the bleeding volume was ≥ 1,000 mL or Hb was ≤100 g/L.

Observation Index

(1) Vital signs: heart rate (HR), mean arterial pressure (MAP), and stroke volume variation (SVV) were monitored before transfusion and transfusion for 10 min by a PICCO monitor (purchased from Beijing Shimao Medical Equipment Trading Co., Ltd.).

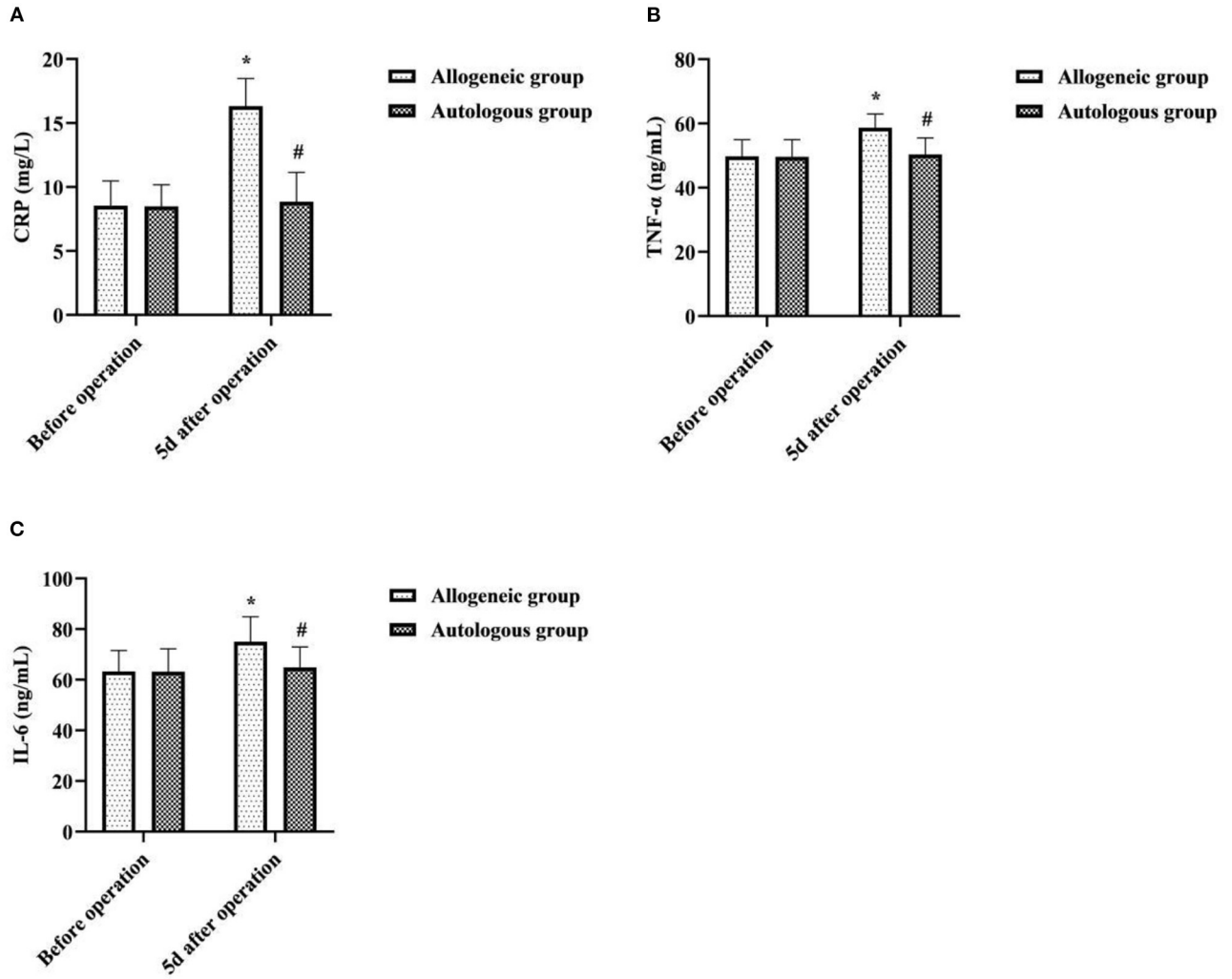


FIGURE 3 | Effect of different blood transfusion methods on patients' inflammatory factors. **(A)** CRP, **(B) TNF-α**, and **(C)** IL-6. Compared with the same group before operation, $^{*}P < 0.05$; compared with allogeneic group 5d after operation, $^{\#}P < 0.05$.

(2) Blood routine: The red blood cell (RBC), PLT, HCT and Hb levels were measured before and 5 d after surgery by MAXM automatic hematology analyzer (purchased from Beckman Coulter, Inc.).

(3) T-cell subsets: The $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ levels were measured before and 5 d after surgery by a Cytomics FC500 flow cytometer (purchased from Beckman Coulter, Inc.).

(4) Immunoglobulins: The IgA, IgM, and IgG levels were measured before and 5 d after surgery by enzyme-linked immunosorbent assay (The kit was purchased from Roche).

(5) Inflammatory factors: C-reactive protein (CRP), tumor necrosis factor (TNF)-α and interleukin (IL)-6 levels were measured before and 5 d after surgery by enzyme-linked immunosorbent assay (The kit was purchased from Shanghai Sange Biotechnology Co., Ltd.).

(6) Adverse reaction rate: Allergy, fever, hemolysis and other adverse reactions occurred during blood transfusion in the two groups were counted.

Statistical Methods

SPSS 22.0 software was applied, and the measurement data were expressed as mean ± standard deviation ($M \pm SD$) and compared by t-test. Count data were expressed as ratio, and the χ^2 test was used for comparison. $P < 0.05$ was considered statistically significant.

RESULTS

Effect of Different Blood Transfusion Methods on Patients' Vital Signs

There was no statistical significance in the intra-group and inter-group comparisons of HR, MAP, and SVV between the two

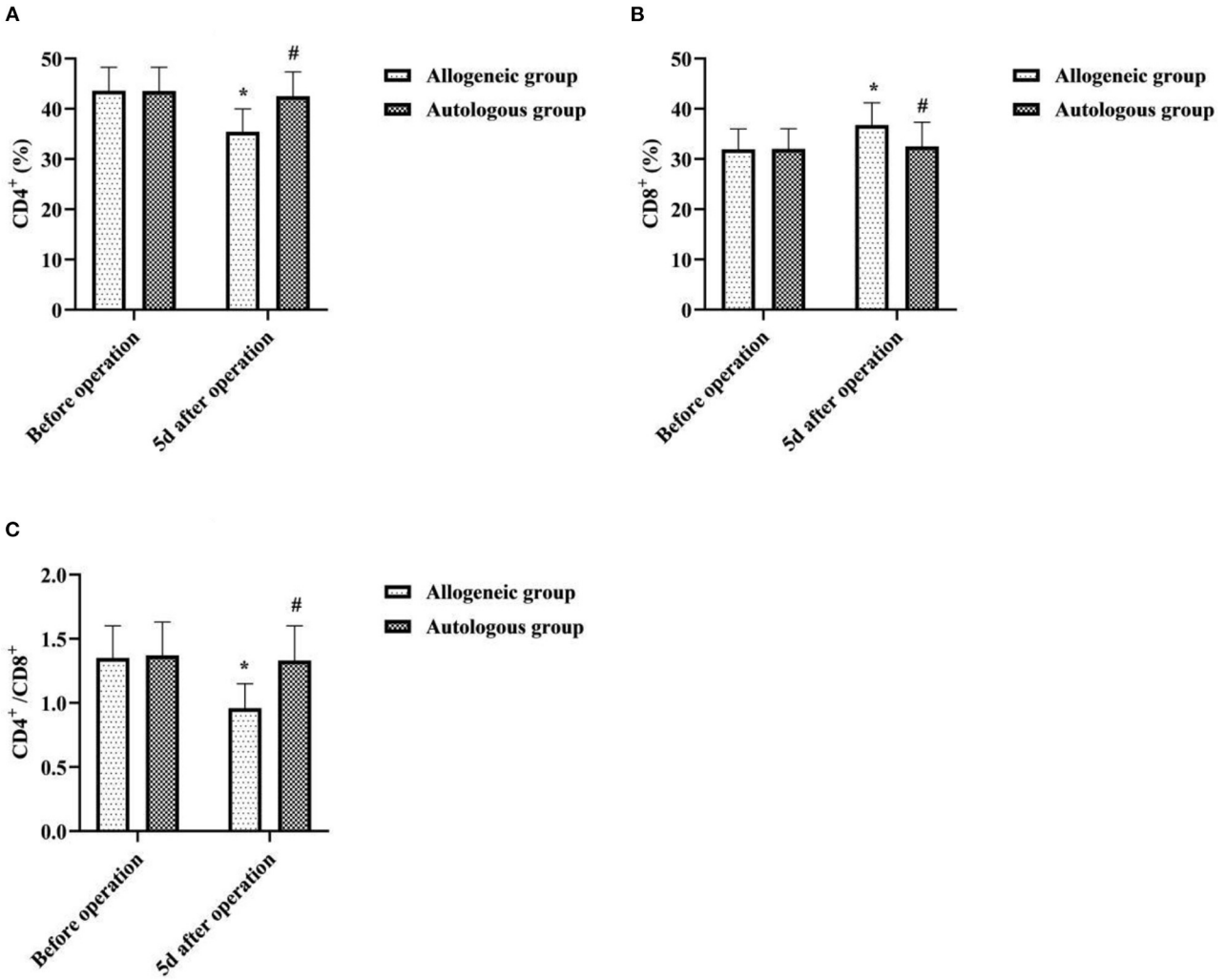


FIGURE 4 | Effect of different blood transfusion methods on patients' T-cell subsets. **(A)** $CD4^+$, **(B)** $CD8^+$, and **(C)** $CD4^+/CD8^+$. Compared with the same group before operation, $^*P < 0.05$; compared with allogeneic group 5d after operation, $^{\#}P < 0.05$.

groups before transfusion and transfusion for 10 min ($P > 0.05$) (**Figure 1**).

Effect of Different Blood Transfusion Methods on Patients' Blood Routine

5d after operation, the RBC, PLT, HCT, and Hb of the allogeneic group were lower than those before operation, and the autologous group was higher than that of the allogeneic group ($P < 0.05$) (**Figure 2**).

Effect of Different Blood Transfusion Methods on Patients' Inflammatory Factors

5d after operation, the CRP, TNF-α, and IL-6 of the allogeneic group were higher than those before operation, and the autologous group was lower than that of the allogeneic group ($P < 0.05$) (**Figure 3**).

Effect of Different Blood Transfusion Methods on Patients' T-Cell Subsets

5d after operation, the $CD4^+$, $CD4^+/CD8^+$ of the allogeneic group were lower than before operation, and the $CD8^+$ was higher than before operation. The $CD4^+$ and $CD4^+/CD8^+$ of the autologous group were higher than that of the allogeneic group, and $CD8^+$ was lower than that of the allogeneic group ($P < 0.05$) (**Figure 4**).

Effect of Different Blood Transfusion Methods on Patients' Immunoglobulins

5d after operation, the IgA, IgG, and IgM of the allogeneic group were lower than those before operation, and the autologous group was higher than that of the allogeneic group ($P < 0.05$) (**Figure 5**).

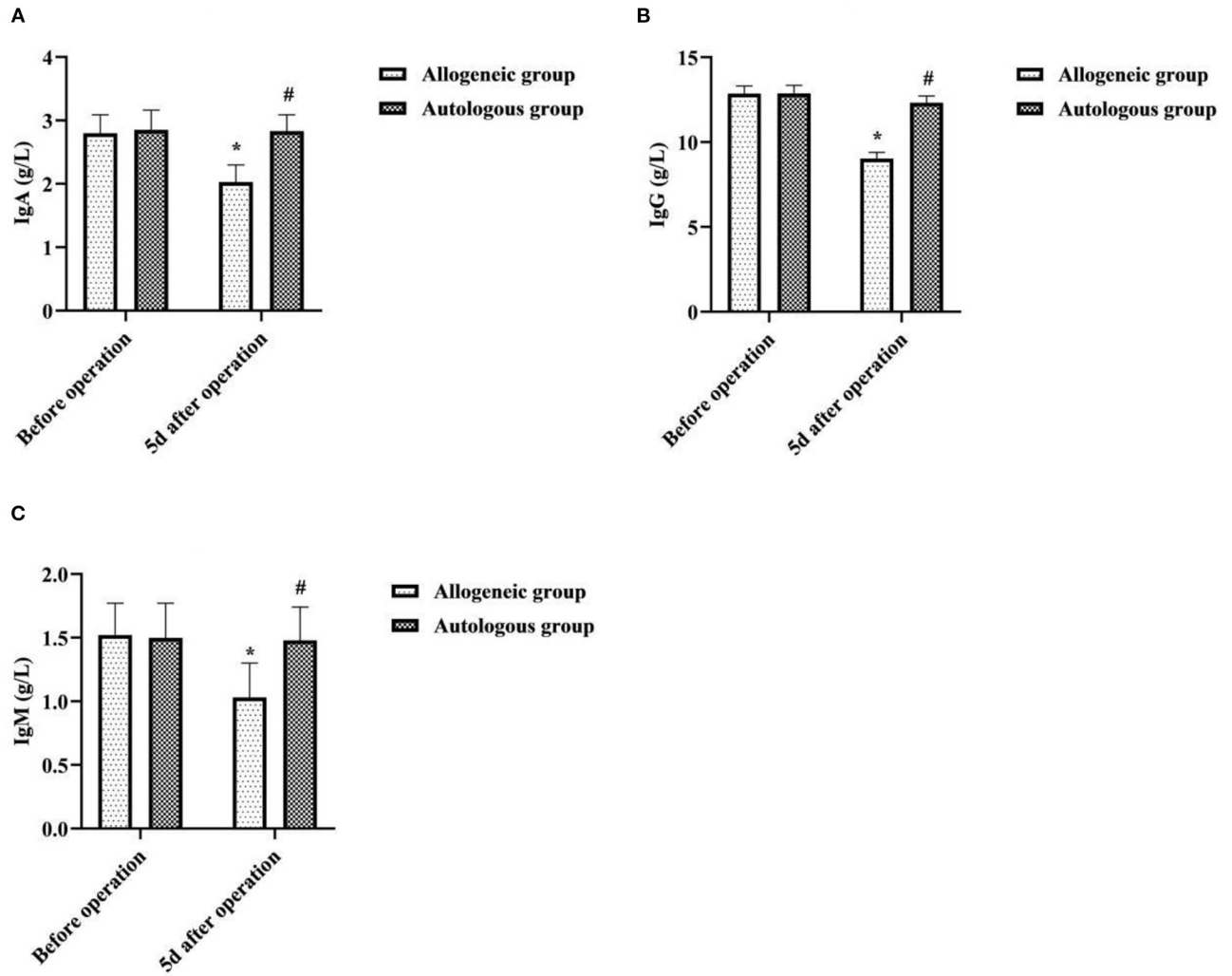


FIGURE 5 | Effect of different blood transfusion methods on patients' immunoglobulin's. **(A)** IgA, **(B)** IgG, and **(C)** IgM. Compared with the same group before operation, $^{*}P < 0.05$; compared with allogeneic group 5d after operation, $^{\#}P < 0.05$.

Adverse Reaction Rate of Different Blood Transfusion Methods

During blood transfusion, there was no significant difference in the adverse reaction rate between the two groups ($P > 0.05$) (**Table 2**).

DISCUSSION

In recent years, due to social factors such as late marriage and late childbirth, and second child policy, the number of advanced maternal age and scarred uterus re-pregnancy in China has been increasing, and the cesarean delivery rate has also increased, and in some areas it has exceeded 50% (12). It is reported that cesarean section patients are prone to severe bleeding that is not easy to control during the perinatal period, which is one of the main reasons for the poor prognosis or even death of mothers and babies (13). So, timely, reasonable, and adequate blood transfusion treatment is of great significance for suppressing perinatal hemorrhage and ensuring the safety of mothers and babies. Allogeneic transfusion is the main method at present, but it has been plagued by problems such as tight blood source and many adverse reactions of blood transfusion. It has been reported that ANH autologous transfusion may be superior to allogeneic blood transfusion in terms of blood safety (14). However, this blood transfusion method uses exogenous fluid for dilution, and whether the blood transfusion will affect the vital signs, immune function, and inflammation levels of patients undergoing cesarean section is still unknown. This study provided a comparative analysis in this regard.

It has been suggested that blood volume increases in women after pregnancy and that ANH autologous transfusion can achieve a reduction in blood viscosity, increase blood oxygen uptake, reduce cardiac burden, and protect the myocardium through preoperative blood sampling and dilution (15). In this

TABLE 2 | Adverse reaction rate of different blood transfusion methods (*n*, %).

Group	Allergy	Fever	Hemolysis	Others	Total
Allogeneic group ($n = 55$)	1 (1.82)	2 (3.64)	1 (1.82)	3 (5.45)	7 (12.73)
Autosomal group ($n = 55$)	1 (1.82)	1 (1.82)	0 (0.00)	2 (3.64)	4 (7.28)
χ^2 value					0.909
P value					0.340

study, there was no statistical significance in the intra-group and inter-group comparisons of HR, MAP, and SVV between the two groups before transfusion and transfusion for 10 min ($P > 0.05$). It showed that ANH autologous transfusion helps to maintain hemodynamic stability in patients undergoing cesarean section. To analyze the reasons, HES, as an artificial colloidal fluid with large molecular weight, has the pharmacological properties of being unable to penetrate the vessel wall, long intravascular retention time, and good effect of maintaining plasma colloidal osmotic pressure (16). Therefore, compared with isotonic crystalloids, it can achieve hemodynamic stability with less dosage and faster effect, and is one of the most commonly used resuscitation fluids in hemorrhagic shock. Surgery may result in loss of tangible components of blood, and allogeneic transfusions may result in destruction of blood components due to the long storage time of blood. In this study, 5d after operation, the RBC, PLT, HCT, and Hb of the allogeneic group were lower than those before operation, and the autologous group was higher than that of the allogeneic group ($P < 0.05$). It was suggested that ANH autologous transfusion is an effective way to improve hematoprotection and prevent the development of postoperative anemia. Analyze the reasons. Compared with allogeneic blood transfusion, ANH autologous blood transfusion is performed by drawing autologous blood before surgery and returning it to the patient during surgery, which not only reduces the loss of red blood cells and platelets during surgery, but also has a short storage time and does not require refrigeration, so the blood components are less damaged, which facilitates the patient's postoperative recovery. CRP, TNF-α, and IL-6 are all key cytokines that initiate inflammatory or immune responses when the body perceives inflammatory stimuli such as trauma (17, 18). In this study, 5d after operation, the CRP, TNF-α, and IL-6 of the allogeneic group were higher than those before operation, and the autologous group was lower than that of the allogeneic group ($P < 0.05$). It was suggested that allogeneic transfusion can lead to varying degrees of inflammatory response in patients undergoing cesarean section, whereas ANH autologous transfusion has a mild effect on the level of inflammation in patients. This may be related to the fact that the blood dilution of ANH autotransfusion reduces concentrations of cortisol and catecholamines in plasma, and that the blood released out of the body after hemodilution is not involved in the acute phase response.

As an immunogenic and reactogenic substance, blood can be accompanied by a series of adverse reactions involving immune regulation in the process of blood transfusion therapy, mainly manifested as immunosuppression (19). Both T-cell subsets and immunoglobulins are important indicators to assess the immune function of the body, with the former playing a central regulatory role in cellular immunity and the latter being closely related to humoral immunity undertaken by B cells (20, 21). When allogeneic blood enters the human body as foreign protein antigen, the differentiation of T lymphocytes into $CD4^+$ cells is inhibited, cytotoxic T lymphocytes ($CD8^+$ T cells) are activated, and then the proportion of $CD4^+/CD8^+$ is unbalanced, resulting in abnormal immune function. In this study, 5d after operation, the $CD4^+$, $CD4^+/CD8^+$, IgA, IgG and IgM of the allogeneic group were lower than before operation, and the $CD8^+$ was higher than before operation. The $CD4^+$, $CD4^+/CD8^+$, IgA, IgG and IgM of the autologous group were higher than that of the allogeneic group, and $CD8^+$ was lower than that of the allogeneic group ($P < 0.05$). It indicated that allogeneic transfusion can cause a decrease in immune function in the recipient, while ANH autologous transfusion has less effect on immune function in patients undergoing cesarean section. Analysis of the causes may be related to a decrease in the immune function of red blood cells due to the long storage time of the stock blood used for allogeneic transfusion. Numerous studies (22–24) have shown that the erythrocyte system has some immune functions that cannot be replaced by other immune cells, namely, reducing free radical damage, scavenging immune complexes, and participating in immune defense. Under normal circumstances, stock blood used for allogeneic transfusion can be stored at a constant temperature of 4°C for 2–3 weeks. However, the longer the storage time, the more serious the deformation and aging of RBCs, the gradual decrease of RBC-C3b receptor activity, the excessive accumulation of related metabolites, the increase of immune complexes, and finally the impaired immune function of RBCs (25). In contrast, autologous blood of ANH autologous transfusion has a short retention time outside the body and does not require refrigeration, has few changes in red blood cells and their associated metabolites, and is free of alloantigens and proteins, and has few white blood cell fragments, thus causing minimal suppression of the immune system. The results of this study also showed that the incidence of adverse transfusion reactions such as allergy, fever, and hemolysis was slightly lower in the autologous group than in the allogeneic group ($P > 0.05$). It can be seen that ANH autologous transfusion is safer and will not increase the incidence of adverse blood transfusion reactions.

CONCLUSION

Through the comparative analysis of the above results, we found that both allogeneic and ANH autologous transfusion had little effect on the vital signs of patients undergoing cesarean section, but ANH autologous transfusion was more helpful in stabilizing the postoperative blood routine, *T*-cell subpopulation, immunoglobulin, and inflammation levels, and was a safe and effective way of blood transfusion. It is worth noting that although ANH autologous transfusion is a safe and effective way of blood transfusion, it can not completely replace allogeneic blood transfusion. Some studies

(26) pointed out that when high-dose HES is used, due to the dilution effect, it may cause dose-related abnormal blood coagulation and decrease of HCT. Therefore, when the body has massive bleeding and the amount of recovered blood is also large, RBC, PLT and coagulation factors need to be supplemented at the same time in order to avoid serious coagulation dysfunction. The specific blood transfusion method should also depend on the specific situation of the patient.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Naval Military Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FG and HT are responsible for the design of the study and manuscript writing. XW is the instructor of the entire study, responsible for the inclusion of cases, and data statistics. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Yapca OE, Topdagi YE, Al RA. Fetus delivery time in extraperitoneal versus transperitoneal cesarean section: a randomized trial. *J Matern Fetal Neonatal Med.* (2020) 33:657–63. doi: 10.1080/14767058.2018.1499718
2. Zou YQ, Chen XX, Feng Y. Clinical study on perinatal outcomes of 80 cases with unicornuate uterus pregnancy. *Zhonghua Fu Chan Ke Za Zhi.* (2020) 55:510–5. doi: 10.3760/cma.j.cn112141-20200107-00019
3. Hulse W, Bahr TM, Morris DS, Richards DS, Ilstrup SJ, Christensen RD. Emergency-release blood transfusions after postpartum hemorrhage at the Intermountain Healthcare hospitals. *Transfusion.* (2020) 60:1418–23. doi: 10.1111/trf.15903
4. Lecarpentier E, Gris JC, Cochery-Nouvellon E, Mercier E, Abbas H, Thadhani R, et al. Urinary placental growth factor for prediction of placental adverse outcomes in high-risk pregnancies. *Obstet Gynecol.* (2019) 134:1326–32. doi: 10.1097/AOG.0000000000003547
5. Wright GP, Wolf AM, Waldherr TL, Ritz-Holland D, Laney ED, Chapman HA, et al. Preoperative tranexamic acid does not reduce transfusion rates in major oncologic surgery: Results of a randomized, double-blind, and placebo-controlled trial. *J Surg Oncol.* (2020) 122:1037–42. doi: 10.1002/jso.26142
6. Terai A, Terada N, Yoshimura K, Ichioka K, Ueda N, Utsunomiya N, et al. Use of acute normovolemic hemodilution in patients undergoing radical prostatectomy. *Urology.* (2005) 65:1152–6. doi: 10.1016/j.urology.2004.12.034
7. Bennett J, Haynes S, Torella F, Grainger H, McCollum C. Acute normovolemic hemodilution in moderate blood loss surgery: a randomized controlled trial. *Transfusion.* (2006) 46:1097–103. doi: 10.1111/j.1537-2995.2006.00857.x
8. Iwase Y, Kohjitani A, Tohya A, Sugiyama K. Preoperative autologous blood donation and acute normovolemic hemodilution affect intraoperative blood loss during sagittal split ramus osteotomy. *Transfus Apher Sci.* (2012) 46:245–51. doi: 10.1016/j.transci.2012.03.014
9. Oppitz PP, Stefani MA. Acute normovolemic hemodilution is safe in neurosurgery. *World Neurosurg.* (2010) 79:719–24. doi: 10.1016/j.wneu.2012.02.041
10. Irlbeck T, Zwißler B, Bauer A. ASA-Klassifikation : Wandel im Laufe der Zeit und Darstellung in der Literatur [ASA classification : transition in the course of time and depiction in the literature]. *Anaesthesist.* (2017) 66:5–10. doi: 10.1007/s00101-016-0246-4
11. Akinlusi FM, Rabiu KA, Durojaiye IA, Adewunmi AA, Ottun TA, Oshodi YA. Cesarean delivery-related blood transfusion: correlates in a tertiary hospital in Southwest Nigeria. *BMC Pregnancy Childbirth.* (2018) 18:24. doi: 10.1186/s12884-017-1643-7
12. Su Y, Heitner J, Yuan C, Si Y, Wang D, Zhou Z, et al. Effect of a text messaging-based educational intervention on cesarean section rates among pregnant women in china: quasirandomized controlled trial. *JMIR Mhealth Uhealth.* (2020) 8:e19953. doi: 10.2196/19953
13. Khanal V, Karkee R, Lee AH, Binns CW. Adverse obstetric symptoms and rural-urban difference in cesarean delivery in Rupandehi district, Western Nepal: a cohort study. *Reprod Health.* (2016) 13:17. doi: 10.1186/s12978-016-0128-x
14. Sarkanović ML, Gvozdenović L, Savić D, Ilić MP, Jovanović G. Autologous blood transfusion in total knee replacement surgery. *Vojnosanit Pregl.* (2013) 70:274–8. doi: 10.2298/VSP1303274L
15. van der Post JA, van Buul BJ, Hart AA, van Heerikhuize JJ, Pesman G, Legros JJ, et al. Vasopressin and oxytocin levels during normal pregnancy: effects of chronic dietary sodium restriction. *J Endocrinol.* (1997) 152:345–54. doi: 10.1677/joe.0.1520345
16. Duncan AE, Jia Y, Soltesz E, Leung S, Yilmaz HO, Mao G, et al. Effect of 6% hydroxyethyl starch 130/0.4 on kidney and haemostatic function in cardiac surgical patients: a randomized controlled trial. *Anaesthesia.* (2020) 75:1180–90. doi: 10.1111/anae.14994
17. Li K, Xu Y, Hu Y, Liu Y, Chen X, Zhou Y. Effect of enteral immunonutrition on immune, inflammatory markers and nutritional status in gastric cancer patients undergoing gastrectomy: a randomized double-blinded controlled trial. *J Invest Surg.* (2020) 33:950–9. doi: 10.1080/08941939.2019.1569736
18. Nelson KA, Aldea GS, Warner P, Latchman Y, Gunasekera D, Tamir A, et al. Transfusion-related immunomodulation: gamma irradiation alters the effects of leukoreduction on alloimmunization. *Transfusion.* (2019) 59:3396–404. doi: 10.1111/trf.15555
19. Arasaratnam RJ, Tzannou I, Gray T, Aguayo-Hiraldo PI, Kuvalekar M, Naik S, et al. Dynamics of virus-specific T cell immunity in pediatric liver transplant recipients. *Am J Transplant.* (2018) 18:2238–49. doi: 10.1111/ajt.14967
20. Longbrake EE, Mao-Draayer Y, Cascione M, Zielinski T, Bame E, Brassat D, et al. Dimethyl fumarate treatment shifts the immune environment toward an anti-inflammatory cell profile while maintaining protective humoral immunity. *Mult Scler.* (2021) 27:883–94. doi: 10.1177/1352458520937282
21. Li H, Zhang XS. Impacts of moxibustion on erythrocyte immune function and T-lymphocyte subsets in athletes. *Zhongguo Zhen Jiu.* (2013) 33:415–8.
22. Evers D, Middelburg RA, de Haas M, Zalpuri S, de Vooght KM, van de Kerkhof D, et al. Red-blood-cell alloimmunisation in relation to antigens' exposure and their immunogenicity: a cohort study. *Lancet Haematol.* (2016) 3:e284–92. doi: 10.1016/S2352-3026(16)30019-9
23. Wang S, Gao G, He Y, Li Q, Li Z, Tong G. Amidation-Modified Apelin-13 regulates pparγ and perilipin to inhibit adipogenic differentiation and promote lipolysis. *Bioinorg Chem Appl.* (2021) 2021:3594630. doi: 10.1155/2021/3594630
24. Sparrow RL, Veale MF, Healey G, Payne KA. Red blood cell (RBC) age at collection and storage influences RBC membrane-associated carbohydrates and lectin binding. *Transfusion.* (2007) 47:966–8. doi: 10.1111/j.1537-2995.2007.01230.x
25. Chong Sung K, Kum Suk P, Mi Ja Y, Kyoung Ok K. Effects of intravascular volume therapy using hydroxyethyl starch (130/0.4) on post-operative bleeding and transfusion requirements in children undergoing cardiac surgery: a randomized clinical trial. *Acta Anaesthesiol Scand.* (2006) 50:108–11. doi: 10.1111/j.1399-6576.2005.00881.x

26. Porter Starr KN, Orenduff M, McDonald SR, Mulder H, Sloane R, Pieper CF, et al. Influence of weight reduction and enhanced protein intake on biomarkers of inflammation in older adults with obesity. *J Nutr Gerontol Geriatr.* (2019) 38:33–49. doi: 10.1080/21551197.2018.1564200

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Guo, Tang and Wei. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 22 February 2022
doi: 10.3389/fsurg.2021.833879

Construction of a Training Content System for New Nurses in Cancer Hospital Based on Competency

Miao Liu[1†], *Jingzhi Geng*[1†], *Jian Gao*[2], *Zhihong Mei*[3], *Xueyan Wang*[1], *Sicong Wang*[1] *and Yan Liu*[4*]

[1] *Department of Gynecologic Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China,* [2] *Department of Radiation Therapy, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China,* [3] *Department of Internal Medicine, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China,* [4] *Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Objective: To construct a training content system for new nurses in cancer hospitals based on postcompetency and to provide guidance for clinical new nurse training.

Methods: Based on literature review, semistructured interviews, and questionnaire surveys, a new draft of the nurse training content system was initially established, and 17 experts were selected to make two rounds of inquiry on the system by the Delphi method, so as to construct a new nurse training content system.

Results: The effective rate of recovery of the two rounds of expert correspondence was 100%, the cooperation among experts was high, and the authoritative coefficient of experts was 0.89. The content system of new nurse training constructed included 2 first-class indexes, 5 second-class indexes, and 45 third-class indexes.

Conclusion: The new nurse training content system is closely combined with clinical work, pays attention to improving nurses' competence, reflects the characteristics of nursing work in cancer hospitals, has a certain scientific and practical significance, and can provide guidance for the training of new nurses in cancer hospitals.

Keywords: competency, cancer care, new nurse, Delphi technique, index system

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Lihong Chen,
The First Affiliated Hospital of Fujian Medical University, China
Li Zhu,
Central South University, China

***Correspondence:**
Yan Liu
15201119199@139.com

[†]*These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *12 December 2021*
Accepted: *31 December 2021*
Published: *22 February 2022*

Citation:
Liu M, Geng J, Gao J, Mei Z, Wang X, Wang S and Liu Y (2022) Construction of a Training Content System for New Nurses in Cancer Hospital Based on Competency. Front. Surg. 8:833879. doi: 10.3389/fsurg.2021.833879

INTRODUCTION

In recent years, the incidence and mortality of cancer have remained high, and the demand for cancer care has become increasingly prominent. A large number of new nurses join the cancer specialist hospital every year. The process of changing from nursing students to working as new nurses is full of challenges (1, 2). In order to meet the requirements of clinical nursing work in a short period of time, it is necessary to carry out standardized training for new nurses. The current reference to the new nurse-standardized training programs (trial), some of which are not completely applicable to cancer hospitals, and the training plan should be improved and optimized according to the nursing characteristics of cancer hospitals, for example, tumor treatment methods including surgical treatment, radiotherapy, chemotherapy, gene targeted

therapy, biological treatment, etc. (3). New nurses need to understand a variety of treatment methods and adverse reaction processing, the management of related drugs, the maintenance of a variety of venous lines, the first-aid for a drug anaphylactic shock, observation and care of bone marrow suppression, prevention and care of radiation inflammation, psychological care for patients with facial defects, improvement in the hospice care for patients at the end stage, implementation of the nurse occupational protection, etc. Nursing postcompetency is based on the cognition and construction method, which reflects the ability of nurses to use various nursing skills, professional knowledge, values, critical thinking, and information as a whole (4). Multiple studies have shown that a competency-based training system can urge new nurses to improve their professional knowledge and skills, change their working attitudes, etc., and ultimately improve the level of work (5, 6). This study was designed to build a training content system for new nurses in cancer hospitals based on postcompetency, so as to guide the training of new nurses, improve their quality, and make them better qualified for the job.

INFORMATION AND METHODS

Draft Framework for Initially Constructing a New Induction Nursing Training System for Oncology Specialty

Through literature review and semistructured interviews, combined with the new nurse training status and needs of the baseline survey, the new nurse standardized training program (trial), the existing training programs, and characteristics of tumor hospitals, the draft framework of the new nurse training system in tumor hospitals based on job competency was prepared. Using the method of objective sampling, a questionnaire survey was conducted among 17 experts from a certain tertiary grade A cancer hospital. The draft framework has been revised and adjusted. Through the analysis and arrangement of the preliminary survey results, a formal draft was formed.

Design of Expert Consultation Questionnaire

The questionnaire is divided into two parts. Part I: The core part of the expert inquiry is the new nurse based on the post-competency evaluation index system expert inquiry table, using Likert grade 5 scoring method (5 points-very important, 4 points-important, 3 points-generally important, 2 points-not too important, and 1 point-not important) to determine the importance of each index items, and put forward items or suggestions for addition or deletion. Part II: Basic information sheet of experts, including general information of experts (age, length of service, educational background, etc.); judgment basis (including theoretical analysis, work experience, references, and intuitive selection; the degree of influence was divided into large, medium, and small grades); familiarity with the content of the study (divided into six levels of very familiar, familiar, more familiar, generally familiar, less familiar, and very unfamiliar).

Implementation of Delphi Expert Consultation

Number and Criteria for Selection of Experts

The number of experts depends on the content of the study, and the appropriate number of general experts is 15–50. The selected experts should have certain academic authority, professional knowledge, and clinical experience in the corresponding research fields. Inclusion criteria are as follows: a) Being engaged in tumor nursing, nursing teaching, and nursing management for $\geq$10 years; b) Title above supervisor nurse, bachelor's degree or above; and c) Mastered the nursing knowledge and skills of this major, and have rich experience in teaching management, and also has mastered the knowledge and skills of nursing, with a rich experience in teaching management; and d) actively participating in this research.

Implementation Process of Expert Inquiry

A questionnaire was distributed by a specially assigned person for the job and the experts were required to reply within 1 week. The experts scored and revised the importance of each index according to their own cognition and understanding of it. A total of 17 valid questionnaires were collected during the first letter of inquiry. Statistical analysis was performed on the results. In combination with the opinions of the experts, the items with the significant average score $>$3 points and the coefficient of variation $<$0.35 were retained. The questionnaire used in the first round was deleted, supplemented, and modified to form the second round of questionnaire, and the second round of expert consultation was conducted 2 weeks later. A total of 17 valid questionnaires were collected during the second consultation. After the analysis of the second round of questionnaires, it was found that the opinions of the experts were consistent, and hence the expert inquiry was ended.

Statistical Methods

The SPSS 17.0 statistical software was used to analyze the data. The enthusiasm of experts was expressed by the effective recovery rate of the questionnaire, and the degree of expert authority was expressed by the authority coefficient. The degree of dispersion of expert opinions has been expressed by the coefficient of variation (CV) and coordination coefficient (W), where CV = standard deviation/mean value. The smaller the coefficient of variation, the more unanimous the opinion of experts. The value of W was statistically tested by the non-parametric test of multiple related samples. The significant value indicated good coordination after the test. W was in the range of 0–1, and the larger the W was, the better the coordination would be. The importance scores of each item were expressed as mean and SD ($\bar{x} \pm s$), and the weight of each item was determined by the analytic hierarchy process.

RESULTS

General Information for 17 Experts

According to the requirements of the Delphi method for expert selection, combined with the specific characteristics and feasibility of this study, 17 nursing experts from the Level A tertiary hospitals were selected as the inquiry objects.

TABLE 1 | General information for 17 experts.

General information		Number	Constituent ratio (%)
Age (years)	30–40	12	70.59
	41–50	4	23.53
	>50	1	5.88
Professional title	Nurse-in-charge	4	23.53
	Deputy director of the nurse	9	52.94
	Chief nurse	4	23.53
Academic degree	Undergraduate course	12	70.59
	Master	5	29.41
Working years (years)	10–15	4	23.53
	16–20	7	41.18
	>20	6	35.29

They were from different professional departments, such as oncology, radiotherapy, thoracic surgery, gynecology and oncology, head and neck surgery, breast surgery, hepatobiliary surgery, pancreatic biology, colorectal surgery, orthopedics, neurosurgery, and nursing. The basic situation of the experts is shown in **Table 1**.

Positive Coefficient of Experts

The expert positive coefficient refers to the attention and cooperation of experts in research. Experts' enthusiasm for this research is not high, which will affect the objectivity and reliability of the consultation. The expert's positive coefficient is expressed by the effective recovery rate of questionnaires. In the first and second rounds of this study, a total of 17 questionnaires were distributed and 17 valid questionnaires were returned. The questionnaire recovery rate was 100%, which showed that the experts were highly motivated.

Authority of Experts (Cr)

The authority coefficient of an expert is determined by the judgment basis coefficient (*Ca*) and familiarity coefficient (*Cs*) of the expert, and its calculation formula is $Cr = (Ca+Cs)/2$. The judgment basis coefficient, familiarity coefficient, and authority coefficient of the expert in this study are 0.93, 0.82, and 0.87, respectively, as shown in **Figure 1**. Generally, it is considered that *Cr* is greater than 0.7, the consulting result is reliable, and the prediction accuracy is improved with the improvement of an expert authority. Therefore, the degree of expert authority in this study was high, and the results were credible.

Coordination of Expert Advice

The degree of dispersion of the expert inquiry was expressed by the coordination coefficient (*W*). The coefficient of variation of the whole index ranged from 0–0.25, all of which were less than 0.35. The range of the matching coefficient is 0–1. A larger *W* indicates a better coordination degree. The coordination coefficients of all levels are shown in **Table 2**. It can be seen from the table that the *W* values of the first, second, and third level indicators are 1.000, 1.000, and 0.978, respectively. The *P*-values calculated by the Chi-square test are all less than 0.05. Statistics show that experts have a high degree of recognition of all indicators, and the result is satisfactory.

Results of Expert Communications

The degree of expert opinion set is expressed with the mean and SD of the index importance assignment. The larger the mean value of significant distribution, the smaller the SD, indicating the high importance of the index. The results of expert inquiry showed that the mean range of important assignments for the whole index was 3.44–5.00, and the SD range was 0–0.95. The small difference indicated that the expert opinion was centralized. After two rounds of expert consultation, it was finally determined that the training content system for new nurses in tumor specialized hospitals included two level I indicators, five level II indicators, and 45 level III indicators. **Tables 3**, **4** show the specific contents.

DISCUSSION

The Scientificity and Reliability of This Study

In the Delphi expert inquiry method, the selection of experts is related to the rationality and reliability of the research results (7). In the process of selecting experts for this study, nursing experts from departments such as oncology, internal medicine, radiotherapy, thoracic surgery, gynecology and oncology, head and neck surgery, breast surgery, liver and gallbladder surgery, pancreas and stomach surgery, colorectal surgery, orthopedics, neurosurgery, and nursing were selected and could continue to participate in the two rounds of consultation in this study. These experts had high academic levels and rich clinical experience in relevant fields, ensuring the scientificity and authority of research results.

The results obtained from this study showed that the recoveries of the two rounds of questionnaires were 100%, indicating that the enthusiasm of experts was high. The expert's judgment basis coefficient, familiarity coefficient, and authority coefficient are 0.93, 0.82, and 0.87, respectively, which are all greater than 0.7, indicating that the expert's authority is high. The *W* values of the indicators in the second round were 1.000, 1.000, and 0.978, respectively. The *P*-values calculated by the Chi-square test were all less than 0.05, showing statistical significance, indicating that experts had a high degree of approval for all indicators. These research results indicated the reliability and scientificity of the evaluation index system.

The Content of New Nurse Training System in Tumor Specialized Hospital Based on Competency

After two rounds of the Delphi expert consultation, the content of a competency-based training system for new nurses in cancer hospitals was finally established in this study. There were two level I indicators: knowledge and skills and comprehensive

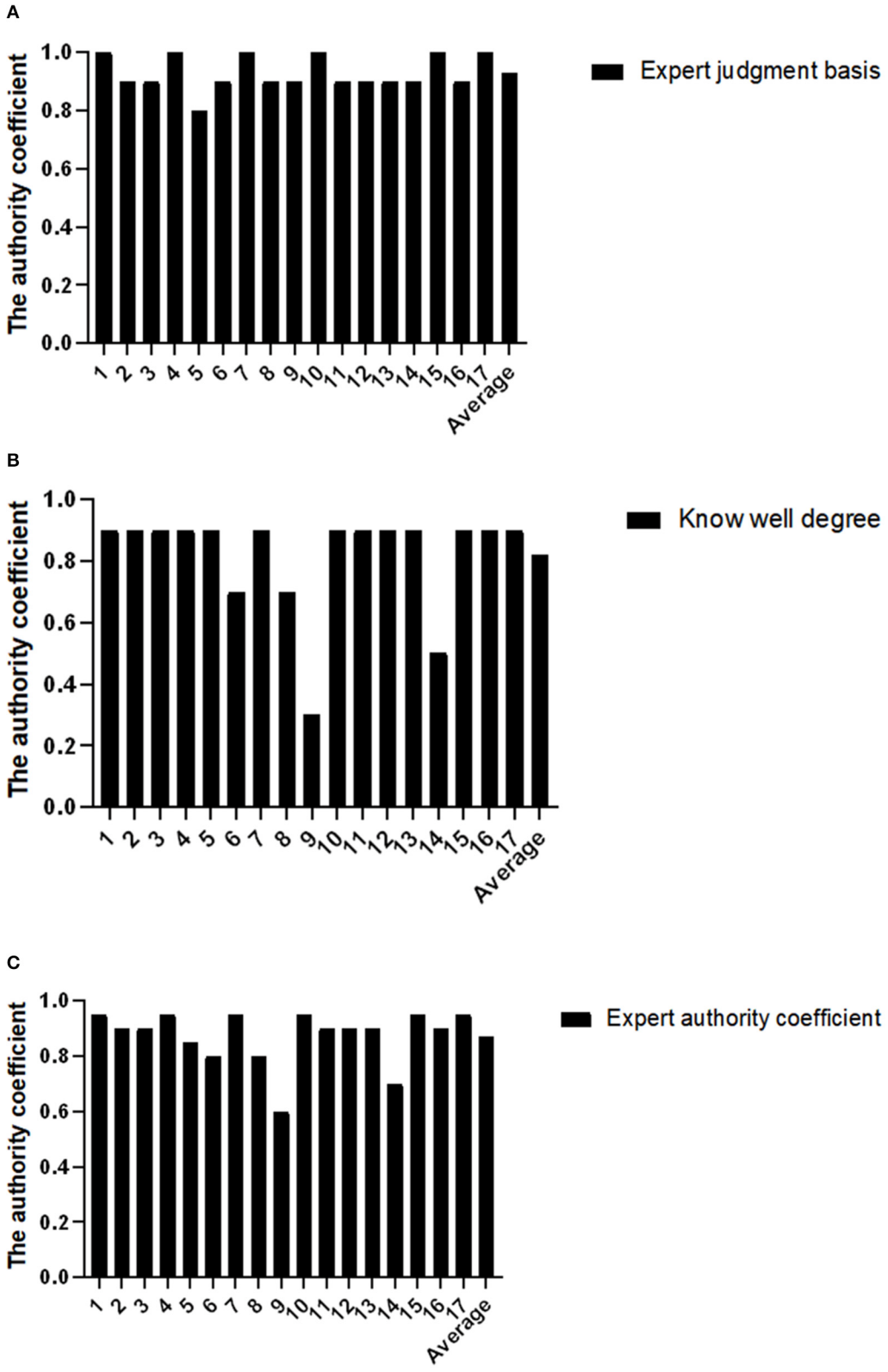


FIGURE 1 | Degree of authority of the inquiry experts. **(A)** Expert judgment basis; **(B)** Know well degree; **(C)** Expert authority coefficient.

TABLE 2 | Test results of coordination degree of two rounds of expert inquiry.

Number of consultations	Indicator hierarchy	Coordination factor (w)	Chi-square value	*P value*
Round 1	Level 1 indicators	1.000	17.000	<0.001
	Level 2 indicators	1.000	68.000	<0.001
	Level 3 indicators	0.966	1,477.957	<0.001
Round 2	Level 1 indicators	0.235	4.000	0.046
	Level 2 indicators	1.000	68.000	<0.001
	Level 3 indicators	0.978	1,496.007	<0.001

TABLE 3 | Results of level I and level II indexes of new nurse training content system.

Indicator code	Indicator name	Importance assignment	Variable coefficient	Weight
I-1	Knowledge skills	4.94 ± 0.25	0.051	0.510
I-2	Comprehensive ability accomplishment	4.75 ± 0.45	0.095	0.490
II-1	Nursing theory knowledge	4.81 ± 0.40	0.083	0.491
II-2	Common nursing operation technology	5.00 ± 0.00	0.000	0.510
II-3	Ability of practice	4.69 ± 0.48	0.102	0.326
II-4	Emergency capability	4.88 ± 0.34	0.070	0.339
II-5	Professional quality	4.81 ± 0.40	0.083	0.335

ability and accomplishment, five level II indicators: nursing theoretical knowledge, common operation technology, practical ability, emergency ability, and professional quality. The results showed that ① in the training system, the common nursing operation technology (0.510) ranked first in the weight value of the level II, and its level III indicator included basic nursing technology, tumor specialized nursing technology, emergency nursing technology, and the use of instruments and equipment. The weight of common nursing operation techniques was higher than that of nursing theoretical knowledge, which might be related to the fact that the new nurses had just finished their school study career, and their theoretical knowledge was relatively solid, but their operation skills were relatively weak. The highest weight in the three indicators was emergency care technology (0.271). As the number of critically ill patients increases, the management of critically ill patients becomes more challenging, says Kaldan (8). High-quality critical care practice is essential for critical patient management. Research results showed that the ability to provide emergency treatment and cooperate with emergency treatment for critically ill patients was urgently needed in clinical practice, but training in emergency techniques was not widely available during the study period (9). Therefore, the weight of emergency nursing technology, as an important influencing factor of critical patient management and urgently needed work ability in clinical practice, is in the first place of the level III indicators. ② The nursing theoretical knowledge (0.491), which included 13 parts such as rules

TABLE 4 | New nurse training content system level III index results.

Indicator code	Indicator name	Importance assignment	Variable coefficient	Weight
I-1	Knowledge skills			
II-1	Nursing theory knowledge			
III-1	First-aid knowledge	4.88 ± 0.34	0.070	0.089
III-2	Nursing safety management	4.81 ± 0.40	0.083	0.088
III-3	Occupational protection knowledge	4.81 ± 0.40	0.083	0.088
III-4	Hospital infection prevention control knowledge	4.75 ± 0.45	0.095	0.087
III-5	Nursing core system	4.81 ± 0.54	0.112	0.085
III-6	Nursing norm standard	4.75 ± 0.68	0.143	0.080
III-7	Tumor nursing specialist knowledge	4.44 ± 0.89	0.200	0.076
III-8	Basic nursing knowledge	4.44 ± 0.73	0.164	0.074
III-9	Nursing related laws regulations	4.19 ± 0.83	0.198	0.071
III-10	Hospital regulations	4.31 ± 0.95	0.220	0.070
III-11	Oncology specialist knowledge	4.06 ± 0.85	0.209	0.065
III-12	Psychological nursing	4.00 ± 0.82	0.205	0.064
III-13	Standardized treatment of pain	3.94 ± 0.77	0.195	0.063
II-2	Common nursing operation technology			
III-14	Emergency nursing technique	5.00 ± 0.00	0.000	0.271
III-15	Basic nursing technology	4.63 ± 1.03	0.222	0.247
III-16	Tumor specialist nursing technology	4.63 ± 0.62	0.134	0.241
III-17	Instrument equipment use	4.63 ± 0.62	0.134	0.241
I-2	Comprehensive ability accomplishment			
II-3	Ability of practice			
III-18	Condition observation	4.63 ± 0.72	0.156	0.085
III-19	Symptom care	4.56 ± 0.73	0.160	0.083
III-20	Nursing document writing	4.56 ± 0.63	0.138	0.083
III-21	Information system operation	4.56 ± 0.63	0.138	0.083
III-22	Teamwork	4.50 ± 0.82	0.182	0.080
III-23	Communication	4.44 ± 0.73	0.164	0.081
III-24	Health education	4.38 ± 0.81	0.185	0.080
III-25	Nursing rounds	4.25 ± 0.78	0.184	0.078
III-26	Autonomous learning	4.25 ± 0.68	0.160	0.078
III-27	Discussion on nursing problems	4.00 ± 0.63	0.158	0.073
III-28	Workplan co-ordination capacity	4.00 ± 0.82	0.205	0.071
III-29	Critical thinking ability	3.81 ± 0.83	0.218	0.067
III-30	Ward management	3.44 ± 0.89	0.259	0.058
II-4	Emergency capability			
III-31	Emergency ability to use drugs treat adverse reactions	4.94 ± 0.25	0.051	0.148

(Continued)

TABLE 4 | Continued

Indicator code	Indicator name	Importance assignment	Variable coefficient	Weight
III-32	Patient safety event emergency response capability	4.88 ± 0.34	0.070	0.146
III-33	Emergency ability to cope with sudden changes in illness	4.88 ± 0.50	0.102	0.141
III-34	Emergency treatment ability of chemotherapeutic drug extravasation	4.81 ± 0.40	0.083	0.150
III-35	Emergency treatment ability of chemotherapeutic drug overflow	4.75 ± 0.45	0.095	0.143
III-36	Fire safety emergency capability	4.63 ± 0.50	0.108	0.139
III-37	Ability to handle emergencies such as water power outages	4.63 ± 0.62	0.134	0.133
II-5	Professional quality			
III-38	Professional ethics	4.88 ± 0.34	0.070	0.141
III-39	Solitary spirit	4.88 ± 0.34	0.070	0.141
III-40	Medical ethics	4.75 ± 0.58	0.122	0.132
III-41	Emotional control	4.69 ± 0.60	0.128	0.130
III-42	Humanistic care	4.50 ± 0.73	0.162	0.119
III-43	Nurse etiquette	4.31 ± 0.70	0.162	0.114
III-44	Courtyard view culture	4.25 ± 0.86	0.202	0.114
III-45	Professional identity planning	4.25 ± 0.93	0.219	0.109

and regulations, core system, basic knowledge, and specialized knowledge, ranked second in the weight of secondary indicators. Tariman's research shows that knowledge is one of the main factors affecting the ability of nurses specializing in the treatment of tumors to work (10). Therefore, the theoretical knowledge has a higher weight in the new nurse training system of tumor hospitals. The first-aid knowledge (0.089) had the highest weight in the level III indicators, which was consistent with the result that the weight of emergency care technology was in the first place. The knowledge related to emergency treatment is of high importance in tumor hospitals, which may be related to the poor general condition of tumor patients, urgent condition change, and the rapid development of disease courses. The weights of nursing safety management, occupational protection knowledge, hospital infection prevention and control knowledge, nursing core system, and nursing specification standard in the three-level indicators were located at a higher level (0.080–0.088). Considering that these contents were closely related to the daily nursing work, it was the bottom line of nursing work, and any mistake would cause adverse consequences, so the importance was higher. The laws and regulations related to nursing (0.071) and hospital rules and regulations (0.070) in the level III indicators included the duties and rights of nurses. The duties of nurses were clearly reflected in the core system of nursing, nursing norms and standards, and other related contents. However, the rights of nurses had a low degree of a close relationship with clinical adverse events. Therefore, the weights of nursing laws and regulations and hospital rules and regulations were lower than those of nursing safety management. The weights of psychological care and standardized pain treatment (0.064 and 0.0629) were relatively low. Compared with these two contents, emergency knowledge and other issues were considered, which was related to the low urgency of clinical needs. However, the hospice care and symptom care for cancer patients involve psychological and pain related contents, so the relevant training contents were retained in two rounds of an expert consultation. ③ The third important factor in the weight of secondary indicators was emergency response ability, which included adverse drug reactions, chemotherapy extravasation, safety and fire protection, etc. Patient safety is the primary content of medical work, and the emergency ability of nurses is closely related to the clinical outcome and safety problems of patients. However, the emergency ability of new nurses is generally weak (11). Strengthening the emergency ability of new nurses can effectively improve the competency (12). The highest weight of the level III indicators was emergency response ability to medication and adverse reaction after treatment (0.148), which included medication error, anaphylactic shock, infusion and blood transfusion reaction, etc. Medication and treatment are frequently performed by nurses every day, and adverse reactions have immediate and severe consequences. For example, patients undergoing chemotherapy are prone to drug allergic reactions due to drug accumulation in the body at the later stage of treatment. With the increase in treatment cycles, the allergic reactions gradually aggravate. Therefore, nurses need to have a certain emergency ability to ensure smooth treatment of patients and treatment safety (13, 14). ④ The professional accomplishment (0.335) ranked fourth in the weight of secondary indicators. Nursing is a subject that not only pays attention to the practical operation but is also a specialty with high requirements for professional accomplishment. The professional ethics and self-caution in the level III indicators were ranked first in the weight (0.141). Regular nurses who attach importance to the cultivation of professional ethics have a high degree of awareness of their own professional behavior and the teachers have a high degree of satisfaction with their work performance (15). According to Monroe's research, nurses who had worked for less than 10 years had low scores of professional values, and the cultivation of professional ethics could improve the professional values of the nurses, improve the quality of nursing work, and reduce the turnover rate (16). The cultivation of professional ethics and the spirit of self-caution is conducive to improving the quality of nursing work and the professional values of new nurses. The weight of emotional control (0.130) was higher than that of humanistic care and nurse etiquette. Considering that the emotions of cancer patients were generally poor, nurses contacted patients most frequently before their death. When faced with the dying state of the patients they were nursing, the nurses would have psychological fluctuations such as regret, anxiety, and fear (17, 18). Emotional control can reduce

the negative emotions of nurses and improve their enthusiasm in dealing with work. The occupational identity and planning weights of the level III indicators were the lowest (0.109), which was considered related to the ability that was not considered as a clinically urgent need. However, the study has pointed out that the professional identity has a positive correlation with the competency and job performance of new nurses (19). Factors that affected the professional identity of new nurses included educational background, internship time, labor and personnel relations, etc. It is recommended that targeted training programs be adopted for new nurses with different academic qualifications (20). Through systematic and targeted training, we can improve the professional identity of new nurses and ultimately improve the post-competency. ⑤ Practical ability (0.326) ranked fifth in the weight of secondary indicators, including condition observation, file writing, system operation, critical thinking, and ward management. The content with the lowest weight of the level was ward management (0.058), but ward management is not only the responsibility of the management position, nurses need to provide patients, families, and other medical staff with nursing related knowledge, also need to effectively take charge of the daily management affairs of the ward and to ensure the smooth progress (21). A good ward manager should have solid knowledge theory, operation technology, good overall planning ability, and communication ability, etc., can do a good job in the ward management, so for new nurse training ward management cannot as the focus, suggestions in the follow-up stratified training to follow up.

CONCLUSION

In the new nurse training content system based on post-competency in cancer hospital constructed in this study, the expert opinions of evaluation indicators at all levels tend to be consistent, with high credibility and a certain degree of science and authority, which can provide a reference for the training of new nurses in the cancer hospital. This study did not test the effectiveness and effect of the training content system. Therefore, the effect of the study of this training content system will be the main content of the next study. It was suggested that hospice care and spiritual care should be included in future research so that new nurses with different academic qualifications could receive targeted training according to the difficulty of the training content.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

ML and JGe are mainly responsible for data statistics and paper writing. JGa and ZM are mainly responsible for data search and training system construction. XW and SW are mainly responsible for designing schemes and overall research. YL is mainly responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by Special Fund for Hospital Management Research Project LC2018D04.

ACKNOWLEDGMENTS

We are grateful to the experts who helped us in the research.

REFERENCES

1. Wildermuth MM, Weltin A, Simmons A. Transition experiences of nurses as students and new graduate nurses in a collaborative nurse residency program. *J Prof Nurs.* (2020) 36:69–75. doi: 10.1016/j.profnurs.2019.06.006
2. Shatto B, Lutz L M. Transition from education to practice for new nursing graduates: a literature review. *Creat Nurs.* (2017) 23:248–54. doi: 10.1891/1078-4535.23.4.248
3. Asber SR. Retention outcomes of new graduate nurse residency programs: an integrative review. *J Nurs Adm.* (2019) 49:430–5. doi: 10.1097/NNA.0000000000000780
4. Chen SF, Fang YW, Wang MH, Wang TF. Effects of an adaptive education program on the learning, mental health and work intentions of new graduate nurses. *Int J Environ Res Public Health.* (2021) 18:5891. doi: 10.3390/ijerph18115891
5. Liu Y, Aungsuroch Y. Current literature review of registered nurses' competency in the global community. *J Nurs Scholarsh.* (2018) 50:191–9. doi: 10.1111/jnu.12361
6. Tan X, Acquah I, Liu H, Li W, Tan S. A critical review on saline wastewater treatment by membrane bioreactor (MBR) from a microbial perspective. *Chemosphere.* (2019) 220:1150–62. doi: 10.1016/j.chemosphere.2019.01.027
7. Charette M, Goudreau J, Bourbonnais A. How do new graduated nurses from a competency-based program demonstrate their competencies? A focused ethnography of acute care settings. *Nurse Educ Today.* (2019) 79:161–7. doi: 10.1016/j.nedt.2019.05.031
8. Kaldan G, Nordentoft S, Herling SF, Larsen A, Thomsen T, Egerod I. Evidence characterising skills, competencies and policies in advanced practice critical care nursing in Europe: a scoping review protocol. *BMJ Open.* (2019) 9:31504. doi: 10.1136/bmjopen-2019-031504
9. Egerod I, Kaldan G, Nordentoft S, Larsen A, Herling SF, Thomsen T, et al. Skills, competencies, and policies for advanced practice critical care nursing in Europe: a scoping review. *Nurse Educ Pract.* (2021) 54:103142. doi: 10.1016/j.nepr.2021.103142
10. Tariman JD, Katz P, Bishop-Royse J, Hartle L, Szubski KL, Enecio T, et al. Role competency scale on shared decision-making nurses: Development and psychometric properties. *SAGE*

Open Med. (2018) 6:2105879614. doi: 10.1177/20503121188 07614
11. Xie J, Wang L, Wang S, Duan Y, Wang K, Zhong Z, et al. What influences new graduate nurses' core competencies transformation to clinical in China? A cross-sectional study. *Nurse Educ Today.* (2021) 100:104855. doi: 10.1016/j.nedt.2021.104855
12. Kukkonen P, Leino-Kilpi H, Koskinen S, Salminen L, Strandell-Laine C. Nurse managers' perceptions of the competence of newly graduated nurses: a scoping review. *J Nurs Manag.* (2020) 28:4–16. doi: 10.1111/jonm.12891
13. Södersved Källestedt ML, Asp M, Letterstål A, Widarsson M. Perceptions of managers regarding prerequisites for the development of professional competence of newly graduated nurses: a qualitative study. *J Clin Nurs.* (2020) 29:4784–94. doi: 10.1111/jocn.15522
14. Widarsson M, Asp M, Letterstål A, Källestedt ML. Newly graduated swedish nurses' inadequacy in developing professional competence. *J Contin Educ Nurs.* (2020) 51:65–74. doi: 10.3928/00220124-20200115-05
15. Pogue D T, O'Keefe M. The effect of simulation-enhanced orientation on graduate nurses: an integrative review. *J Contin Educ Nurs.* (2021) 52:150–6. doi: 10.3928/00220124-20210216-10
16. Monroe HA. Nurses' professional values: influences of experience and ethics education. *J Clin Nurs.* (2019) 28:2009–19. doi: 10.1111/jocn.14806
17. Rush KL, Janke R, Duchscher JE, Phillips R, Kaur S. Best practices of formal new graduate transition programs: AN integrative review. *Int J Nurs Stud.* (2019) 94:139–58. doi: 10.1016/j.ijnurstu.2019.02.010
18. Forbes T R, Scott E S, Swanson M. New graduate nurses' perceptions of patient safety: describing and comparing responses with experienced nurses. *J Contin Educ Nurs.* (2020) 51:309–15. doi: 10.3928/00220124-20200 611-06
19. Horii S, Pham HT, Dang TT, Nguyen CT, Amaike N. Nurses' perception of individual and organizational changes caused by a novel clinical training system for new graduate nurses: a qualitative research using photovoice. *Nurse Educ Today.* (2021) 102:104901. doi: 10.1016/j.nedt.2021. 104901
20. Gregg JC. Perceptions of nurse managers and nurse preceptors: are new graduate nurses displaying competency according to the new graduate nurse performance survey? *J Nurses Prof Dev.* (2020) 36:88–93. doi: 10.1097/NND.0000000000000615
21. Lindfors K, Meretoja R, Kaunonen M, Paavilainen E. Preceptors' perceptions of the elements of a successful and an unsuccessful orientation period for newly graduated nurses. *J Nurs Manag.* (2018) 26:256–62. doi: 10.1111/jonm.12541

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Liu, Geng, Gao, Mei, Wang, Wang and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 23 February 2022
doi: 10.3389/fsurg.2022.850662

Explore the Application Value of Prospective Monitoring Model in the Nursing Management of Breast Cancer Patients During Perioperative Period

Huan Zhang, Yu Duan and Fengming Zhou*

Breast Cancer Center, Affiliated Tumor Hospital of Chongqing University, Chongqing, China

Purpose: To explore the application value of prospective monitoring model in the nursing management of breast cancer patients during perioperative period.

Methods: 300 perioperative breast cancer patients admitted to our hospital from January to August 2021 were randomly divided into the control group ($n = 150$) and the model group ($n = 150$). Both groups used routine nursing management, and the model group added nursing management based on a prospective monitoring model. The quality of surgical nursing, circumference of the upper limbs, and the scores of disability of arm-shoulder-hand (DASH), exerciseofself-care agencyscale (ESCA), social self-esteem scale (SSES), multidimensional fatigue symptom inventory-short form (MFSI-SF) and functional assessment of cancer therapy-breast cancer (FACT-B) were compared of the two groups.

Results: Postoperatively, the quality of surgical nursing was better in the model group than in the control group ($P < 0.05$). At 3 months postoperatively, the number of cases of upper limb lymphedema was higher in both groups than before ($P < 0.05$), but there was no statistical difference between the two groups in the preoperative and 3 months postoperative comparisons ($P > 0.05$). At 3 months postoperatively, the total DASH score was higher than preoperatively in both groups, but lower in the model group than in the control group ($P < 0.05$). After nursing, the ESCA and SSES scores of each dimension were higher in both groups than before, and the model group was higher than the control group ($P < 0.05$). At 3 months postoperatively, the total MFSI-SF score was lower than preoperatively in both groups, and lower in the model group than in the control group ($P < 0.05$). At 3 months postoperatively, the FACT-B scores of each dimensions were higher in the model group than in the control group ($P < 0.05$).

Conclusion: The implementation of nursing management based on a prospective monitoring model for breast cancer patients during the perioperative period has important clinical value in improving the quality of surgical nursing and improving postoperative upper limb lymphedema, upper limb function, self-care ability, social self-esteem, cancer-related fatigue symptoms, quality of life, etc.

Keywords: breast cancer, perioperative, prospective monitoring model, value, application

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Xiaming Pei,
Hunan Cancer Hospital, China
Jianhua Xiao,
University of South China, China

****Correspondence:***
Huan Zhang
www.yzpxb2020@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *08 January 2022*
Accepted: *31 January 2022*
Published: *23 February 2022*

Citation:
Zhang H, Duan Y and Zhou F (2022) Explore the Application Value of Prospective Monitoring Model in the Nursing Management of Breast Cancer Patients During Perioperative Period. Front. Surg. 9:850662. doi: 10.3389/fsurg.2022.850662

INTRODUCTION

Breast cancer has the highest incidence of malignant tumors among women in China and worldwide (1, 2). In China, the 5-year survival rate for breast cancer patients is about 73%, much lower than the 90% in the United States. The combination of surgery, radiation and chemotherapy treatment creates favorable conditions for saving the lives of breast cancer patients and prolonging their postoperative survival. However, the treatment is prone to several complications, such as upper limb lymphedema (3), upper limb dysfunction (4), subcutaneous effusion (5), flap necrosis (6), cancer-related fatigue (7), pain syndrome (8), Toxic side effects during radiotherapy and chemotherapy (9), anxiety and depression (10), and sleep disorders (11). All of these complications can seriously impair the physical, functional, emotional and family/social health of patients, which in turn affects the postoperative recovery process and the quality of postoperative survival. For this reason, while clinically providing advanced surgical techniques for breast cancer patients, it is also necessary to focus on the postoperative rehabilitation.

Combined with previous studies, our rehabilitation care for perioperative breast cancer patients lacks individual relevance and overall predictability. On the one hand, the health education for patients by medical and nursing staff is too mechanical and formalized, without paying attention to the real feelings and needs of each patient from a humanistic perspective, resulting in patients' deviation or disinterest in the content of the education, thus failing to achieve the purpose of cultivating patients' health self-care ability. On the other hand, the focus of medical staff's care is to solve the problems that patients have already shown. The lack of prospective intervention for possible complications or psychological problems is not conducive to the resolution of postoperative physical and mental problems. A new, intuitive, and comprehensive humanized nursing management program is yet to be implemented.

The prospective detection model is a set of clinical care management protocols proposed by Stout et al. (12) for the perioperative and Post-discharge follow-up phases of breast cancer. In previous studies abroad, it has the roles of providing health education guidance, monitoring breast cancer treatment-related physical and mental problems and dysfunction, identifying early injuries, introducing means of rehabilitation interventions when determining impairments, and promoting patients' health self-care behaviors. In recent years, our department has introduced a nursing management program based on a prospective monitoring model into the nursing management of perioperative breast cancer patients, and observed the impact of the prospective monitoring model on the postoperative recovery of breast cancer patients in China, in order to provide a favorable reference for the selection of a nursing model for perioperative breast cancer patients in China.

MATERIALS AND METHODS

Research Object

Three hundred perioperative breast cancer patients admitted to our hospital from January to August of 2021 were selected. Inclusion criteria: age ≥20 years; belonged to primary breast cancer; first diagnosis of breast cancer by pathological examination or imaging techniques; clinical stage 0∼III; single lesion without lymph node or distant metastasis; those who intended to be treated by modified radical surgery or breast-conserving surgery in our hospital; those who communicated well and could cooperate with the study; those who voluntarily signed the informed consent form. Exclusion criteria: combination of other malignant tumors or breast cancer caused by metastasis from other malignant tumors; combination of upper limb disability; combination of cardiogenic, nephrogenic or dystrophic edema; contraindication to surgery; pregnancy or lactation; combination of diabetes mellitus, immune disorders or severe liver diseases; severe intellectual deficiency, mental illness or cognitive impairment. Patients who met the inclusion criteria were randomly and equally divided into the control group ($n = 150$), and the model group ($n = 150$). Comparing the general conditions of age, menstruation, and type of surgery between the two groups, there were no statistical differences and were comparable ($P > 0.05$). As shown in **Table 1**.

TABLE 1 | Comparison of general conditions of two groups.

Itmes	Control group ($n = 150$)	Model group ($n = 150$)	t/χ^2 value	P value
Age (years old)	45.26 ± 6.02	44.98 ± 5.89	0.407	0.684
BMI (kg/m^2)	22.89 ± 1.54	22.78 ± 1.62	0.603	0.547
Years of education (years)	12.54 ± 1.56	12.60 ± 1.55	0.334	0.739
Menopause or not (%)			0.484	0.487
Yes	79 (52.67)	85 (56.67)		
No	71 (47.33)	65 (43.33)		
Location of onset (%)			0.120	0.729
Left	77 (51.33)	74 (49.33)		
Right	73 (48.67)	76 (50.67)		
Pathological type (%)			0.140	0.708
Invasive cancer	102 (68.00)	105 (70.00)		
Non-invasive cancer	48 (32.00)	45 (30.00)		
Clinical stage (%)			1.113	0.774
0	12 (8.00)	10 (6.67)		
I	64 (42.67)	57 (38.00)		
II	44 (29.33)	50 (33.33)		
III	30 (20.00)	33 (22.00)		
Surgery type (%)			0.133	0.715
Modified radical mastectomy	97 (64.67)	100 (66.67)		
Breast conservation	53 (35.33)	50 (33.33)		

Research Methods

Routine nursing management for the control group. That was: preoperative stage: routine preoperative preparations (such as skin preparation, drug preparation, preoperative examination,

etc.); reminded to start fasting and drinking at 22:00 on the night preoperatively; relieved patients' preoperative anxiety, etc. Early postoperative stage: wound and drainage tube care, elevation and braking of the affected limb, distribution of case management manuals, instruction on rehabilitation of the affected limb and discharge precautions, etc. Follow-up stage: patients were followed up by telephone 3 days after discharge. The follow-up visit includes answering patients' concerns, instructing them on the methods of living food, pipe maintenance and rehabilitation training, and helping them to arrange matters related to hospital admission and return to hospital for review.

The model group was applied routine nursing management + nursing management based on a prospective monitoring model. This was:

Preoperative stage: The investigators used an assessment tool to conduct a baseline assessment of the patients and, based on the assessment, provided health education on preoperative and postoperative care plans before surgery. Patients were instructed to learn skills and methods of injury recognition, self-monitoring, self-management, and health promotion before surgery. Specifically: ① Preoperatively, organizing patients to watch breast cancer health education videos and distributing case management manuals for learning about surgery, treatment-related knowledge, procedures and precautions; ② Individualized psychological care for the patient's psychological state was carried out, such as instructing the patient to relieve psychological pressure through relaxation training or meditation; ③ Instructing patients in postoperative rehabilitation nursing methods, such as raising and braking the upper limbs, and informing patients about the methods of ankle pump exercise, movement and functional exercise of the affected limb; ④ Guiding patients to self-care nursing methods for postoperative wounds and drainage tubes to prevent complications; ⑤ Guiding patients to self-identify and self-detect possible precursor symptoms, and informing patients of ways to avoid future risks, such as avoiding the use of affected limbs to measure blood pressure, blood draw, and infusion to prevent lymphedema; ⑥ Analysis and prevention of various problems that might occur intraoperatively by means of quality control management methods or failure mode and effect analysis (13). For example, we strictly checked the instruments and equipment in the operating room before surgery to ensure their normalcy, sterility and integrity, and completely recorded the use and handling of intraoperative items.

Early postoperative stage: that was the period of time from the end of surgery to discharge. Patients' physical and mental status was reassessed by the researcher and self-assessed at any time by the patients themselves. Based on the assessment results, the patient's early rehabilitation training components were again developed and directed. Specifically: ① On the day after surgery, guiding patients to exercise the ankle pump to promote blood and lymphatic return to the lower extremities; ② On the 1st postoperative day, patients underwent aerobic exercise and health care providers again provided health education on postoperative care, exercise and functional exercise, and nutrition; ③ Conducting a health talk on breast cancer-related knowledge every Thursday to instruct patients on damage recognition and self-management methods; ④ On the day of discharge, re-guidance Post-discharge motor function training, risk identification, injury management, psychological counseling, and self-monitoring for patients and their families; ⑤ Baseline data testing was repeated during this period, and individualized intervention protocols were initiated once patients' self-assessment reports or researcher monitoring identified physical impairment (for example, when the arm circumference difference of the same measurement point of the affected and healthy limb was >2.0 cm, or when there was obvious pain or limited mobility).

Post-discharge continuous monitoring stage: nn the basis of routine return to hospital and review follow-up, the researchers assessed the physical and mental status of patients at 1, 2 and 3 months after surgery, and patients self-assessed at any time. Based on the assessment results, the researchers provided health education to patients on self-monitoring and self-management, and taught them injury recognition (e.g., early detection of related sequelae) and health promotion (e.g., methods of functional rehabilitation of the affected limb, maintaining healthy lifestyle behaviors) skills. At follow-up, patients were assessed for recovery of the affected limb, cause-related fatigue, occurrence of postoperative complications, quality of life, and self-care ability. Individualized interventions were initiated if changes were monitored during this period compared to the preoperative period, and if not, follow-up was continued after a 1-month interval.

Observation Index

Quality of surgical nursing: postoperatively, the quality of surgical nursing in both groups was assessed by our own "Surgical Nursing Care Quality Assessment Form". The Cronbach's α coefficient was 0.735. It contained 6 dimensions: material management, aseptic situation, nursing records, health education, basic nursing, knowledge assessment. Each item was scored from 0 to 100, and the score was positively correlated with the quality of surgical nursing.

Upper limb circumference: Preoperatively and 3 months postoperatively, upper limb circumference was measured in both groups to assess the occurrence of upper limb lymphedema. Upper limb lymphedema was diagnosed if the difference in arm circumference between the same measurement point on the healthy and the affected side was >2.0 cm.

Disability of arm-shoulder-hand (DASH) score: The functional recovery of the affected limbs in both groups was assessed by DASH preoperatively and 3 months postoperatively. It contained 2 parts, A (23 items) and B (7 items). Each item was scored 1–5, total score = (A+B total score −30) /1.2. Total score 0∼100 represented normal∼extremely restricted upper limb function.

Exercise of self-care agency scale (ESCA) score: Before and after nursing, the self-care ability of both groups was assessed by ESCA. It included 4 dimensions: health knowledge level (0–68 scores), self-concept (0–32 scores), self-responsibility (0–24 scores) self-nursing skills (0–48 scores). Scores were directly proportional to self-care ability.

Social self-esteem scale (SSES) scores: Before and after care, social self-esteem was assessed by SSES in both groups. It included 20 items in 3 dimensions: social self-esteem, behavioral self-esteem, and appearance self-esteem. A total of 100 points were scored, and the scores were proportional to the level of self-esteem.

Multidimensional fatigue symptom inventory-short form (MFSI-SF) score: Preoperatively and 3 months postoperatively, the degree of cancer-caused fatigue was assessed by MFSI-SF in both groups. It contained 5 dimensions: physical fatigue (0–24 scores), mental fatigue (0–20 scores), emotional fatigue (0–20 scores), general fatigue (0–20 scores), and vitality (0–24 scores). The total score was the total score of the first 4 dimensions–vitality score. The total score was proportional to the level of fatigue.

Functional assessment of cancer therapy-breast cancer (FACT-B) score: 3 months postoperatively, the quality of life was assessed by FACT-B in both groups. It included 5 dimensions: somatic condition (0–28 scores), functional condition (0–28 scores), emotional condition (0–24 scores), social/family condition (0–28 scores), and additional concerns (0–36 scores). The score was directly proportional to the quality of life.

Statistical Methods

SPSS 22.0 software was applied, and the measurement data were expressed as mean ± standard deviation and compared by *t*-test. Count data were expressed as ratios, and the χ^2 test was used for comparison. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of the Quality of Surgical Nursing of Two Groups

Postoperatively, the model group had better quality of nursing scores than the control group on material management, aseptic situation, nursing records, health education, basic nursing, knowledge assessment ($P < 0.05$). As shown in **Figure 1**.

Comparison of Upper Limb Lymphedema of Two Groups

At 3 months postoperatively, the number of cases of upper limb lymphedema was higher in both groups than before ($P < 0.05$), but there was no statistical difference between the two groups in the preoperative and 3 months postoperative comparisons ($P > 0.05$). As shown in **Figure 2**.

Comparison of Total DASH Scores of Two Groups

At 3 months postoperatively, the total DASH score was higher than preoperatively in both groups, but lower in the model group than in the control group ($P < 0.05$). As shown in **Figure 3**.

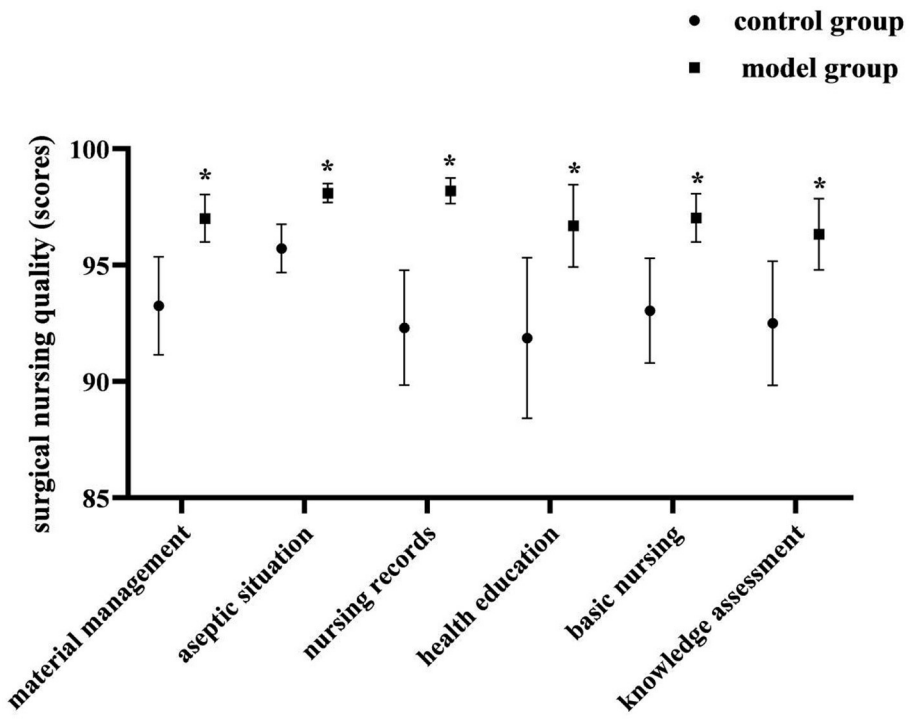


FIGURE 1 | Comparison of the quality of surgical nursing of two groups. Compared with the control group in the same dimension, *$P < 0.05$.

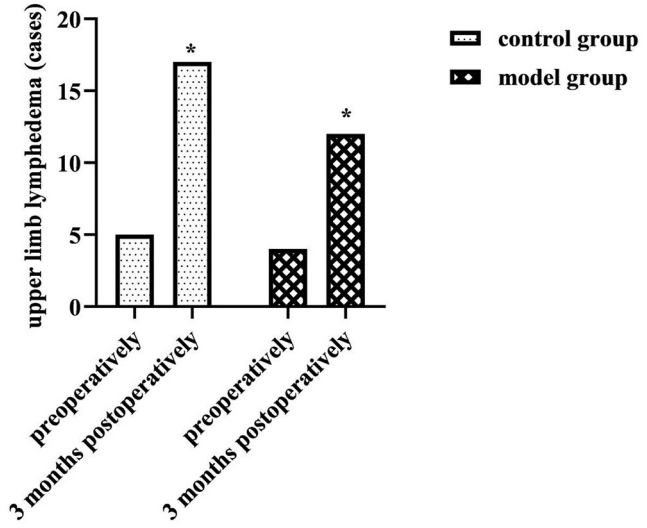


FIGURE 2 | Comparison of upper limb lymphedema of two groups. Compared with the same group preoperatively, $^{*}P < 0.05$.

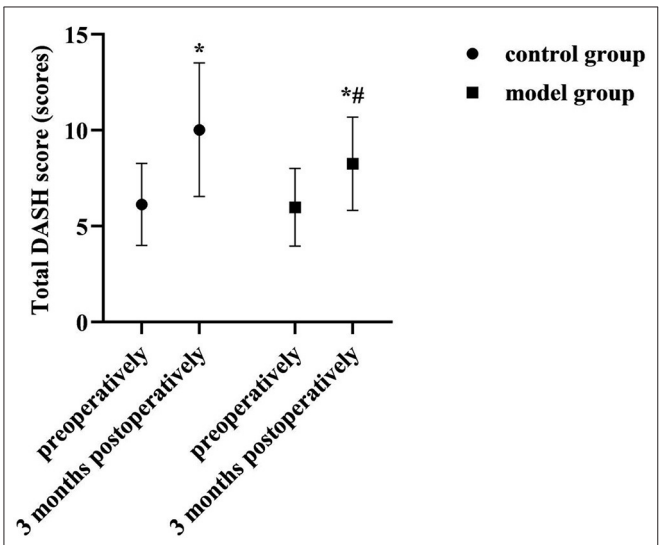


FIGURE 3 | Comparison of total DASH scores of two groups. Compared with the same group preoperatively, $^{*}P < 0.05$; compared with the control group 3 months postoperatively, $^{\#}P < 0.05$.

Comparison of ESCA Scores of Each Dimension of Two Groups

After nursing, the ESCA scores of each dimension were higher in both groups than before, and the model group was higher than the control group ($P < 0.05$). As shown in **Figure 4**.

Comparison of SSES Scores of Each Dimension of Two Groups

After nursing, the SSES scores of each dimension were higher in both groups than before, and the model group was higher than the control group ($P < 0.05$). As shown in **Figure 5**.

Comparison of Total MFSI-SF Scores of Two Groups

At 3 months postoperatively, the total MFSI-SF score was lower than preoperatively in both groups, and lower in the model group than in the control group ($P < 0.05$). As shown in **Figure 6**.

Comparison of FACT-B Scores of Each Dimension of Two Groups

At 3 months postoperatively, the FACT-B scores of each dimension were higher in the model group than in the control group ($P < 0.05$). As shown in **Figure 7**.

DISCUSSION

Surgery is an indispensable part of the comprehensive treatment of breast cancer, and high-quality surgical care is of great significance to increase the success rate of surgery and prolong the survival rate of patients. In the results of this study, the quality of surgical nursing was better in the model group than in the control group ($P < 0.05$). Analyzing its reasons, this study implements a nursing management program based on a prospective monitoring model. Through prospective intervention methods such as quality control management or failure mode effect analysis, it analyzes the causes of various problems and loopholes that may occur during surgery under the conventional nursing mode, and proposes appropriate and effective intervention plans and improvements accordingly. Therefore, the purpose of significantly improving the quality of surgical care can be achieved.

Upper extremity lymphedema is one of the most common complications during the 3 months to 3 years after breast cancer surgery (14). Statistically, its incidence could increase from 5 to 11% at 3–6 months postoperatively and up to 75% at 2 years postoperatively (15). It can cause chronic swelling, pain, numbness, dysfunction and other symptoms in the affected limb, subsequently leading to a series of physical, psychological and social problems (16). The incidence of upper limb lymphedema in the control group (3.33%) and model group (2.67%) preoperatively in this study was similar to previous statistics. At 3 months postoperatively, the incidence of lymphedema was higher in both the control group (11.33%) and the model group (8%) than preoperatively ($P < 0.05$), but there was no statistical difference between the two groups ($P > 0.05$). This suggested that the use of a prospective monitoring model for breast perioperative patients was no different from conventional care in preventing postoperative upper limb lymphedema. This might be related to the occult of the onset of upper limb lymphedema as a chronic complication (17). Moreover, the disease mostly occurs after 3 months postoperatively, while the postoperative observation period in this study was intercepted only up to 3 months postoperatively. Therefore, the results of this study cannot prove the long-term effect of the prospective monitoring model in the prevention and treatment of upper limb lymphedema.

Upper limb dysfunction is another common complication of breast cancer surgery. Its onset is associated with inadequate

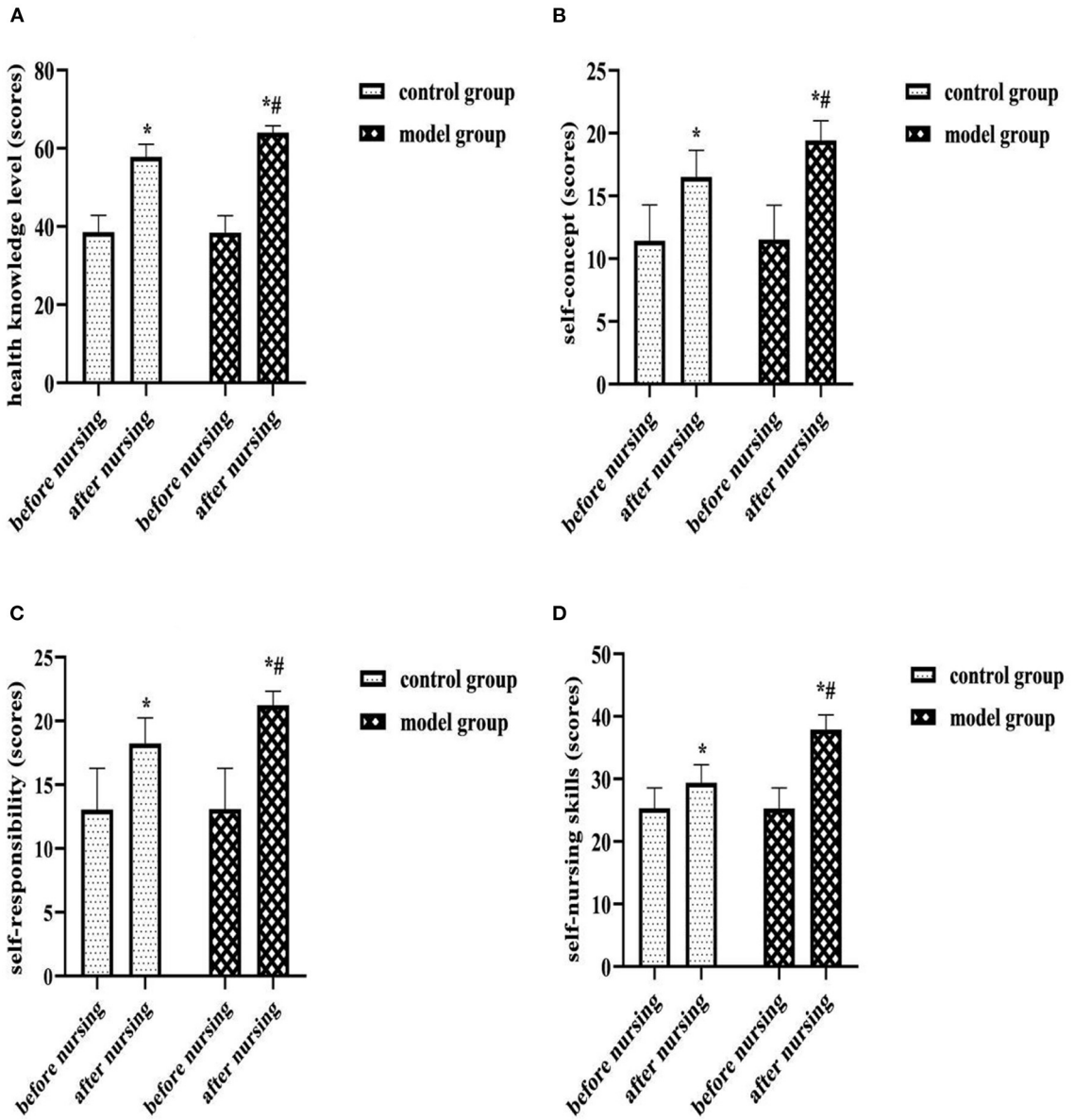


FIGURE 4 | (A) Health knowledge level (scores). **(B)** Self-concept (scores). **(C)** Self-responsibility (scores). **(D)** Self-nursing skills (scores). Comparison of ESCA scores of each dimension of two groups. Compared with the same group before nursing, $^{*}P < 0.05$; compared with the control group after nursing, $^{\#}P < 0.05$.

execution or inappropriate modalities of postoperative functional training of patients, inadequate education or inadequate expertise of health care professionals. In the results of this study, at 3 months postoperatively, the total DASH score was higher than preoperatively in both groups, but lower in the model group than in the control group ($P < 0.05$); After nursing, the ESCA scores of each dimension were higher in both groups than before, and the model group was higher than the control group ($P < 0.05$). Analyzing the reasons for this, we provided repeated rehabilitation training instruction and injury recognition, self-monitoring and self-management education during the preoperative, early postoperative and Post-discharge continuous monitoring stages in the care management of the model group. This not only helped to meet patients' needs for knowledge about breast cancer rehabilitation and strengthen their understanding and memory of the knowledge, but also helped to promote patients' health self-care behaviors and implementation. Moreover, continuous monitoring management and individualized intervention during the follow-up period after discharge can effectively ensure the integrity and continuity of postoperative functional training of patients, and play a certain role in supervising and regulating patients' health self-care behaviors. Therefore, the implementation of nursing management based on the prospective monitoring model is

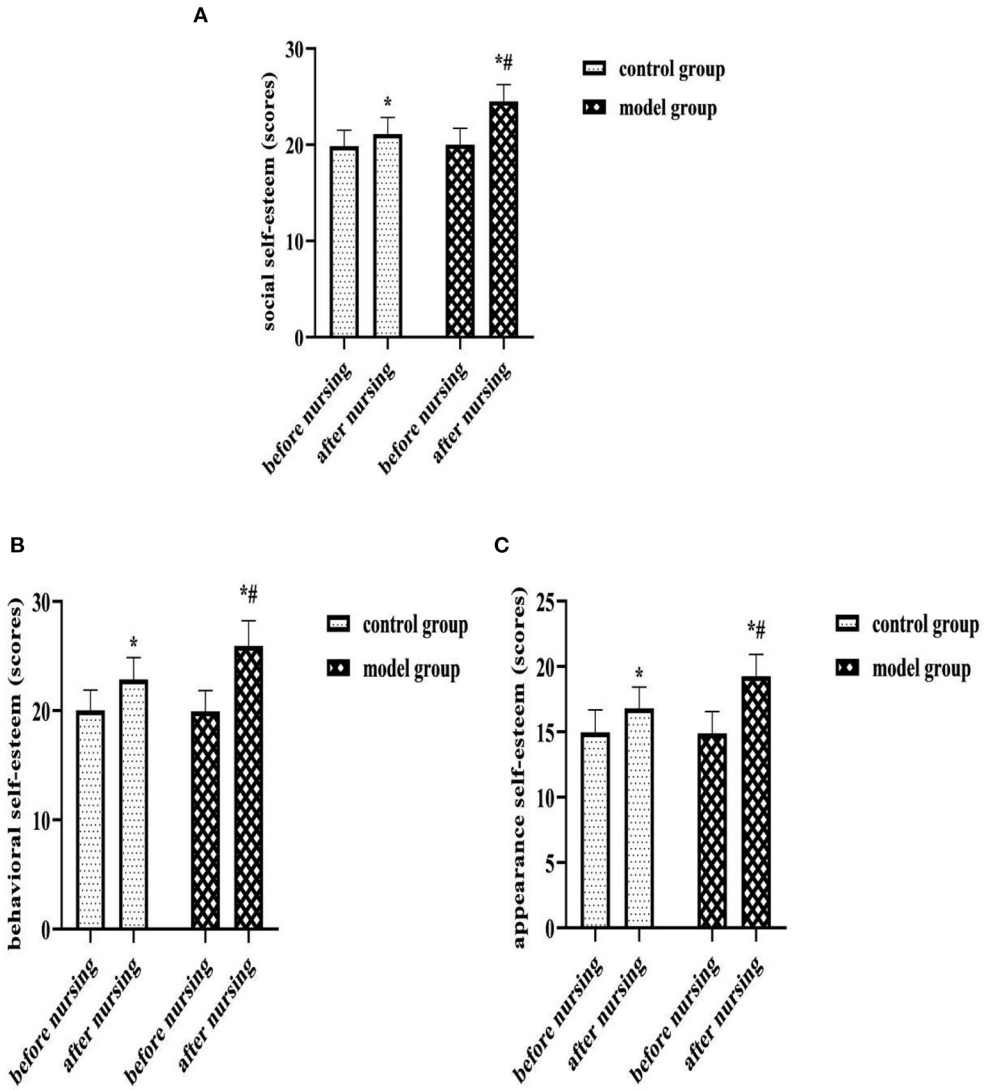


FIGURE 5 | (A) Social self-esteem (scores). **(B)** Behavioral self-esteem (scores). **(C)** Appearance self-esteem (scores). Comparison of SSES scores of each dimension of two groups. Compared with the same group before nursing, $^{*}P < 0.05$; compared with the control group after nursing, $^{\#}P < 0.05$.

very beneficial to promote the rehabilitation of the affected limb function and the self-care ability of patients after breast cancer surgery.

Self-esteem is the result of self-evaluation and social comparison triggered by social situations, social self-esteem is a self-maintenance mechanism for individuals under external pressure, and a high social self-esteem state can effectively isolate individuals from stress in the environment (18). Based on the dual pressure of life threatening and loss of female physical characteristics, breast cancer surgery patients have more sensitive internal indicators and lower self-esteem levels compared to patients with other malignancies (19). After care in this study, patients in the model group had significantly higher social, behavioral, and appearance self-esteem levels than the control group ($P < 0.05$). Analyzing the reasons, the application of the prospective monitoring model in this group, the researchers' interval assessment of patients' physical and mental status could identify their potential negative emotional threats and psychiatric treatment needs through their behavioral responses in a timely manner, and provided positive psychological counseling accordingly, which could help patients relieve psychological stress, correct disease perceptions, establish treatment concepts, and rebuild their self-image in a timely manner. As a result, it was beneficial to restore the patient's level of social self-esteem.

Cancer-related fatigue is a persistent subjective feeling of fatigue and lack of energy associated with tumors or antineoplastic treatment (20). It can affect many aspects of

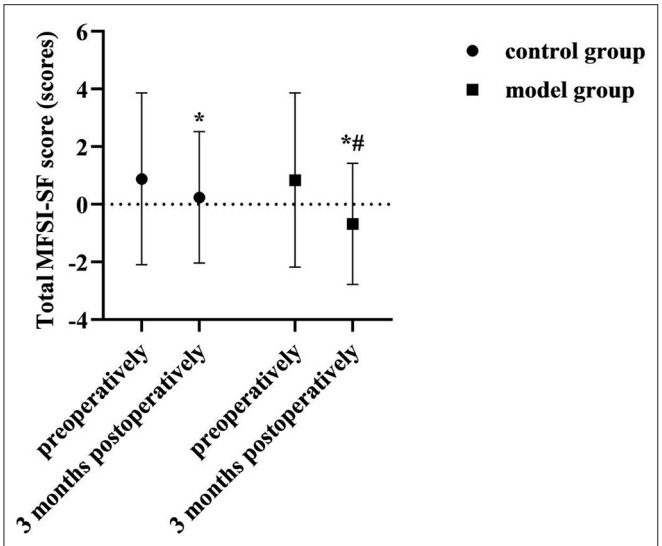


FIGURE 6 | Comparison of total MFSI-SF scores of two groups. Compared with the same group preoperatively, $^{*}P < 0.05$; compared with the control group 3 months postoperatively, $^{\#}P < 0.05$.

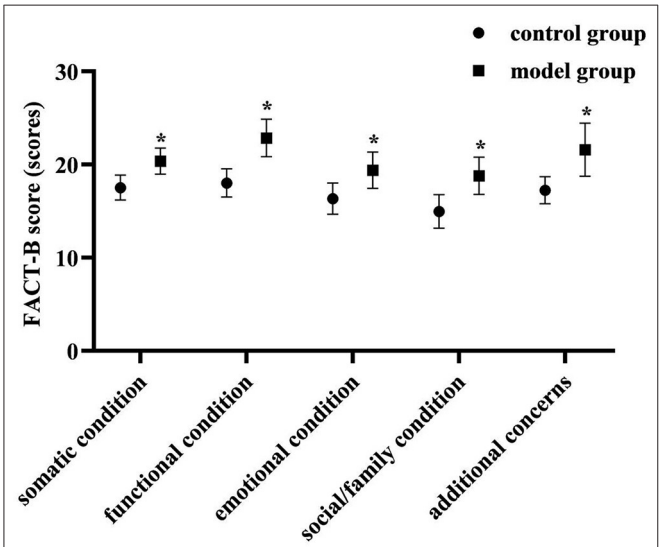


FIGURE 7 | Comparison of FACT-B scores of each dimension of two groups. Compared with the control group in the same dimension, $^{*}P < 0.05$.

patients, such as body, emotion, function, cognition and social interaction, etc., so it is also closely related to the decline of the patient's quality of life (21). At 3 months postoperatively in this study, the total MFSI-SF score was lower than preoperatively in both groups, and lower in the model group than in the control group ($P < 0.05$). At 3 months postoperatively, the FACT-B scores of each dimensions were higher in the model group than in the control group ($P < 0.05$). This suggested that the implementation of care management based on a prospective monitoring model contributed to the improvement of fatigue symptoms and quality of life in patients after breast cancer surgery. After breast cancer surgery, the inevitable decrease in self-care ability and negative psychological status can cause cancer-related fatigue symptoms. In this study, the monitoring and positive guidance of patients' physical and mental status were emphasized in the preoperative, early postoperative and Post-discharge continuous monitoring stages. Among them, the method of instructing patients in relaxation training and aerobic exercise training helped to reduce the level of physical fatigue of patients; the method of instructing patients to meditate helped to reduce the level of mental fatigue of patients. And helping patients learned self-monitoring and self-management was helpful for timely individualized intervention plans when abnormal physical and mental states were found. Thus, the implementation of nursing management based on a prospective monitoring model for perioperative breast cancer patients is an effective way to reduce cancer-related fatigue and improve the quality of life of patients after surgery.

CONCLUSION

Supportive care is an extremely important part of the rehabilitation process for breast cancer patients. The application of the prospective monitoring model of this study in breast cancer patients during perioperative period could effectively address multiple issues, including improving the quality of surgical nursing for breast cancer patients, protecting musculoskeletal health after surgery, promoting patients' health self-care behaviors and abilities, rebuilding social self-esteem and self-image, reducing cancer-caused fatigue symptoms, and improving quality of life.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Tumor Hospital of Chongqing University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors of this study have made equal contributions, including research design, result testing, data statistics, and paper writing.

FUNDING

Decision Consultation and Management Innovation Project of Shapingba District, Chongqing, Jcd202118.

REFERENCES

1. Barzaman K, Karami J, Zarei Z, Hosseinzadeh A, Kazemi MH, Moradi-Kalbolandi S, et al. Breast cancer: biology, biomarkers, and treatments. *Int Immunopharmacol*. (2020) 84:106535. doi: 10.1016/j.intimp.2020.106535
2. Britt KL, Cuzick J, Phillips KA. Key steps for effective breast cancer prevention. *Nat Rev Cancer*. (2020) 20:417–36. doi: 10.1038/s41568-020-0266-x
3. Surmeli M, Cinar Ozdemir O. The effect of upper limb lymphedema in posture of patients after breast cancer surgery. *J Back Musculoskelet Rehabil*. (2021) 29. doi: 10.3233/BMR-210049
4. Siqueira TC, Frágoas SP, Pelegrini A, de Oliveira AR, da Luz CM. Factors associated with upper limb dysfunction in breast cancer survivors. *Support Care Cancer*. (2021) 29:1933–40. doi: 10.1007/s00520-020-05668-7
5. Yang C, Wang X, Zhang G, Yang L, Guo X, Wang X, et al. Assessment of the use of latissimus dorsi restoration during modified radical mastectomy in breast cancer patients. *Mol Clin Oncol*. (2017) 7:1089–92. doi: 10.3892/mco.2017.1435
6. Pruimboom T, Schols RM, van Kuijk SM, van der Hulst RR, Qiu SS. Indocyanine green angiography for preventing postoperative mastectomy skin flap necrosis in immediate breast reconstruction. *Cochrane Database Syst Rev*. (2020) 4:CD013280. doi: 10.1002/14651858.CD013280.pub2
7. Gupta A, Hussain SM, Nayyar HK, Sonthwal N, Manaktala R, Chaturvedi H. Perception, magnitude, and implications of cancer-related fatigue in breast cancer survivors: study from a developing country. *J Cancer Res Ther*. (2021) 17:998–1002. doi: 10.4103/jcrt.JCRT_151_19
8. Reghunathan M, Rahgozar P, Sbitany H, Srinivasa DR. Breast reconstruction does not increase the incidence of postmastectomy pain syndrome: results of a meta-analysis. *Ann Plast Surg*. (2020) 84:611–7. doi: 10.1097/SAP.0000000000002062
9. Liyanage PY, Hettiarachchi SD, Zhou Y, Ouhtit A, Seven ES, Oztan CY, et al. Nanoparticle-mediated targeted drug delivery for breast cancer treatment. *Biochim Biophys Acta Rev Cancer*. (2019) 1871:419–33. doi: 10.1016/j.bbcan.2019.04.006
10. Lovelace DL, McDaniel LR, Golden D. Long-term effects of breast cancer surgery, treatment, and survivor care. *J Midwifery Womens Health*. (2019) 64:713–24. doi: 10.1111/jmwh.13012
11. Schreier AM, Johnson LA, Vohra NA, Muzaffar M, Kyle B. Post-treatment symptoms of pain, anxiety, sleep disturbance, and fatigue in breast cancer survivors. *Pain Manag Nurs*. (2019) 20:146–51. doi: 10.1016/j.pmn.2018.09.005
12. Stout NL, Binkley JM, Schmitz KH, Andrews K, Hayes SC, et al. A prospective surveillance model for rehabilitation for women with breast cancer. *Cancer*. (2012) 118:2191–200. doi: 10.1002/cncr.27476
13. Pueyo-López C, Sánchez-Cuervo M, Vélez-Díaz-Pallarés M, Ortega-Hernández-Agero T, Salazar-López de Silanes EG. Healthcare failure mode and effect analysis in the chemotherapy preparation process. *J Oncol Pharm Pract*. (2021) 27:1588–95. doi: 10.1177/1078155220962189
14. Borman P, Yaman A, Yasrebi S, Özdemir O. The importance of awareness and education in patients with breast cancer-related lymphedema. *J Cancer Educ*. (2017) 32:629–33. doi: 10.1007/s13187-016-1026-1
15. Ammitzbøll G, Johansen C, Lanng C, Andersen EW, Kroman N, Zerahn B, et al. Progressive resistance training to prevent arm lymphedema in the first year after breast cancer surgery: results of a randomized controlled trial. *Cancer*. (2019) 125:1683–92. doi: 10.1002/cncr.31962
16. Simon M, Vignes S. Enquête en médecine générale sur les lymphœdèmes du membre supérieur après cancer du sein [General practitioner questionnaire concerning upper limb lymphedema after breast cancer]. *J Med Vasc*. (2019) 44:3–8. doi: 10.1016/j.jdmv.2018.11.004
17. Polat AV, Ozturk M, Polat AK, Karabacak U, Bekci T, Murat N. Efficacy of ultrasound and shear wave elastography for the diagnosis of breast cancer-related lymphedema. *J Ultrasound Med*. (2020) 39:795–803. doi: 10.1002/jum.15162
18. Aprilianto E, Lumadi SA, Handian FI. Family social support and the self-esteem of breast cancer patients undergoing neoadjuvant chemotherapy. *J Public Health Res*. (2021) 10:2234. doi: 10.4081/jphr.2021.2234
19. Yektatalab S, Ghanbari E. The relationship between anxiety and self-esteem in women suffering from breast cancer. *J Midlife Health*. (2020) 11:126–32. doi: 10.4103/jmh.JMH_140_18
20. Thong MSY, van Noorden CJF, Steindorf K, Arndt V. Cancer-related fatigue: causes and current treatment options. *Curr Treat Options Oncol*. (2020) 21:17. doi: 10.1007/s11864-020-0707-5
21. Pearson EJM, Morris ME, di Stefano M, McKinstry CE. Interventions for cancer-related fatigue: a scoping review. *Eur J Cancer Care*. (2018) 27. doi: 10.1111/ecc.12516

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhang, Duan and Zhou. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 23 February 2022
doi: 10.3389/fsurg.2022.842823

Expression of Enhancer-Binding Protein CEBPA mRNA and Protein in Ovarian Cancer and Its Relationship With Pathobiological Characteristics

Shufang Mi[1]*, *Limei Zhang*[1], *Mo Li*[1], *Zhiting Dong*[2], *Chenchen Tian*[1] and *Minwen Fu*[2]

[1] Gynaecology and Obstetrics, Affiliated Hospital of Beihua University, Jilin City, China, [2] Gynaecology and Obstetrics, Jilin City Maternity Hospital, Jilin City, China

Ovarian cancer is a common malignant tumor, its early onset is hidden, lack of specific symptoms, the location of the lesion is particularly hidden, which makes it difficult to find ovarian lesions by general detection, making it difficult to make an early clinical diagnosis. Therefore, it is still the focus and difficulty of ovarian cancer research to find the means of early diagnosis and prognosis of ovarian cancer. Cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT) enhancer-binding protein α (CEBPA) has been proved to be involved in cell metabolism, proliferation, and differentiation. In this study, the expression of CEBPA mRNA and protein in normal ovary, epithelial ovarian cyst, ovarian borderline tumor, and ovarian cancer was detected, the relationship between CEBPA and pathobiological characteristics of ovarian cancer was discussed, and its influence on the prognosis of patients with ovarian cancer was analyzed. The results showed that the expression of CEBPA mRNA and protein in patients with ovarian borderline tumor and ovarian cancer is high, and the expression of CEBPA has no obvious correlation with the pathobiological characteristics of patients with ovarian cancer, and the high expression of CEBPA has an important value in the diagnosis of ovarian cancer, and it is also a poor prognostic factor of the disease.

Keywords: ovarian cancer, CCAAT enhancer-binding protein α, protein, pathobiological characteristics, prognosis

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Xiaming Pei,
Hunan Cancer Hospital, China
Qiang Wang,
Guizhou University, China

***Correspondence:**
Shufang Mi
caohua64@126.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *24 December 2021*
Accepted: *12 January 2022*
Published: *23 February 2022*

Citation:
Mi S, Zhang L, Li M, Dong Z, Tian C and Fu M (2022) Expression of Enhancer-Binding Protein CEBPA mRNA and Protein in Ovarian Cancer and Its Relationship With Pathobiological Characteristics. Front. Surg. 9:842823. doi: 10.3389/fsurg.2022.842823

INTRODUCTION

Ovarian cancer is closely related to factors, such as heredity and hormone level. It is a complicated process that involves many factors, genes, and steps, and the peak period of ovarian cancer is over 45 years old (1). The clinical manifestations of ovarian cancer are mostly pain, and some patients may be accompanied by lower abdominal mass, irregular menstruation, etc. According to the global cancer report, in 2020, 4.43 million cases of cancer deaths among women worldwide, i.e., 210,000 cases of ovarian cancer (2). The main features of ovarian cancer are high morbidity and mortality, early-onset concealment, lack of specific symptoms, rapid progression, and high malignancy (3, 4). In addition, the ovary is deep in the pelvic cavity, with a special shape, particularly, hidden lesion location and diverse histological types. Therefore, it is difficult to detect ovarian lesions in general detection, making early clinical diagnosis more difficult (5). Cytoreductive surgery and adjuvant chemotherapy are common methods for the treatment of ovarian cancer, which are effective for more than 80% of patients with ovarian cancer and have achieved remarkable curative effects.

However, due to the serious drug resistance of chemotherapy drugs, the recurrence rate of patients after treatment is high and the prognosis is not good (6). Therefore, we need to take measures to improve patient outcomes.

Cytosine-cytosine-adenosine-adenosine-thymidine/enhancer-binding proteins (C/EBPs) is a transcriptional regulatory factor of eukaryotic cells discovered by Graves' team in 1987. The C/EBP family has six members, C/EBPα, C/EBPβ, C/EBPγ, C/EBPδ, C/EBPε and C/EBPζ, and C/EBP α [CCAAT enhancer-binding protein α (CEBPA)], that contains 358 amino acids and is encoded by the CEBPA gene, with a total length of 3,318 bp and no intron (7). This transcription factor can inhibit cell proliferation by interacting with other proteins or regulating the chromatin remodeling complex. At the same time, CEBPA is involved in the regulation of hematopoiesis and the terminal differentiation of adipocytes, different epithelial cells, and other types of cells (8, 9). CEBPA not only balances cell proliferation and differentiation but also regulates cell metabolism, inhibits the process of the cell cycle, and participates in the mitosis of many cell lines. These functions can well-show the cell growth inhibition activity of CEBPA (10, 11).

Up to now, there has been no report describing how CEBPA is expressed in ovarian cancer tissues, and how the change of its expression affects the occurrence, prognosis of ovarian cancer. By detecting the expression of CEBPA mRNA and protein in ovarian cancer, the relationship between CEBPA level and clinicopathological features of ovarian cancer and its influence on the prognosis of patients were analyzed, so as to provide some basis for guiding the clinical treatment of ovarian cancer.

MATERIALS AND METHODS

Research Object

From June 2015 to June 2018, 14 cases of normal ovary patients with non-ovarian diseases who received gynecological surgery, 38 cases of epithelial ovarian cyst, 10 cases of ovarian borderline tumor, and 71 cases of ovarian cancer in our hospital were selected. The mean age of the research object was (52.94 ± 5.18) years, there was no difference in age between the four groups. Inclusion criteria were as follows: confirmed by pathological examination; patients were scheduled for surgical treatment, and the complete lesion tissue/paracancerous tissue was obtained during the operation, but no radiotherapy, chemotherapy, and biological immunotherapy were performed before operation; Cognitive function was normal; clinical data were complete. Exclusion criteria were as follows: complicated with serious organic diseases; combined with other malignant tumors; complicated with immune system diseases; coagulation dysfunction; and mental disorder.

Research Methods

Tissue Collection

Normal ovary, epithelial ovarian cyst, ovarian borderline tumor, and ovarian cancer tissues were cut out during operation, then frozen in liquid nitrogen for 30 min and stored in −80°C refrigerator. Part of the tissue was fixed with 10% formaldehyde, then embedded in paraffin, 4-μm thick sections were prepared for later use.

TABLE 1 | Primer sequence.

Primer	Forward (5′ → 3′)	Reverse (5′ → 3′)
CEBPA	AACACGAAGCACGATCAGTCC	CTCATTTTGGCAAGTATCCGA
GAPDH	TGTTGCCATCAATGACCCCTT	CTCCACGACGTACTCAGCG

Cytosine-Cytosine-Adenosine-Adenosine-Thymidine Enhancer-Binding Protein α mRNA Detection

Total RNA was extracted from frozen samples with TRIZOL reagent. According to the instructions of the reverse transcription PCR (RT-PCR) kit, RT reaction was carried out with corresponding RT primers to synthesize the first strand of cDNA. The conditions were as follows: 42°C for 60 min, 99°C for 5 min, 4°C for 5 min, and −20°C for storing the first strand of cDNA. Real-time fluorescence quantitative PCR was used for amplification, pre-denaturation at 95°C for 3 min, then 94°C for 30 s, 72°C for 30 s, totally 23–31 cycles, prolonged at 72°C for 10 min, stored at 16°C, and put into 1.5% agarose gel electrophoresis to detect PCR products. The experiment followed the corresponding kit instructions, and the primers are shown in **Table 1**. GAPDH was used as an endogenous reference, and expression was calculated using $2^{-\Delta\Delta Ct}$, compared the level of CEBPA mRNA in different tissues.

Detection of CEBPA Protein

The western blotting (WB) was used to detect the total protein. After the total protein was extracted with radioimmunoprecipitation assay (RIPA) buffer containing a protease inhibitor, the concentration of protein was measured by a decanoic acid protein assay kit. An equal amount of protein was separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Then, the protein was transferred to the polyvinylidene fluoride film at a constant voltage of 80 V. Five percent skim milk was used to seal the solution for 1 h, then primary antibody CEBPA (1:100) and GAPDH were added and incubated at 4°C by gently shaking overnight, washed with buffer solution (TBST) at room temperature for 3 times. The next day, the second biotin-labeled goat anti-rabbit immunoglobulin G (IgG) was oscillated at 37°C for 2 h. TBST was used at room temperature for 3 times. The polyvinylidene fluoride film was colored and photographed in a dark environment, taking GAPDH as internal control.

Positive Expression of CEBPA

The positive expression of CEBPA was detected by immunohistochemistry. The prepared paraffin slices were baked at 60°C for 2 h, dewaxed, and rehydrated. Then incubated with 0.3% H_2O_2 formaldehyde solution at room temperature for 30 min. The antigen was repaired in citric acid buffer under high pressure for 2 min. After waiting for the temperature to

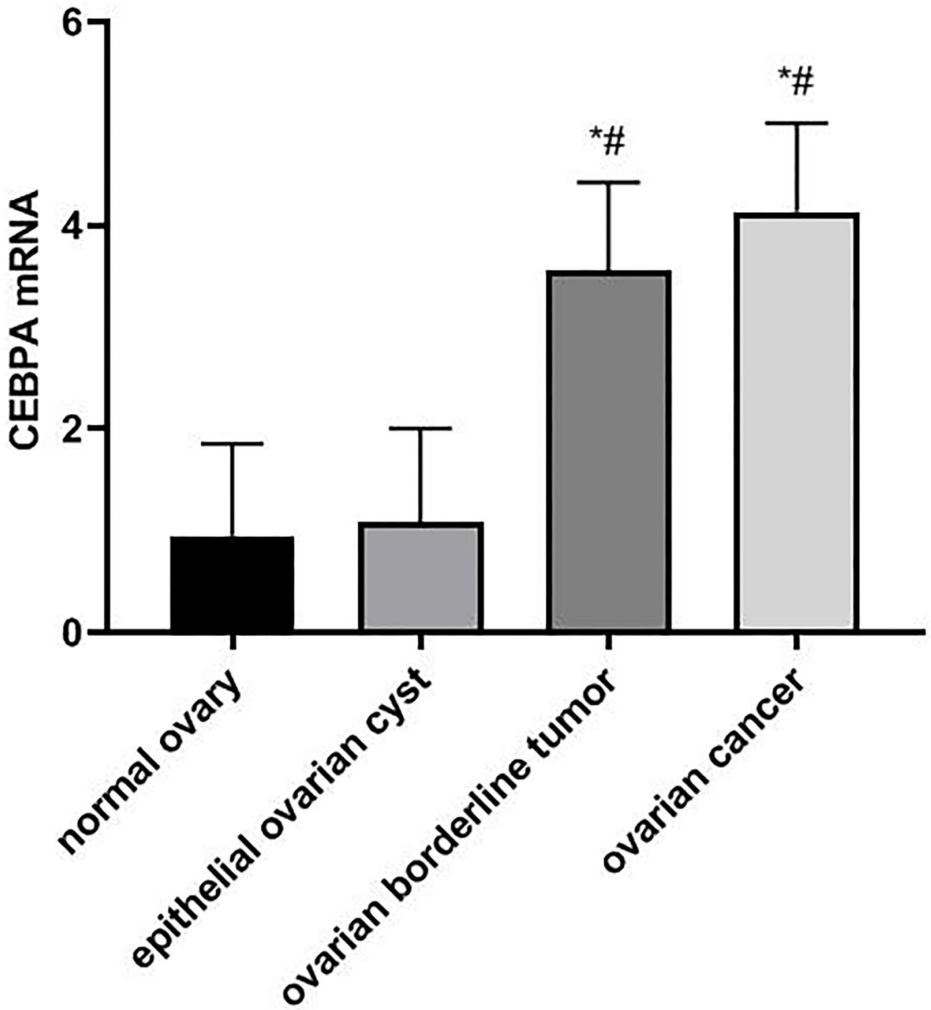


FIGURE 1 | Comparison of CEBPA mRNA expression in ovarian tissues of four groups of patients. Compared with normal ovary, $^{*}p < 0.05$; Compared with an epithelial ovarian cyst, $\#p < 0.05$. CEBPA, CCAAT enhancer-binding protein alpha.

be the same as room temperature, washed with phosphate-buffered saline (PBS) buffer for three times. The primary antibody was diluted with antibody diluent and incubated at 4°C. The next morning, the box containing slices was taken out. The secondary antibody was dropped and incubated at room temperature for 1 h. 3,3′-Diaminobenzidine (DAB) was used for color rendering, observed under a microscope, and the color rendering was terminated in time. After the color rendering was completed, distilled water was washed, hematoxylin was re-dyed for 20 s, alcohol was dehydrated with different concentration gradients, xylene was transparent, and neutral gum was sealed. The stained sections were observed under a microscope.

Immunohistochemical results showed that the cells with brown or brown granules in the cytoplasm were positive cells by immunohistochemical staining. The semi-quantitative integral method was used to judge the expression, and the percentage of staining intensity and positive cells was recorded as 0–3 points, respectively. The staining intensity score was: 0 points (no staining), 1 point (light staining), 2 points (moderate staining), and 3 points (deep staining). The positive cell count score was as follows: 10 visual fields were randomly selected and the average positive percentage was calculated. 0 points (the number of positive cells <10%), 1 point (10–24%), 2 points (25–50%), 3 points (>50%). The scoring standard for protein staining results was determined by multiplying the staining intensity by the number of positive cells. The staining results were recorded as 0 points (–), 1–3 points (+), 4–6 points (++), and 7–9 points (+ + +). Staining results (–) were regarded as negative, and staining results (+), (++), and (+ + +) were regarded as positive. All tissue specimens were independently evaluated by two pathologists, discrepant results were evaluated by a third physician, and a consistent result was chosen for the final evaluation.

FIGURE 2 | Comparison of CEBPA protein expression in ovarian tissues of four groups of patients. CEBPA, CCAAT enhancer-binding protein alpha.

TABLE 2 | Positive expression rate of CEBPA in different ovarian tissues.

Group	Case number	Expression of CEBPA protein				Positive expression rate
		−	+	++	+++	
Normal ovary	14	13	1	0	0	7.14%
Epithelial ovarian cyst	38	28	8	2	0	26.32%
Ovarian borderline tumor	10	5	1	2	2	50.00%
Ovarian cancer	71	22	24	18	7	69.01%

CEBPA, CCAAT enhancer-binding protein alpha.

Observation Index

The clinicopathological data of patients with ovarian cancer were collected, such as age, the International Federation of Gynecology and Obstetrics (FIGO) stage, histologic type, degree of histological differentiation, and lymph node metastasis, to compare CEBPA expression in patients with different types of ovarian cancer. The receiver operating curve (ROC) curve was drawn to analyze the diagnostic efficacy of CEBPA levels in ovarian cancer patients. Follow-up work will be completed in June 2021. During this period, ovarian cancer patients were followed up by telephone, letters, and hospital records to record their survival. Overall survival was defined as the time from the day of surgery to death or loss of follow-up.

Statistical Methods

The Statistical Product and Service Solutions (SPSS) 22.0 software was adopted, the measurement data were expressed as ($\pm$s), the Student-Newman-Keuls (SNK)-q method was used for paired comparison, and variance analysis was used for multiple group comparisons. The counting data were expressed by rate (%), and the comparison between groups adopts the χ^2 test. The ROC curve was constructed, and the area under the curve (AUC) was calculated to evaluate the diagnostic efficacy of CEBPA level for ovarian cancer. Kaplan-Meier survival curve was used to analyze the prognosis of patients. $P < 0.05$ means the difference was statistically significant.

RESULTS

Comparison of CEBPA mRNA Expression in Ovarian Tissues of Four Groups of Patients

The results of real-time quantitative PCR showed that the expressions of CEBPA mRNA in ovarian tissues of patients with normal ovary, epithelial ovarian cyst, ovarian borderline tumor, and ovarian cancer were 0.95 ± 0.90, 1.08 ± 0.92, 3.56 ± 0.86, and 4.13 ± 0.87, respectively. Compared with normal ovary and epithelial ovarian cysts, the expression level of CEBPA mRNA in patients with ovarian borderline tumor and ovarian cancer was significantly higher ($F = 123.223$, $p < 0.05$), as shown in **Figure 1**.

TABLE 3 | Relationship between the expression of CEBPA and the pathobiological characteristics of ovarian cancer patients [*n* (%)].

Project	Total number of cases ($n = 71$)	CEBPA negative expression group ($n = 22$)	CEBPA positive expression group ($n = 49$)	χ^2 value	*P*-value
Age				0.280	0.596
<50 years old	29	10 (45.45%)	19 (38.78%)		
≥50 years old	42	12 (54.55%)	30 (61.22%)		
FIGO stage				0.126	0.723
I,II	28	8 (36.36%)	20 (40.82%)		
III,IV	43	14 (63.64%)	29 (59.18%)		
Histologic type				1.656	0.647
Serous cystadenocarcinoma	32	10 (45.45%)	22 (44.90%)		
Mucosal cystadenocarcinoma	11	5 (22.73%)	6 (12.24%)		
Endometrial carcinoma of ovary	25	6 (27.27%)	19 (38.78%)		
Clear cell carcinoma	3	1 (4.55%)	2 (4.08%)		
Degree of histological differentiation				4.553	0.103
Highly differentiated	15	8 (36.36%)	7 (14.29%)		
Middle differentiation	42	11 (50.00%)	31 (63.27%)		
Poorly differentiated	14	3 (13.64%)	11 (22.45%)		
Lymph node metastasis				0.006	0.937
Without	35	11 (50.00%)	24 (48.98%)		
With	36	11 (50.00%)	25 (51.02%)		

CEBPA, CCAAT enhancer-binding protein alpha.

Comparison of CEBPA Protein Expression in Ovarian Tissues of Four Groups of Patients

The result of the WB experiment showed that the expression level of CEBPA protein in patients with ovarian borderline tumor and ovarian cancer was significantly higher than that in patients with normal ovary and an epithelial ovarian cyst ($p < 0.05$), as shown in **Figure 2**.

The Positive Expression Rate of CEBPA in Different Ovarian Tissues

In normal ovarian and epithelial ovarian cysts, the positive expression rate of CEBPA was low. However, in ovarian borderline tumor and ovarian cancer tissues, the number of positive cells of CEBPA was significantly increased, and the staining was significantly deepened, and the positive expression rate was significantly higher than that of normal ovary and epithelial ovarian cyst tissues ($\chi^2 = 34.932$, $p < 0.05$), as shown in **Table 2**.

The Relationship Between the Expression of CEBPA and the Pathobiological Characteristics of Ovarian Cancer Patients

There was no significant correlation between the expression of CEBPA and the age, FIGO stage, histologic type, degree of histological differentiation, and lymph node metastasis of ovarian cancer patients ($p > 0.05$), as shown in **Table 3**.

Diagnostic Efficacy of CEBPA Level in Ovarian Cancer

The receiver operating curve analysis showed that the AUC of CEBPA level in the diagnosis of ovarian cancer was 0.898 (95% CI 0.834–0.962), the critical value was 2.36, the best cut-off value was 0.809, the sensitivity was 98.6%, and the specificity was 82.3%, as shown in **Figure 3**.

Relationship Between CEBPA Level and Prognosis of Patients

According to the median expression of CEBPA level, ovarian cancer patients were divided into CEBPA low expression and CEBPA high expression. Ended in June 2021, all patients were followed up. Kaplan-Meier survival curve analysis showed that the median survival time of patients with CEBPA high expression was 25 months, which was lower than 31 months of patients with CEBPA low expression, and the Log-rank test was $p = 0.034$, as shown in **Figure 4**.

DISCUSSION

At present, the pathogenesis of ovarian cancer is still unknown. The pathogenesis of ovarian cancer is the result of multiple factors, which are closely related to genetic factors, hormone secretion, and the living environment (12). Due to the diversity of ovarian tissue structure and relatively complex endocrine function, the early clinical features of ovarian cancer are not obvious and lack typicality, which often leads to an extremely low detection rate of ovarian malignant tumors. Most patients

are diagnosed accompanied by metastasis and spread of the abdomen and pelvic cavity, which has a negative impact on patients' life safety (13). Surgery and chemotherapy are the traditional treatments for ovarian cancer. Although they can improve patients' symptoms and prolong their life, patients are prone to drug resistance to chemotherapy, and the survival rate of patients is still not ideal and the recurrence rate is high, so the mortality rate of ovarian cancer remains high (14). Therefore, it is urgent to find reliable molecular markers.

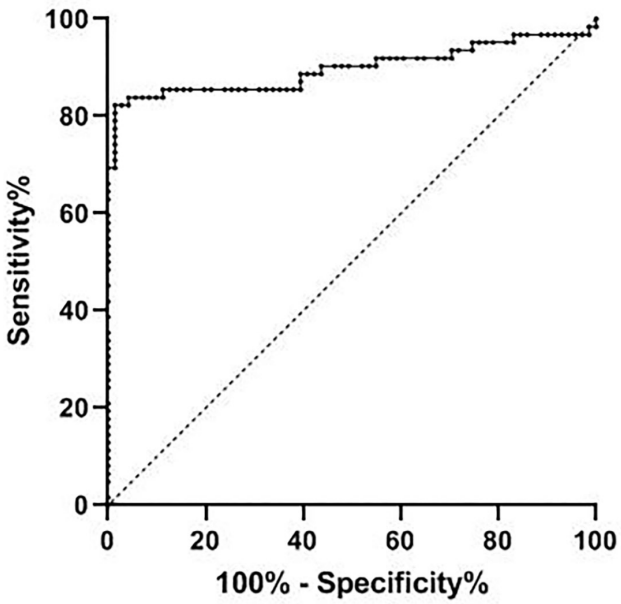


FIGURE 3 | Diagnostic efficacy of CEBPA level in ovarian cancer. CEBPA, CCAAT enhancer-binding protein alpha.

Cytosine-cytosine-adenosine-adenosine-thymidine enhancer-binding protein alpha is the first member of the leucine zipper transcription factor family, which can affect the density and differentiation of immune cells, and is very important for inhibiting self-renewal in the hematopoietic process, cell cycle arrest, and bone marrow differentiation (15). The expression level of CEBPA is the highest in the placenta and also has a high expression level in the liver, lung, skeletal muscle, but its expression level in the brain, testis, and ovary is very low, even cannot be detected (16). CEBPA has a tissue-specific expression pattern, and its expression is upregulated during granulocyte differentiation and downregulated during monocyte transduction. CEBPA mRNA and protein have been reported in various cancer diseases (17). Chapiro et al. revealed that the upregulation of CEBPA may lead to the occurrence of precursor B-cell acute lymphoblastic leukemia, and CEBPA was activated by rearrangement with immunoglobulin gene enhancers and immunoglobulin heavy chain genes containing t(14;19)(q32;q13). CEBPA may have the characteristics of carcinogenesis and tumor inhibition in the occurrence of human leukemia (18). Lu et al. consider that CEBPA mRNA and protein levels were upregulated in some hepatocellular carcinoma (HCC) and had the activity of promoting growth in HCC cells (19). Research by Lourenço and Coffer showed that the downregulation of CEBPA expression had been confirmed in a variety of solid tumors, such as liver cancer, breast cancer, and lung cancer. CEBPA can inhibit the growth of tumors, and the inactivation of expression in these tumors was caused by promoter methylation and gene mutation (20).

Sundfeldt et al. found by immunohistochemistry that CEBPA protein was preferentially expressed in epithelial/tumor cells of

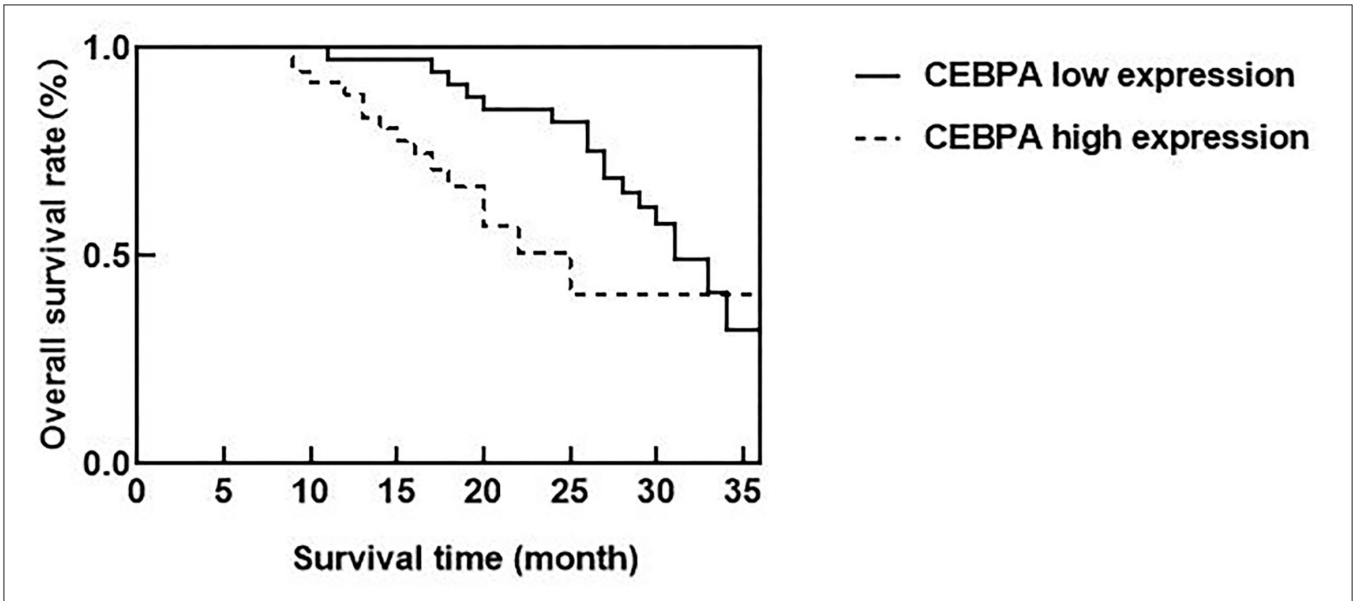


FIGURE 4 | Relationship between CEBPA level and prognosis of patients. CEBPA, CCAAT enhancer-binding protein alpha.

ovarian cancer tissue samples, which was independent of tumor stage and grade. CEBPA was expressed in epithelial cells but not in stroma. The main expression site was the cytoplasm of cancer cells. CEBPA might be involved in the proliferation process of epithelial ovarian tumor cells *in vivo*, which could play an important role as an early molecular event (21). Yoon and Smart identified nine potential p53 binding sites in the CEBPA promoter and discovered the new role of CEBPA as a p53-regulated DNA damage-inducing gene. CEBPA was a DNA damage-inducing p53 regulatory mediator of G(1) checkpoint in keratinocytes (22). In ovarian cancer, the abnormality of p53 is common, which may affect the role of CEBPA to some extent, and then change the patient's prognosis. In addition, the development of ovarian cancer is considered to be closely related to the levels of androgen and gonadotropin, while CEBPA may control the literalization process by regulating the genes needed to maintain extensive vascular network formation of luteal cells and play an intermediary role in terminal differentiation of granulosa cells. CEBPA has involved the occurrence of ovarian cancer through gonadotropin and other related ways (23). Through real-time fluorescence quantitative PCR, WB, immunohistochemistry, and other experiments, our results showed that compared with normal ovarian and epithelial ovarian cyst patients, the expression of CEBPA mRNA and protein in patients with ovarian borderline tumor and ovarian cancer were higher, which proves that the upregulation of CEBPA may play a role in the pathogenesis of ovarian cancer. At the same time, we found that there was no correlation between the expression of CEBPA and the age, FIGO stage, histologic type, degree of histological differentiation, and lymph node metastasis of ovarian cancer patients. The occurrence of ovarian cancer may involve the changes of many proto-oncogene and tumor suppressor genes, which are related to the balance of proto-oncogene or tumor suppressor genes. The mechanism of action of CEBPA in ovarian cancer needs further study, and more large-scale studies are needed to explore the relationship between the expression level of CEBPA and the pathobiological characteristics.

The ROC curve was further constructed in this study and found that the AUC of CEBPA level in diagnosing ovarian cancer was 0.898, which indicated that CEBPA level was of high value in diagnosing ovarian cancer. The possible reason for our analysis is that CEBPA has an extensive mutation in human tumors, and the mutation rate of CEBPA in ovarian cancer may have a higher mutation rate, thus inhibiting the anti-proliferative effect of CEBPA. In addition, genome mutation or post-translational regulation/modification can reduce the effect of CEBPA. Therefore, we believe that the overexpression of CEBPA can be regarded as a diagnostic molecule in ovarian cancer patients and can be considered as a target for ovarian cancer treatment. Clinically, it is necessary to strengthen the detection of CEBPA levels in patients with ovarian lesions, so as to evaluate the disease situation of patients and formulate corresponding treatment plans according to the evaluation results, which will have a positive effect on improving the prognosis of patients. In addition, the research of Konopka et al. shows that the existence of CEBPA is positively correlated with the adverse clinical outcomes of patients, and the upregulation of CEBPA expression has a negative impact on the survival rate of patients with ovarian cancer, which can be an effective molecular marker for predicting prognosis (24). According to our results, among ovarian cancer patients, the median survival time of patients with CEBPA high expression is shorter than that of patients with CEBPA low expression, and the overexpression of CEBPA level constitutes a factor of poor prognosis of ovarian cancer patients. This may be due to the obvious carcinogenic effect of CEBPA in ovarian cancer (25). Clinicians can consider measuring the expression level of CEBPA when treating patients with ovarian cancer, which is helpful to evaluate the prognosis of patients and improve their living standards.

CONCLUSION

To sum up, the expression of CEBPA mRNA and protein in patients with ovarian borderline tumor and ovarian cancer is high, and the expression of CEBPA has no obvious correlation with the pathobiological characteristics of patients with ovarian cancer, and the high expression of CEBPA has important value in the diagnosis of ovarian cancer, and it is also a poor prognostic factor of the disease. CEBPA is expected to become a new biomarker for diagnosing and evaluating the prognosis of ovarian cancer, which may play a role in the treatment choice of patients with ovarian cancer. However, the results of this study need to be verified by more patients, to further explore the specific mechanism of CEBPA expression in ovarian cancer.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Hospital of Beihua University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LZ is responsible for the writing of the article. ML is responsible for the design of the study. ZD is responsible for the operation of the experiment. CT is responsible for the recording of the results. MF is responsible for the statistics of the data. SM is not the instructor of the whole study and is responsible for the revision of the paper. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the 13th Five-Year Plan Science and Technology project of the Education Department of Jilin Province (JJKH20200072KJ).

REFERENCES

1. Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: evolution of management in the era of precision medicine. *CA Cancer J Clin*. (2019) 69:280–304. doi: 10.3322/caac.21559
2. Soerjomataram I, Bray F. Planning for tomorrow: global cancer incidence and the role of prevention 2020–2070. *Nat Rev Clin Oncol*. (2021) 18:663–72. doi: 10.1038/s41571-021-00514-z
3. Colombo N, Sessa C, du Bois A, Ledermann J, McCluggage WG, McNeish I, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. *Ann Oncol*. (2019) 30:672–705. doi: 10.1093/annonc/mdz062
4. Chandra A, Pius C, Nabeel M, Nair M, Vishwanatha JK, Ahmad S, et al. Ovarian cancer: current status and strategies for improving therapeutic outcomes. *Cancer Med*. (2019)8:7018–31. doi: 10.1002/cam4.2560
5. Rojas V, Hirshfield KM, Ganesan S, Rodriguez-Rodriguez L. Molecular characterization of epithelial ovarian cancer: implications for diagnosis and treatment. *Int J Mol Sci*. (2016) 17:2113. doi: 10.3390/ijms17122113
6. van Zyl B, Tang D, Bowden NA. Biomarkers of platinum resistance in ovarian cancer: what can we use to improve treatment. *Endocr Relat Cancer*. (2018)25:R303–18. doi: 10.1530/ERC-17-0336
7. Wilhelmson AS, Porse BT. CCAAT enhancer binding protein alpha (CEBPA) biallelic acute myeloid leukaemia: cooperating lesions, molecular mechanisms and clinical relevance. *Br J Haematol*. (2020) 190:495–507. doi: 10.1111/bjh.16534
8. Zhu Y, Chen X, Mi L, Wang Q, Zhu H, Ju H, et al. Sumoylation of CCAAT-enhancer-binding protein α inhibits lung differentiation in Bronchopulmonary Dysplasia model rats. *J Cell Mol Med*. (2020) 24:7067–71. doi: 10.1111/jcmm.15310
9. Tan S, Hadinoto K, Ebrahimi A, Langrish T. Fabrication of novel casein gel with controlled release property via acidification, spray drying and tableting approach. *Colloids Surf B Biointerfaces*. (2019) 177:329–37. doi: 10.1016/j.colsurfb.2019.02.019
10. Minner S, Lutz J, Hube-Magg C, Kluth M, Simon R, Höflmayer D, et al. Loss of CCAAT-enhancer-binding protein alpha (CEBPA) is linked to poor prognosis in PTEN deleted and TMPRSS2:ERG fusion type prostate cancers. *Prostate*. (2019) 79:302–11. doi: 10.1002/pros.23736
11. Wang S, Gao G, He Y, Li Q, Li Z, Tong G. Amidation-modified apelin-13 regulates PPARγ and perilipin to inhibit adipogenic differentiation and promote lipolysis. *Bioinorg Chem Appl*. (2021) 2021:3594630. doi: 10.1155/2021/3594630
12. Kroeger PT Jr, Drapkin R. Pathogenesis and heterogeneity of ovarian cancer. *Curr Opin Obstet Gynecol*. (2017) 29:26–34. doi: 10.1097/GCO.0000000000000340
13. Kim JY, Cho CH, Song HS. Targeted therapy of ovarian cancer including immune check point inhibitor. *Korean J Intern Med*. (2017) 32:798–804. doi: 10.3904/kjim.2017.008
14. Scaletta G, Plotti F, Luvero D, Capriglione S, Montera R, Miranda A, et al. The role of novel biomarker HE4 in the diagnosis, prognosis and follow-up of ovarian cancer: a systematic review. *Expert Rev Anticancer Ther*. (2017) 17:827–39. doi: 10.1080/14737140.2017.1360138
15. Wattanavanitchakorn S, Rojvirat P, Chavalit T, MacDonald MJ, Jitrapakdee S. CCAAT-enhancer binding protein-α (C/EBPα) and hepatocyte nuclear factor 4α (HNF4α) regulate expression of the human fructose-1,6-bisphosphatase 1 (FBP1) gene in human hepatocellular carcinoma HepG2 cells. *PLoS ONE*. (2018) 13:e0194252. doi: 10.1371/journal.pone.0194252
16. Tian Y, Li G, Shen J, Tao Z, Chen L, Zeng T, et al. Molecular cloning, characterisation, and expression patterns of pigeon CCAAT/enhancer binding protein-α and -β genes. *Br Poult Sci*. (2019) 60:347–56. doi: 10.1080/00071668.2019.1614530
17. Liu Z, Yang J, Ge C, Zhao F, Li H, Yao M, et al. Inhibitor of binding/differentiation 2 (Id2) is regulated by CCAAT/enhancer-binding protein-α (C/EBPα) and promotes the proliferation of hepatocellular carcinoma. *Am J Cancer Res*. (2018) 8:2254–66.
18. Chapiro E, Russell L, Radford-Weiss I, Bastard C, Lessard M, Struski S, et al. Overexpression of CEBPA resulting from the translocation t(14;19)(q32;q13) of human precursor B acute lymphoblastic leukemia. *Blood*. (2006) 108:3560–3. doi: 10.1182/blood-2006-03-010835
19. Lu GD, Leung CH, Yan B, Tan CM, Low SY, Aung MO, et al. C/EBPalpha is up-regulated in a subset of hepatocellular carcinomas and plays a role in cell growth and proliferation. *Gastroenterology*. (2010) 139:632–43.e1–4. doi: 10.1053/j.gastro.2010.03.051
20. Lourenço AR, Coffer PJ. A tumor suppressor role for C/EBPα in solid tumors: more than fat and blood. *Oncogene*. (2017) 36:5221–30. doi: 10.1038/onc.2017.151
21. Sundfeldt K, Ivarsson K, Carlsson M, Enerbäck S, Janson PO, Brännström M, et al. The expression of CCAAT/enhancer binding protein (C/EBP) in the human ovary *in vivo*: specific increase in C/EBPbeta during epithelial tumour progression. *Br J Cancer*. (1999) 79:1240–8. doi: 10.1038/sj.bjc.6690199
22. Yoon K, Smart RC. C/EBPalpha is a DNA damage-inducible p53-regulated mediator of the G1 checkpoint in keratinocytes. *Mol Cell Biol*. (2004) 24:10650–60. doi: 10.1128/MCB.24.24.10650-10660.2004
23. Fan HY, Liu Z, Johnson PF, Richards JS. CCAAT/enhancer-binding proteins (C/EBP)-α and -β are essential for ovulation, luteinization, and the expression of key target genes. *Mol Endocrinol*. (2011) 25:253–68. doi: 10.1210/me.2010-0318
24. Konopka B, Szafron LM, Kwiatkowska E, Podgorska A, Zolocinska A, Pienkowska-Grela B, et al. The significance of c.690G>T polymorphism (rs34529039) and expression of the CEBPA gene in ovarian cancer outcome. *Oncotarget*. (2016) 7:67412–24. doi: 10.18632/oncotarget.11822
25. Saglam O, Tang Z, Tang G, Medeiros LJ, Toruner GA. KAT6A amplifications are associated with shorter progression-free survival and overall survival in patients with endometrial serous carcinoma. *PLoS ONE*. (2020) 15:e0238477. doi: 10.1371/journal.pone.0238477

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Mi, Zhang, Li, Dong, Tian and Fu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 24 February 2022
doi: 10.3389/fsurg.2022.840461

Laparoscopic Radical Resection of Colorectal Cancer in the Treatment of Elderly Colorectal Cancer and Its Effect on Gastrointestinal Function

Biao Liu[1]*, *Chuanhui Yao*[2] *and Haiying Li*[3]

[1] The Third Department of Surgery, Cangxian Hospital, Cangzhou, China, [2] The First Department of Surgery, Cangxian Hospital, Cangzhou, China, [3] Department of Medical Affairs, Cangxian Hospital, Cangzhou, China

Objective: To explore the efficacy and safety of laparoscopic radical resection of colorectal cancer in the elderly patients and its impact on gastrointestinal function.

Methods: A total of 122 elderly patients with colorectal cancer admitted to our hospital from March 2020 to June 2021 were selected as the research subjects, and they were divided into the control group ($n = 61$) and the observation group ($n = 61$). The control group was treated with traditional laparotomy, and the observation group was treated with laparoscopic radical resection of colorectal cancer. The clinical data of operation time, incision length, intraoperative bleeding volume, and hospitalization time in the two groups were recorded. Serum motilin (MTL) and gastrin (GAS) levels were measured pre- and post-operatively. The duration of abdominal distension, the time for the abdominal sound to return to normal, the time for the anal exhaust to normal, and the time for normal food intake were recorded after operation. The patients were followed up for 6 months post-operatively, and the complications during follow-up were recorded.

Results: The total response rate of the observation group (95.08%) was higher than that of the control group (81.97%) ($P < 0.05$). The operation time, incision length, intraoperative bleeding volume, and hospitalization time of the observation group were lower than those of the control group ($P < 0.05$). The duration of abdominal distension, the time for bowel sounds to return to normal, the time for the anus to exhaust gas to normal, and the normal eating time in the observation group were all lower than those in the control group ($P < 0.05$). After surgery, the levels of MTL and GAS in the two groups were lower than those before surgery, and those in the observation group were lower than those in the control group ($P < 0.05$). The total incidence of complications in the observation group (3.28%) was lower than that in the control group (13.12%) ($P < 0.05$).

Conclusion: Laparoscopic radical resection of colorectal cancer in the elderly patients has good effect, short operation time, less trauma, less blood loss during operation, short hospital stay, good recovery of gastrointestinal function, fewer complications, and high safety.

Keywords: colorectal cancer, laparoscopic, efficacy, safety, gastrointestinal tract function

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Wenjie Song,
Fourth Military Medical University, China
Jiangang Liu,
The Second Affiliated Hospital of Shandong First Medical University, China

***Correspondence:**
Biao Liu
lblnhappy@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *21 December 2021*
Accepted: *06 January 2022*
Published: *24 February 2022*

Citation:
Liu B, Yao C and Li H (2022) Laparoscopic Radical Resection of Colorectal Cancer in the Treatment of Elderly Colorectal Cancer and Its Effect on Gastrointestinal Function. Front. Surg. 9:840461. doi: 10.3389/fsurg.2022.840461

INTRODUCTION

The mortality rate of colorectal cancer ranks in the forefront of malignant tumors. The majority of patients with colorectal cancer are elderly patients, with more senile diseases and high post-operative complications (1–3). Surgical radical surgery is the preferred treatment for colorectal cancer (4, 5). Open surgery for colorectal cancer has a definite effect, but this type of surgery has the following disadvantages: (1) patients with large opening have a large amount of bleeding during the operation, larger hidden fluid loss, unstable internal environment, and obvious stress reaction; (2) post-operative patients will have varying degrees of intestinal inflammation, which is a potential adverse effect on the patients' post-operative rehabilitation and nursing care; (3) studies have shown that patients undergoing traditional colorectal surgery suffer from prolonged post-operative pain, prolonged hospitalization, long recovery time for severe intestinal inflammation, long exhaust time, and prolonged initial ambulation (6–8). However, due to the large incision, clear intraoperative vision, and clear anatomical position, open surgery can often get satisfactory surgical results (9, 10). In recent years, with the clinical application and development of the concept of "minimally invasive," laparoscopic surgery has been widely used. With the improvement of surgical methods and the maturity of surgical skills, laparoscopic radical surgery has been able to achieve similar short-term curative effect as open surgery (11, 12). The purpose of this study was to investigate the efficacy, safety, and gastrointestinal effects of laparoscopic radical resection for colorectal cancer in the elderly patients.

MATERIALS AND METHODS

Patients

A total of 122 elderly patients with colorectal cancer who were admitted to our hospital from March 2020 to June 2021 were selected as the research subjects. There were 74 males and 48 females, with the average age of (69.08 $\pm$ 4.36) years old. Inclusion criteria were as follows: Age $>$ 60 years old; the patient's symptoms and pathological biopsy diagnosis were consistent with the diagnostic criteria for colorectal cancer (13); patients who have not received chemoradiotherapy or immunotherapy before operation. Exclusion criteria were as follows: Patients with a previous history of conversion from laparoscopic to laparotomy; patients with coagulation disorder; patients with hematological diseases; severe heart, liver, lung, and renal insufficiency; patients with gastrointestinal bleeding and intestinal obstruction; patients who have a history of chemotherapy or use drugs that affect gastrointestinal motility and hormones; patients who fell off during follow-up. All the patients were divided into the control group ($n = 61$) and the observation group ($n = 61$) according to the random number table. There was no significant difference in general information such as gender and age between the two groups ($P > 0.05$), as shown in **Table 1**.

Treatment Methods

Before surgery, both the groups were given correct anemia, given to maintain water and electrolyte, acid-base balance, and strengthen nutritional supplements. Two days before surgery, half-flow diet was adopted, 1 day before surgery, full-flow diet was adopted, oral intestinal antibiotics were taken from 3 days before surgery, fasting for 12 h before surgery, no drinking for 8 h before surgery, indwelling catheterization was given before surgery, and general enema was given in the morning before surgery to empty intestinal contents.

The control group was treated with traditional laparotomy: All patients were treated with endotracheal intubation and intravenous combined general anesthesia. The position was supine or lithotomy, and the specific incision location was selected according to the tumor site, such as the middle incision of the lower abdomen for sigmoid colon surgery. For the operation of the right hemicolon and descending colon, the midabdominal incision around the umbilicus or the incision through the rectus abdominis was selected. An incision of about 10 cm was made in the abdomen of the patient, through which the mesentery was cut, and the corresponding intestinal segment of colon cancer was removed and ligation was performed with surgical instruments such as forceps. Meanwhile, the lymph nodes in the region were cleared, and the intestinal tube was cut off at 5 cm from the lesion to complete anastomosis.

The observation group was treated with laparoscopic radical resection of colorectal cancer: First, intubation was inserted into the trachea of the patient after general anesthesia, the patient was supine on the sterilized bed sheet, and the parameters of pneumoperitoneum were set with the pressure of 13 mmHg, and an observation hole was set at 10 mm below the umbilicus and 3 mm at the left and right lateral abdominal edge of the umbilicus. An operation hole was set at the left and right McBurney's points with a size of 10 $\sim$ 11 mm, and then the laparoscope was tilted 30° for observation to determine whether there was organ metastasis in the abdominal cavity and whether the tumor eroded the serosal membrane. A cotton tape was placed in the intestine at 9 mm near the tumor, and it was suspended and stretched. Afterward, an ultrasonic knife is used to cut the junction of the peritoneum and the sigmoid mesocolon. During the cutting process, the gap between the loose connective tissue at the root of the membrane and the sigmoid mesocolon can be separated, thereby effectively protecting the ureter. Then, the lymph nodes and the blood vessels under the mesentery were anatomized, so that the sub mesenteric membrane was exposed, and the root of the vein was broken and tied using Hemolock. The thin membrane of blood vessel and intestine under direct vision was disconnected to ensure that the pelvic fascia wall layer is not damaged. The lymph nodes, fat, and connective tissue were cleaned and the anterior fascia behind the rectum was separated until it reaches the levator ani muscle. After segmentation of the anal tail facing band, the sacral fascia, and the coccyx muscle, the mesorectum was severed at the distal anal tail attachment, and all of the mesorectums were excised. The rectum was cut at the position below the tumor using the abdominal linear cutting obturator, and then about 5 cm was cut into the abdomen to enter the abdomen, where the sigmoid colon was cut. The proximal pouch was used to tighten the rectum and then enter the abdominal cavity. After surgical suture, pneumoperitoneum was reset to ensure good anastomosis under direct vision. After air was injected, after passing through the anus to confirm that there is no air leakage in the anastomosis,

TABLE 1 | Comparison of general information between two groups.

Group	Gender		Age (years)	TNM staging			Tumor diameter (cm)	Tumor location	
	Male	Female		I	II	III		Colon cancer	Rectal cancer
Control group	39	22	68.89 ± 4.18	26	23	12	3.49 ± 0.51	36	25
Observation group	35	26	69.30 ± 4.98	22	25	14	3.54 ± 0.53	38	23
t/χ^2	0.549	0.493	0.571	0.531	0.137				
P	0.459	0.623	0.752	0.596	0.711				

the abdominal cavity is cleaned. The material in the abdominal cavity was placed in front of the sacrum through a drainage tube and flowed out through the right lower abdominal wall or the perineum.

All patients pulled out the drainage tube 1d after surgery, so that the abdominal cavity gradually returned to normal mechanism. If fluid exudation occurs at the post-operative incision, the drainage tube should be opened in time.

Observation Indicators

According to the response evaluation criteria in solid tumor (14), the surgical efficacy of patients was evaluated, which could be divided into complete response (CR), partial response (PR), stable disease (SD), and progression of disease (PD), and the total response rate = (CR+PR) cases/total cases × 100%. The clinical data of operation time, incision length, intraoperative bleeding volume, and hospitalization time in the two groups were recorded. About 4 mL of peripheral venous blood was collected pre-operatively and on the 3rd day after surgery, and the serum levels of motilin (MTL) and gastrin (GAS) were detected by radioimmunoassay. The relevant test kits were purchased from Shenzhen Jingmei Biological Technology Co., Ltd. The duration of abdominal distension, the time for the abdominal sound to return to normal, the time for the anal exhaust to normal, and the time for normal food intake were recorded after operation. The patients were followed up for 6 months post-operatively, and the complications during follow-up were recorded.

Statistical Methods

The results of this experiment were statistically analyzed by Statistical Product and Service Solutions (SPSS) 20.0 (SPSS Co., Ltd., Chicago, USA). The count data were expressed by (rate), and chi-square test was used for their comparison between groups. The measurement data were expressed by (mean±SD), and *t*-test was used for their comparison between groups. $P < 0.05$ indicates that the difference is statistically significant.

RESULTS

Comparison of Efficacy Between the Two Groups

In the control group, there were 21 cases of CR, 29 cases of PR, 8 cases of SD, 3 cases of PD, and the total response rate was 81.97% (50/61). In the observation group, there were 26 cases of CR, 32 cases of PR, 2 cases of SD, and 1 case of PD, and the total response rate was 95.08% (58/61). The total response rate of the observation group was higher than that of the control group ($P < 0.05$), as shown in **Figure 1**.

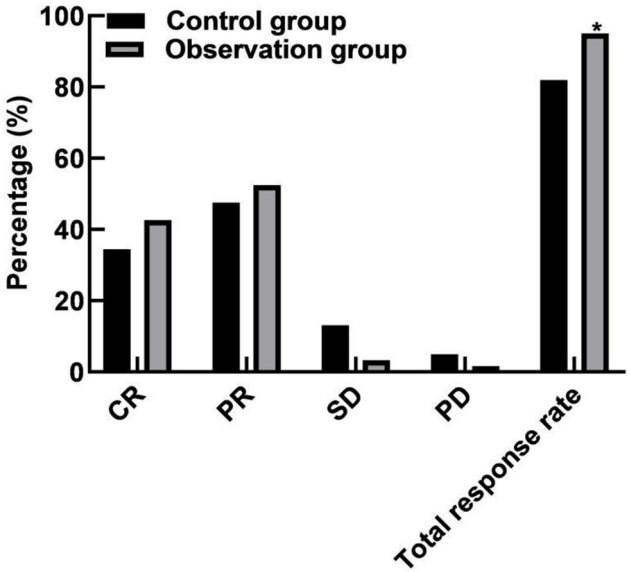


FIGURE 1 | Comparison of efficacy between the two groups. Compared with the control group, *$P < 0.05$.

Comparison of Clinical Indicators Between the Two Groups

The operation time, incision length, intraoperative bleeding volume, and hospitalization time in the observation group were lower than those in the control group ($P < 0.05$), as shown in **Figure 2**.

Comparison of Gastrointestinal Function Recovery Between the Two Groups

The duration of continuous abdominal distension, the time for bowel sounds to return to normal, the normal time of anal exhaust, and the normal eating time of the observation group were lower than those of the control group ($P < 0.05$), as shown in **Figure 3**.

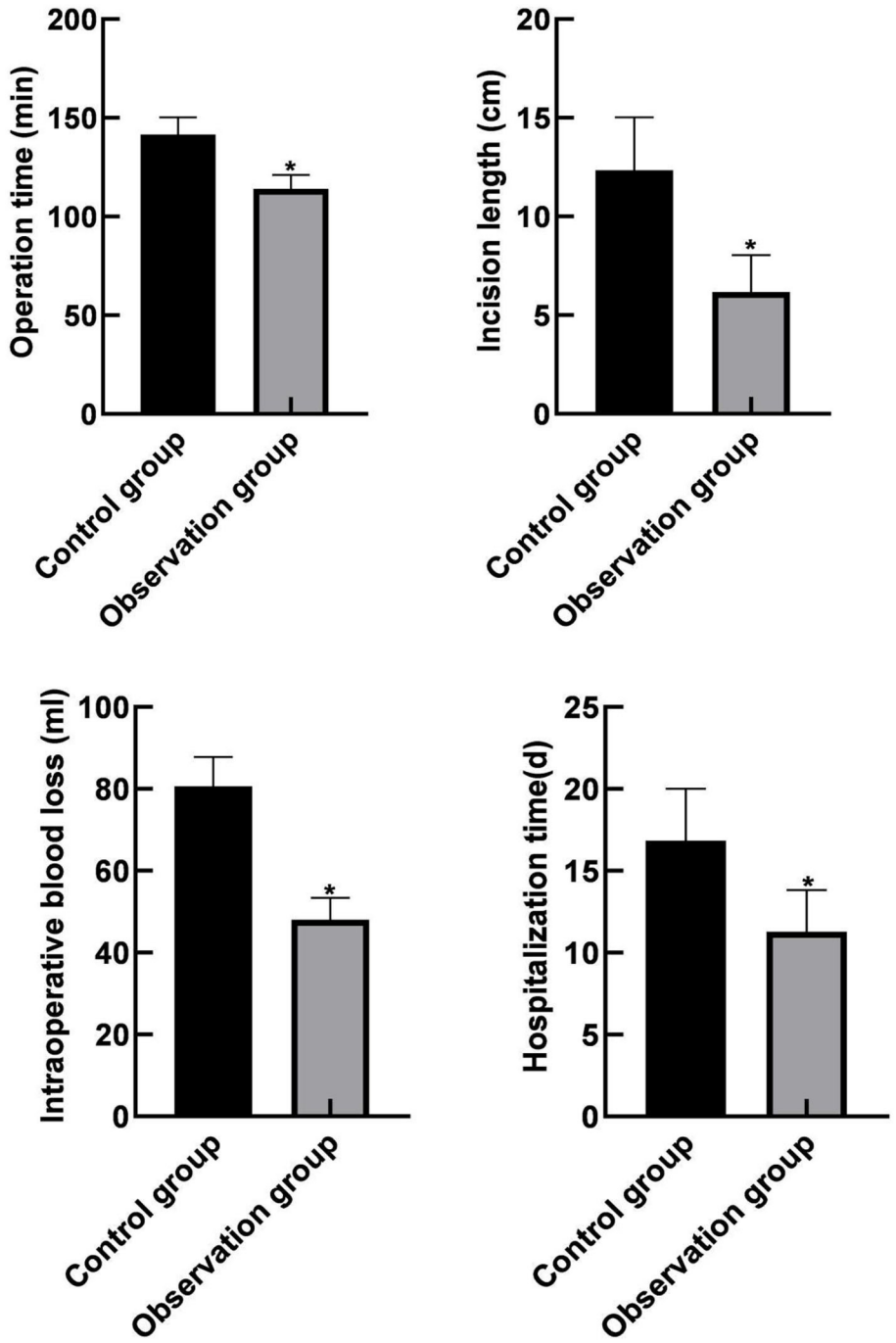


FIGURE 2 | Comparison of clinical indicators between the two groups. Compared with the control group, *$P < 0.05$.

Comparison of Gastrointestinal Function Levels Between the Two Groups

The post-operative MTL and GAS levels of the two groups were lower than those before the operation, and the observation group was lower than the control group ($P < 0.05$), as shown in **Figure 4**.

Comparison of Complications Between the Two Groups

The total incidence of complications in the observation group (3.28%) was lower than that in the control group (13.12%) ($P < 0.05$), as shown in **Figure 5**.

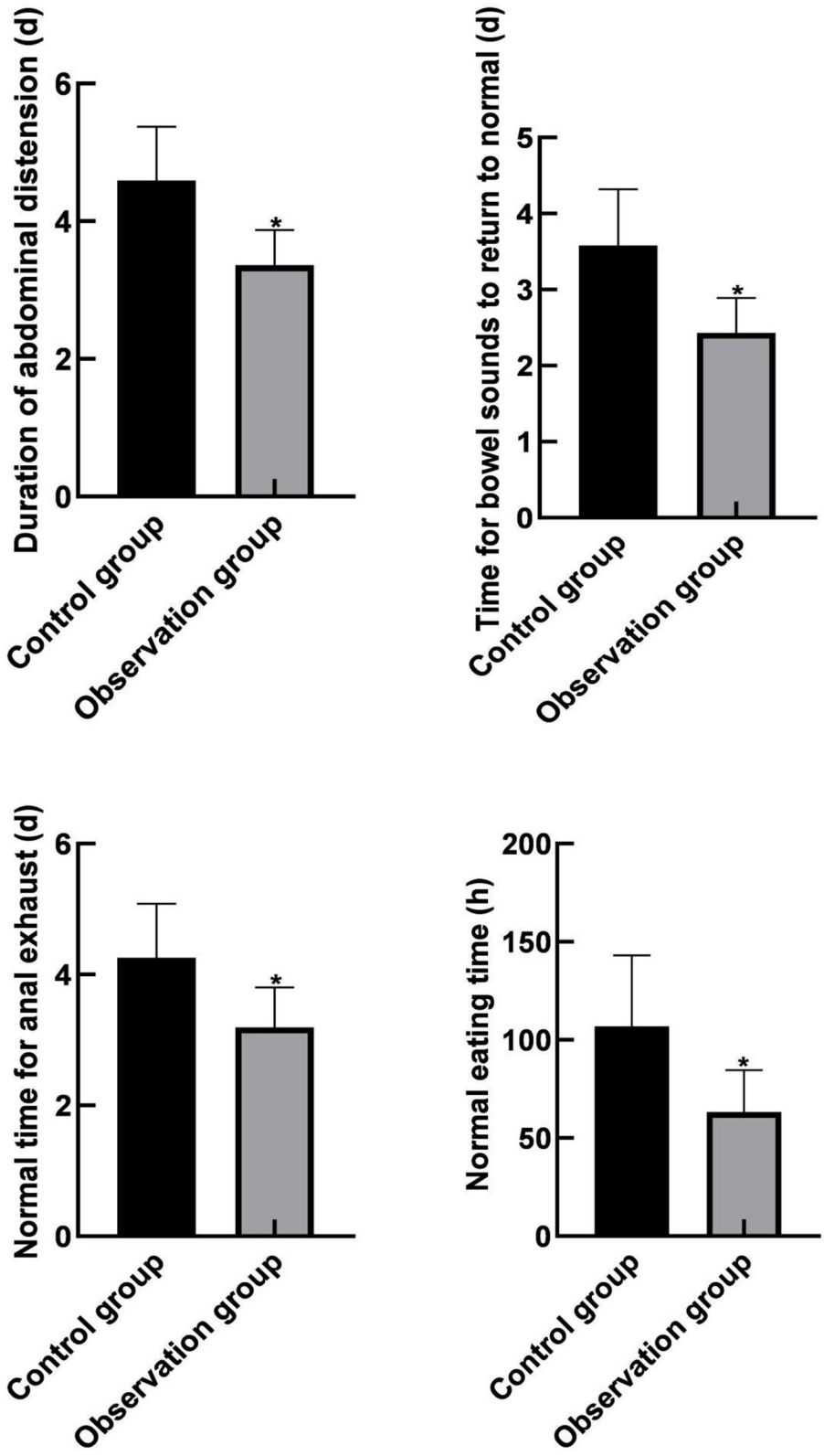


FIGURE 3 | Comparison of gastrointestinal function recovery between the two groups. Compared with the control group, $^{*}P < 0.05$.

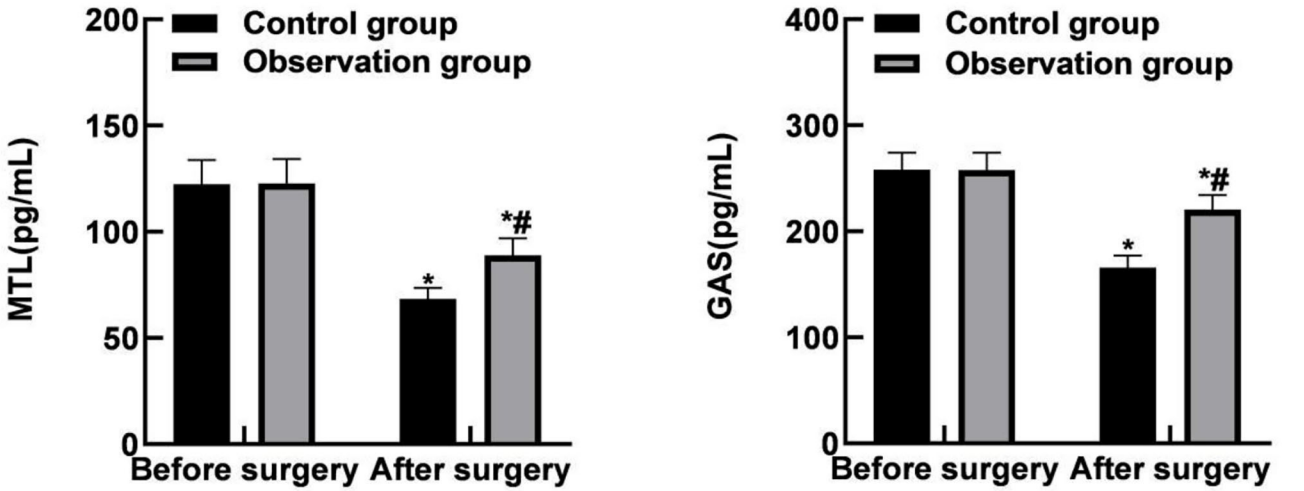


FIGURE 4 | Comparison of gastrointestinal function levels between the two groups. Compared with the same group before surgery, $^{*}P < 0.05$; Compared with the control group, $^{\#}P < 0.05$.

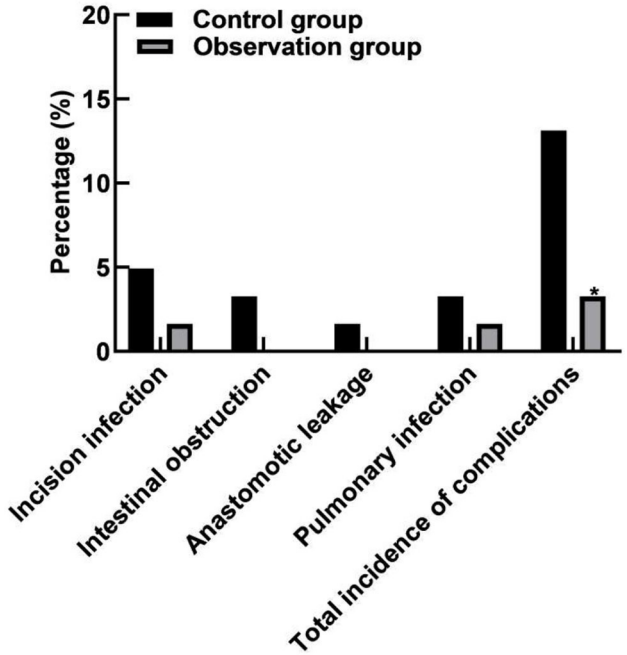


FIGURE 5 | Comparison of complications between the two groups. Compared with the control group, $^{*}P < 0.05$.

DISCUSSIONS

In recent years, with the improvement of multidisciplinary comprehensive treatment and diagnosis including surgery, radiotherapy, pathological diagnosis, and imaging diagnosis, as well as the development and application of cytotoxic drugs and highly selective molecular targeted drugs, the survival time of patients with colorectal cancer has been significantly prolonged (15–17). Neoadjuvant therapy can reduce the local recurrence rate of some stage II and III rectal cancers and improve the 5-year survival rate of patients. However, as far as the current medical level is concerned, the most effective treatment is still early radical surgery (18–20).

The results of this study showed that the total response rate of the observation group (95.08%) was higher than that of the control group. And the operation time, incision length, intraoperative bleeding volume, and hospitalization time of the observation group were lower than those of the control group. This indicates that compared with the traditional laparotomy, laparoscopic radical resection for colorectal cancer has the advantages of shorter operation time, less trauma, less intraoperative bleeding, shorter hospitalization time, and better curative effect. The reasons were analyzed as follows: Compared with traditional surgery, laparoscopy has the effect of enlarging the visual field, which can make the visual field of laparoscopic radical surgery for colorectal cancer clearer. It is beneficial for laparoscopic multi-angle observation of adjacent tissues, revealing that the anatomical space is not easy to be observed during laparotomy. The trauma is small, and it only needs a few small openings in the abdomen. During the operation, the inflammatory reaction was mild, the amount of bleeding and fluid loss was small, and the internal environment was relatively stable in laparotomy. Post-operative patients had mild pain response, rapid recovery, and significantly reduced exhaust time and total hospitalization time as compared with those after laparotomy (21–23). Moreover, the results of this study showed that the duration of abdominal distension, the time for bowel sounds to return to normal, the time for normal anal exhaust, and the time for normal food intake in the observation group were all lower than those in the control group. After operation, the levels of MTL and GAS in the two groups were lower than those before operation, and the levels in the observation group were lower than those in the control group. These results indicated

that laparoscopic radical resection of colorectal cancer could effectively promote the recovery of gastrointestinal function in patients. The analyzed reason is that the recovery speed of gastrointestinal function in patients with colorectal cancer after surgery is related to surgical trauma and stress, while laparoscopic surgery itself has the characteristics of small incision and small trauma, which can avoid the effects of the above factors on the recovery of gastrointestinal function in patients to a certain extent (24–26).

The results of this study showed that the total incidence of complications in the observation group (3.28%) was lower than that in the control group (13.12%). All these have indicated that laparoscopic radical resection for colorectal cancer in the elderly patients has less complications and high safety. The reasons were analyzed as follows: Large incision in laparotomy, poor blood circulation around the incision, and reduced anti-infection ability; meanwhile, the chance of infection was increased due to the long healing time and increased number of dressing changes (27–29). For one case of anastomotic leakage in the control group, it was probably related to too little free anastomosis broken end, excessive traction of anastomosis intestinal wall, local contusion, lax suture caused by improper use of cutter and stapler, excessive tension of anastomosis outlet, or poor blood supply around anastomosis. There were two cases of pulmonary infection in the control group and only 1 case in the observation group, which may be caused by post-operative incision pain in patients afraid of severe cough, resulting in sputum retention in the throat and increasing the chance of pulmonary infection. However, the incision in the laparoscopic group was significantly smaller than that in the open surgery group, so the incision pain in the laparoscopic group was lighter. In order to avoid the occurrence of lung infection, the patients can be instructed to stop smoking and strengthen breathing exercise 6 weeks before surgery, strengthen chest deep breathing, avoid the fixation or binding of limited breathing after surgery, encourage expectoration, sputum can be given drugs to assist expectoration when expectoration is difficult, and sputum suction device can be used when necessary.

Laparoscopic radical resection of colorectal cancer has the same indications as laparotomy, but not all patients are suitable for laparoscopic surgery (30, 31). For example, for patients with long-term heart disease or lung disease, because they cannot perform pneumoperitoneum treatment for a long time, traditional open surgery must be used. For patients with intestinal obstruction or severe abdominal complications after surgery for certain diseases, laparoscopic surgery can easily cause intestinal dilatation, severe congestion, and difficult surgery, resulting in secondary infection during the operation. For patients whose bleeding cannot be controlled, laparoscopic radical surgery is easy to cause surgical anatomy is not smooth, the field of vision is fuzzy, and cannot effectively complete the laparoscopic surgery. Before the start of laparoscopic surgery, if there is a serious adhesion problem in the abdominal cavity, it is easy to cause intestinal damage such as bleeding in the laparoscopic surgery (32, 33). After summing up the experience of the author's department after surgery, it is believed that the specific location of the tumor should be accurately located before the operation to ensure the smooth completion of the operation. During laparoscopic surgery, try to avoid traction on the tumor, and use cotton tape to ligate the mesentery and tumor intestine to prevent the spread of cancer cells. When separating cancer cell tissue, try to handle it in the interstitial space to avoid intestinal injury. When the tumor is removed, it should be cut in a certain size and range in strict accordance with the requirements of the surgery. It should also be ensured that the cancer cells around the lymph nodes and related tissues are completely removed to ensure that the colon cancer can be cured and the cancer recurrence rate is minimized. Post-operative gauze and thin film bags should be provided to complete the protection of the intestinal incision, and to seal the sleeve to ensure no air leakage. The blood plasma drainage tube should also be retained and located not far from the anastomosis so as not to compress the anastomosis. Through observation of the drainage liquid at the anastomosis, we ensured that the drainage tube could smoothly conduct drainage and prevented the occurrence of inflammation. Because laparoscopic surgery loses the tactile feedback of fingers, and the operation space is narrow, the operation area is sometimes located in the deep pelvic cavity, the operator's hands are far away from the target unit in the operation area, and the exposure of the target unit in the operation area is difficult, which makes the colon dissociation and lymph nodes dissection more difficult than traditional surgery. Therefore, it is necessary to make full preparations before operation.

CONCLUSIONS

Laparoscopic radical resection of colorectal cancer in the elderly patients has good effect, short operation time, less trauma, less blood loss during operation, short hospital stay, good recovery of gastrointestinal function, fewer complications, and high safety.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Cangxian Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

BL wrote the manuscript and is the instructor of the entire research for comprehensive guidance. BL, CY, and HL collected the clinical datas and do statistical analysis. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Haraldsdottir S, Einarsdottir HM, Smaradottir A, Gunnlaugsson A, Halfdanarson TR. Colorectal cancer - review. *Laeknabladid.* (2014) 100:75–82. doi: 10.17992/lbl.2014.02.531
2. Kijima S, Sasaki T, Nagata K, Utano K, Lefor AT, Sugimoto H. Preoperative evaluation of colorectal cancer using CT colonography, MRI, and PET/CT. *World J Gastroenterol.* (2014) 20:16964–75. doi: 10.3748/wjg.v20.i45.16964
3. Wrobel P, Ahmed S. Current status of immunotherapy in metastatic colorectal cancer. *Int J Colorectal Dis.* (2019) 34:13–25. doi: 10.1007/s00384-018-3202-8
4. Voutsadakis I A. The pluripotency network in colorectal cancer pathogenesis and prognosis: an update. *Biomark Med.* (2018) 12:653–65. doi: 10.2217/bmm-2017-0369
5. Devoto L, Celentano V, Cohen R, Khan J, Chand M. Colorectal cancer surgery in the very elderly patient: a systematic review of laparoscopic versus open colorectal resection. *Int J Colorectal Dis.* (2017) 32:1237–42. doi: 10.1007/s00384-017-2848-y
6. Sheng S, Zhao T, Wang X. Comparison of robot-assisted surgery, laparoscopic-assisted surgery, and open surgery for the treatment of colorectal cancer: a network meta-analysis. *Medicine.* (2018) 97:e11817. doi: 10.1097/MD.0000000000011817
7. Inomata M, Yasuda K, Shiraishi N, Kitano S. Clinical evidences of laparoscopic versus open surgery for colorectal cancer. *Jpn J Clin Oncol.* (2009) 39:471–7. doi: 10.1093/jjco/hyp063
8. Gehrman J, Angenete E, Bjorholt I, Lesen E, Haglind E. Cost-effectiveness analysis of laparoscopic and open surgery in routine Swedish care for colorectal cancer. *Surg Endosc.* (2020) 34:4403–12. doi: 10.1007/s00464-019-07214-x
9. Shi L, Guo H, Zheng Z, Liu J, Jiang Y, Su Y. Laparoscopic surgery versus open surgery for colorectal cancer: impacts on natural killer cells. *Cancer Control.* (2020) 27:1148342075. doi: 10.1177/1073274820906811
10. Gogenur M, Watt S K, Gogenur I. Improved immunologic response after laparoscopic versus open colorectal cancer surgery. *Ugeskr Laeger.* (2015) 177:V12140763.
11. Park SJ, Lee KY, Lee SH. Laparoscopic surgery for colorectal cancer in Korea: nationwide data from 2013 to 2018. *Cancer Res Treat.* (2020) 52:938–44. doi: 10.4143/crt.2020.043
12. Giglio MC, Luglio G, Sollazzo V, Liccardo F, Peltrini R, Sacco M, et al. Cancer recurrence following conversion during laparoscopic colorectal resections: a meta-analysis. *Aging Clin Exp Res.* (2017) 29:115–20. doi: 10.1007/s40520-016-0674-7
13. Qaseem A, Crandall CJ, Mustafa RA, Hicks LA, Wilt TJ, Forciea MA, et al. Screening for colorectal cancer in asymptomatic average-risk adults: a guidance statement from the American college of physicians. *Ann Intern Med.* (2019) 171:643–54. doi: 10.7326/M19-0642
14. Lalchandani UR, Sahai V, Hersberger K, Francis IR, Wasnik AP. A radiologist's guide to response evaluation criteria in solid tumors. *Curr Probl Diagn Radiol.* (2019) 48:576–85. doi: 10.1067/j.cpradiol.2018.07.016
15. Connell LC, Mota JM, Braghiroli MI, Hoff PM. The rising incidence of younger patients with colorectal cancer: questions about screening, biology, and treatment. *Curr Treat Options Oncol.* (2017) 18:23. doi: 10.1007/s11864-017-0463-3
16. Cremolini C. When to use triplet chemotherapy as first-line treatment in metastatic colorectal cancer. *Clin Adv Hematol Oncol.* (2019) 17:433–5.
17. Pappas-Gogos G, Baltagiannis EG, Kyrochristos ID, Ziogas DE, Goussia A, Mitsis M, et al. Predictive and patient-monitoring biomarkers: precision in the management of colorectal cancer. *Biomark Med.* (2020) 14:335–9. doi: 10.2217/bmm-2020-0025
18. Wang GR, Wang ZW, Jin ZY. Application and progress of texture analysis in the therapeutic effect prediction and prognosis of neoadjuvant chemoradiotherapy for colorectal cancer. *Chin Med Sci J.* (2019) 34:45–50. doi: 10.24920/003572
19. Tan S, Jiang T, Ebrahimi A, Langrish T. Effect of spray-drying temperature on the formation of flower-like lactose for griseofulvin loading. *Eur J Pharm Sci.* (2018) 111:534–9. doi: 10.1016/j.ejps.2017.10.040
20. Currie AC, Malietzis G, Jenkins JT, Yamada T, Ashrafian H, Athanasiou T, et al. Network meta-analysis of protocol-driven care and laparoscopic surgery for colorectal cancer. *Br J Surg.* (2016) 103:1783–94. doi: 10.1002/bjs.10306
21. Otani T, Isohata N, Kumamoto K, Endo S, Utano K, Nemoto D, et al. An evidence-based medicine approach to the laparoscopic treatment of colorectal cancer. *Fukushima J Med Sci.* (2016) 62:74–82. doi: 10.5387/fms.2016-4
22. Hayashi M, Komeda K, Inoue Y, Shimizu T, Asakuma M, Hirokawa F, et al. Simultaneous laparoscopic resection of colorectal cancer and synchronous metastatic liver tumor. *Int Surg.* (2011) 96:74–81. doi: 10.9738/1383.1
23. Moris D, Tsilimigras DI, Machairas N, Merath K, Cerullo M, Hasemaki N, et al. Laparoscopic synchronous resection of colorectal cancer and liver metastases: a systematic review. *J Surg Oncol.* (2019) 119:30–9. doi: 10.1002/jso.25313
24. Xu X, Guo Y, Chen G, Li C, Wang H, Dong G. Laparoscopic resections of colorectal cancer and synchronous liver metastases: a case controlled study. *Minim Invasive Ther Allied Technol.* (2018) 27:209–16. doi: 10.1080/13645706.2017.1378236
25. Cianchi F, Staderini F, Badii B. Single-incision laparoscopic colorectal surgery for cancer: state of art. *World J Gastroenterol.* (2014) 20:6073–80. doi: 10.3748/wjg.v20.i20.6073
26. Martel G, Crawford A, Barkun J S, Boushey RP, Ramsay CR, Fergusson DA. Expert opinion on laparoscopic surgery for colorectal cancer parallels evidence from a cumulative meta-analysis of randomized controlled trials. *PLoS ONE.* (2012) 7:e35292. doi: 10.1371/journal.pone.0035292
27. Pantalos G, Patsouras D, Spartalis E, Dimitroulis D, Tsourouflis G, Nikiteas N. Three-dimensional versus two-dimensional laparoscopic surgery for colorectal cancer: systematic review and meta-analysis. *In Vivo.* (2020) 34:11–21. doi: 10.21873/invivo.11740
28. Davies MM, Larson DW. Laparoscopic surgery for colorectal cancer: the state of the art. *Surg Oncol.* (2004) 13:111–8. doi: 10.1016/j.suronc.2004.08.003
29. Sawazaki S, Numata M, Morita J, Maezawa Y, Amano S, Aoyama T, et al. Safety of laparoscopic surgery for colorectal cancer in patients with severe comorbidities. *Anticancer Res.* (2018) 38:3767–72. doi: 10.21873/anticanres.12659
30. Liang Y, Li G, Chen P, Yu J. Laparoscopic versus open colorectal resection for cancer: a meta-analysis of results of randomized controlled trials on recurrence. *Eur J Surg Oncol.* (2008) 34:1217–24. doi: 10.1016/j.ejso.2007.11.004
31. Zhou S, Zhu H, Li Z, Ying X, Xu M. Safety of laparoscopic resection for colorectal cancer in patients with liver cirrhosis: a retrospective cohort study. *Int J Surg.* (2018) 55:110–6. doi: 10.1016/j.ijsu.2018.05.730
32. Shimizu H, Yamazaki R, Ohtsuka H, Osaka I, Takuma K, Morita Y. Feasibility of laparoscopic surgery after stent insertion for obstructive colorectal cancer. *Asian J Endosc Surg.* (2018) 11:118–22. doi: 10.1111/ases.12434
33. De'Angelis N, Abdalla S, Bianchi G, Memeo R, Charpy C, Petrucciani N, et al. Robotic versus laparoscopic colorectal cancer surgery in elderly patients: a propensity score match analysis. *J Laparoendosc Adv Surg Tech A.* (2018) 28:1334–45. doi: 10.1089/lap.2018.0115

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Liu, Yao and Li. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 25 February 2022
doi: 10.3389/fsurg.2022.842776

Effect of Dexmedetomidine-Assisted Intravenous Anesthesia on Gastrointestinal Motility in Colon Cancer Patients After Open Colectomy

Chaopeng Ou†, *Shiyang Kang*†, *Ruifeng Xue, Jielan Lai and Yingjun Zhang**

Department of Anesthesiology, Sun Yat-sen University Cancer Center, Guangzhou, China

Background: To explore the effect of dexmedetomidine (Dex)-assisted intravenous anesthesia on gastrointestinal motility in patients with colon cancer (CC) after open colectomy.

Methods: A total of 102 patients with CC, undergoing open colectomy in our hospital from January 2018 to January 2020, were selected and randomly divided into an observation group ($n = 51$) and a control group ($n = 51$). The patients in the control group received a routine combination of intravenous and inhalation anesthesia (CIIA), while those in the observation group received a Dex-assisted CIIA. The systolic blood pressure (SBP), the diastolic blood pressure (DBP), heart rate (HR), and the mean arterial pressure (MAP) were compared at different time points between the two groups. In addition, the intraoperative general conditions, the dosage of anesthetics, and the recovery of gastrointestinal functions were also compared between the two groups. Moreover, before operation and at 24 h after operation, the levels of serum gastrin (GAS) and plasma motilin (MTL) were detected by radioimmunoassay, and the level of plasma cholecystokinin (CCK) was detected by an enzyme-linked immunosorbent assay. The incidence of gastrointestinal complications was recorded in both groups.

Results: At T_1-T_3, the HR, SBP, DBP, and MAP levels were lower in both groups than those at T_0. In addition, they were also lower in the observation group than those in the control group, showing significant differences ($p < 0.05$). The dosage of propofol and remifentanil in the observation group was lower than that in the control group, and there was a significant difference ($p < 0.05$). In the observation group, the postoperative first exhaust time, first defecation time, first ambulation time, and first feeding time were all earlier than those in the control group with significant differences ($p < 0.05$). After the operation, the observation group had higher levels of GAS and MTL but a lower level of CCK than the control group, and the differences were significant ($p < 0.05$). The incidence rate of gastrointestinal complications in the observation group (7.04%) was lower than that in the control group (19.61%), and there was a significant difference ($\chi^2 = 4.346$, $p < 0.05$).

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Guobin Miao,
Tsinghua University, China
Changfu Qin,
Shihezi University, China

***Correspondence:**
Yingjun Zhang
zhangyingj@sysucc.org.cn

†*These authors have contributed equally to this work*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *24 December 2021*
Accepted: *24 January 2022*
Published: *25 February 2022*

Citation:
Ou C, Kang S, Xue R, Lai J and Zhang Y (2022) Effect of Dexmedetomidine-Assisted Intravenous Anesthesia on Gastrointestinal Motility in Colon Cancer Patients After Open Colectomy. Front. Surg. 9:842776. doi: 10.3389/fsurg.2022.842776

Conclusions: Dex-assisted intravenous anesthesia can facilitate the recovery of gastrointestinal motility, can regulate the levels of gastrointestinal hormones, and can stabilize the levels of hemodynamic indexes in patients with CC after open colectomy.

Keywords: dexmedetomidine, intravenous anesthesia, open colectomy, gastrointestinal motility, gastrin

INTRODUCTION

Colon cancer (CC) is a digestive tract malignancy that frequently occurs at the junction of the rectum and the sigmoid colon (1). It clinically manifests as abdominal pain, abdominal masses, changes in defecation habits, anemia, and gastrointestinal irritation and causes intestinal obstruction and intestinal perforation (2). Open colectomy, the current preferred treatment of CC, can radically clear and excise the tumor, producing a definite clinical efficacy (3). However, the gastrointestinal motility changes in some patients due to surgical trauma and intraoperative intravenous anesthesia, which inhibits the postoperative gastrointestinal motility, and in severe cases, affects the respiratory and circulatory function of the patient, thus negatively affecting the postoperative recovery (4). Dexmedetomidine (Dex) is a novel selective α2-adrenergic receptor agonist characterized by high intrinsic activity and short half-life (5). It can inhibit the release of catecholamines and sympathetic nervous excitability in the central sympathetic nervous system, without respiratory depression. Hence, it has been widely used for sedation during anesthesia or mechanical ventilation (6, 7). Previously, the effect of Dex in cancer surgery had been reported (8), but the effect of Dex in intravenous anesthesia on gastrointestinal motility in patients with CC after open colectomy has rarely been reported. In the present study, the effect of Dex-assisted intravenous anesthesia on gastrointestinal motility in patients with CC an after open colectomy was analyzed to provide a basis for the clinical treatment of patients with CC.

MATERIALS AND METHODS

General Data

A total of 102 patients with CC undergoing open colectomy in our hospital from January 2018 to January 2020 were selected. The inclusion criteria were as follows: (1) patients meeting the diagnostic criteria for CC (9) and confirmed by the clinical-pathological examination; (2) those undergoing open colectomy; (3) those in American Society of Anesthesiologists (ASA) classes I-II and TNM stages I-II; (4) those who are not undergoing preoperative radiotherapy and chemotherapy; (5) those with an expected survival time >3 months; and 6) those who and whose families were fully informed of this study and had signed the informed consent. The exclusion criteria were as follows: (1) patients who are complicated with severe insufficiency in the heart, liver, or kidney, immune-related diseases, or systemic acute/chronic infectious diseases; (2) those with a history of allergy to drugs used in this study; or (3) those who are complicated with other malignancies and/or psychological or mental diseases. The patients were divided into an observation group ($n = 51$) and a control group ($n = 51$) using a random number table. General data, such as age, gender, and ASA class, had no significant differences between the two groups of patients ($p > 0.05$) (**Table 1**). This study was approved by the Hospital Ethics Committee.

Anesthesia Methods

The patients in the control group received a routinely combined intravenous and inhalation anesthesia (CIIA). Under routine electrocardiograph monitoring, intravenous access was established. Midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd., NMPN H20143222) at.03 mg/kg, fentanyl (Yichang HumanWell Pharmaceutical Co., Ltd., NMPN H42022076) at 3 μg/kg, propofol injection (Xi'an Libang Pharmaceutical Co., Ltd., NMPN H20040300) at 1.5 mg/kg, and cisatracurium besilate (Jiangsu Hengrui Pharmaceutical Co., Ltd., NMPN H20060869) at 0.6 mg/kg were used for the intravenous target-controlled infusion to induce anesthesia until muscular relaxation, followed by tracheal intubation. Sevoflurane (Hebei Yipin Pharmaceutical Co., Ltd., NMPN H20173156) was intravenously infused at 0.5–2% to maintain anesthesia, propofol injection was infused at 0.07 μg/kg/min with an additional 1.5 μg every 30 min, and cisatracurium besilate was additionally supplemented at 0.3 mg/kg every 30 min until 20 min before the end of the operation.

The patients in the observation group received a Dex-assisted CIIA. At 10 min before anesthesia induction, a loading dose of Dex (Jiangsu Hengrui Pharmaceutical Co., Ltd., NMPN H20090248) was pumped at 1 μg/kg, and the methods of anesthesia induction and maintenance were the same as those in the control group. After the start of the operation, Dex was continuously pumped at 1.5 μg/kg/h until 30 min before the end of the operation. Open colectomy was conducted under general anesthesia in both groups.

Observation Indexes

Changes in SBP, DBP, HR, and Mean Arterial Pressure (MAP) at Different Time Points

The changes in SBP, DBP, HR, and MAP were recorded in both groups before anesthesia induction (T_0), at the time of intubation (T_1), at the time of extubation (T_2), and 5 min after extubation (T_3).

Intraoperative General Conditions and Recovery of Postoperative Gastrointestinal Function

The intraoperative blood loss, intraoperative infusion volume, operation time, and dosage of propofol and remifentanil were compared between the two groups. The postoperative first

TABLE 1 | Comparison of general data between the two groups [*n* (%), χ ± s].

Index		Observation group ($n = 51$)	Control group ($n = 51$)	χ^2/t	*P*
Gender (n)	Male	34 (66.67)	30 (58.82)	0.671	0.413
	Female	17 (33.33)	21 (41.18)		
Age (Y)		55.02 ± 5.63	55.47 ± 5.71	0.401	0.689
ASA class (n)	I	29 (56.86)	27 (52.94)	0.158	0.691
	II	22 (43.14)	24 (47.06)		
TNM stage (n)	I	22 (43.14)	25 (49.02)	0.355	0.551
	II	29 (56.86)	26 (50.98)		
Tumor site (n)	Ileocecal junction	12 (23.53)	14 (27.45)	1.143	0.767
	Transverse colon	7 (13.73)	10 (19.61)		
	Ascending colon	9 (17.65)	7 (13.73)		
	Left hemicolon and sigmoid colon	23 (45.10)	20 (39.22)		
Maximum diameter of tumor (cm)		5.73 ± 1.54	5.66 ± 1.38	0.242	0.809

exhaust time, the first defecation time, the first ambulation time, and the first feeding time were recorded in the two groups.

Indexes of Gastrointestinal Function

Before the operation and at 24 h after operation, 5 ml of fasting venous blood was drawn from each patient in the two groups in the early morning. The serum and plasma were separated by centrifugation and stored at −30°C for later use. The levels of serum gastrin (GAS) and plasma motilin (MTL) were detected by radioimmunoassay using kits manufactured by Shanghai X-Y Biotechnology Co., Ltd., (Shanghai, China), and the level of plasma cholecystokinin (CCK) was detected by ELISA using kits manufactured by Shanghai Enzyme Research Biotechnology Co., Ltd. (Shanghai, China) in strict accordance with the instructions (10, 11).

Gastrointestinal Complications

The incidence of gastrointestinal complications, such as abdominal pain, abdominal distension, nausea, and intestinal obstruction, was recorded in the two groups.

Statistical Analysis

The Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) was used for data analysis. Measurement data were expressed as (χ ± s). Independent-sample (two-sample) *t*-test was used to compare the intergroup difference without time factors, and repeated measures of ANOVA was done to compare the intergroup difference with time factors. Enumeration data were expressed as rate, and χ^2 test was performed for the difference between the two groups. Two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Comparison of Changes in HR, SBP, DBP, and MAP Between the Two Groups at Different Time Points

At T_0, HR, SBP, DBP, and MAP levels had no statistically significant differences between the two groups ($p > 0.05$). At T_1-T_3, HR, SBP, DBP, and MAP levels were lower in both groups than those at T_0, and they were also lower in the observation group than those in the control group ($p < 0.05$) (**Table 2**).

TABLE 2 | Comparison of changes in heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) between the two groups at different time points (χ±s).

Index	Time point	Observation group ($n = 51$)	Control group ($n = 51$)
HR (beats/min)	T_0	105.43 ± 5.27	106.14 ± 5.08
	T_1	92.58 ± 6.25	98.62 ± 5.47
	T_2	88.65 ± 6.89	96.28 ± 6.15
	T_3	82.52 ± 6.43	90.49 ± 6.96
F_{time}/P		85.59/<0.001	
$F_{intergroup}/P$		178.40/<0.001	
$F_{interaction}/P$		7.73/<0.001	
SBP (mmHg)	T_0	120.33 ± 10.21	120.81 ± 10.36
	T_1	113.28 ± 9.15	119.07 ± 9.14
	T_2	104.50 ± 8.74	112.43 ± 9.55
	T_3	93.85 ± 8.36	103.89 ± 10.13
F_{time}/P		41.68/<0.001	
$F_{intergroup}/P$		102.90/<0.001	
$F_{interaction}/P$		4.78/0.002	
DBP (mmHg)	T_0	88.72 ± 8.44	89.15 ± 8.51
T_0	T_1	83.24 ± 9.18	87.64 ± 8.92
T_1	T_2	72.91 ± 9.75	83.27 ± 9.13
T_2	T_3	65.83 ± 10.26	72.58 ± 9.69
F_{time}/P		35.83/<0.001	
$F_{intergroup}/P$		90.89/<0.001	
$F_{interaction}/P$		5.17/0.001	
MAP (mmHg)	T_0	126.87 ± 12.43	130.45 ± 12.19
	T_1	129.95 ± 13.08	122.76 ± 13.05
	T_2	127.89 ± 12.52	121.15 ± 12.58
	T_3	112.46 ± 10.19	104.95 ± 9.82
F_{time}/P		14.03/<0.001	
$F_{intergroup}/P$		57.79/<0.001	
$F_{interaction}/P$		5.07/0.001	

TABLE 3 | Comparison of intraoperative general conditions and dosage of anesthetics between the two groups ($n = 51$, $\bar{x} \pm s$).

Group	Intraoperative blood loss (mL)	Intraoperative infusion volume (L)	Operation time (h)	Propofol (g)	Remifentanil (mg)
Observation group	291.35 ± 17.29	1.33 ± 0.12	2.94 ± 0.35	0.83 ± 0.13	1.669 ± 0.36
Control group	292.73 ± 19.04	1.39 ± 0.27	3.08 ± 0.41	1.05 ± 0.15	2.51 ± 0.49
t	0.383	1.450	1.855	7.915	9.631
P	0.702	0.150	0.067	<0.001	<0.001

TABLE 4 | Comparison of recovery of postoperative gastrointestinal function between the two groups ($n = 51$, $\bar{x} \pm s$).

Group	First exhaust time (h)	First defecation time (d)	First ambulation time (h)	First feeding time (d)
Observation group	37.42 ± 4.65	2.14 ± 0.36	29.81 ± 3.55	3.02 ± 0.43
Control group	51.23 ± 5.34	3.58 ± 0.55	40.13 ± 5.12	3.59 ± 0.47
t	13.928	15.644	11.829	6.390
P	<0.001	<0.001	<0.001	<0.001

Comparison of Intraoperative General Conditions and Dosage of Anesthetics Between the Two Groups

The intraoperative blood loss, the intraoperative infusion volume, and othe peration time had no statistically significant differences between the two groups ($p > 0.05$). The dosage of propofol and remifentanil in the observation group was lower than that in the control group ($p < 0.05$) (**Table 3**).

Comparison of Recovery of Postoperative Gastrointestinal Function Between the Two Groups

In the observation group, the postoperative first exhaust time, the first defecation time, the first ambulation time, and the first feeding time were all earlier than those in the control group ($p < 0.05$) (**Table 4**).

Comparison of Indexes of Gastrointestinal Function Between the Two Groups Before and After the Operation

No statistically significant differences were found in the levels of GAS, MTL, and CCK between the two groups before operation ($p > 0.05$). After the operation, the levels of GAS and MTL rose, while the level of CCK declined in the two groups compared with those before the operation ($p < 0.05$). After the operation, the observation group had significantly higher levels of GAS and MTL but a significantly lower level of CCK than the control group ($p < 0.05$) (**Table 5**).

Comparison of Incidence of Gastrointestinal Complications Between the Two Groups

In the observation group, there were 2 cases of abdominal distension, 1 case of abdominal pain, and 2 cases of nausea after the operation. In the control group, there were 4 cases of abdominal distension, 1 case of abdominal pain, 3 cases of nausea, and 2 cases of intestinal obstruction after the operation. It can be seen that the incidence rate of gastrointestinal complications in the observation group (7.04%) was lower than that in the control group (19.61%) ($\chi^2 = 4.346$, $p < 0.05$).

DISCUSSION

Colon cancer (CC) is a gastrointestinal tract malignancy derived from the colonic mucosal epithelium, manifested as varying degrees of abdominal distension, indigestion, and changes in defecation habits in most patients (12). Radical surgery is an effective treatment means for CC, but some patients suffer from intraoperative hemodynamic fluctuations and enhanced sympathetic nervous excitability due to intestinal obstruction and the intravenous anesthetics used, resulting in postoperative gastrointestinal dysfunction (4, 13). Dex is a fast-onset and short-acting α2-adrenergic receptor agonist with sedative and analgesic effects but no respiratory depression, which can effectively lower sympathetic nervous excitability and restore gastrointestinal function (14).

In this study, at T1-T3, the HR, SBP, DBP, and MAP levels were lower in both groups than those at T0, and they were also lower in the observation group than those in the control group, suggesting that Dex can effectively improve both blood pressure and HR of patients with CC undergoing open colectomy. During intravenous anesthesia, intubation and extubation can cause irritation of varying degrees to patients, leading to fluctuations in blood pressure, HR, and other hemodynamic indexes. Dex can, through binding to α2 receptors, inhibit the further outflow of sympathetic media, thereby weakening the sympathetic nervous excitability during intubation and extubation and keeping hemodynamic indexes stable in patients with CC undergoing open colectomy (15). In this study, the intraoperative blood loss, the intraoperative infusion volume, and the operation time had no significant differences between the two groups, and the dosage of propofol

TABLE 5 | Comparison of indexes of gastrointestinal function between the two groups before and after the operation ($n = 51$, $\bar{x} \pm s$).

Group	GAS (pg/mL)		MTL (pg/mL)		CCK (pg/mL)	
	Before operation	After operation	Before operation	After operation	Before operation	After operation
Observation group	42.54 ± 4.87	83.42 ± 6.56	253.19 ± 18.39	316.22 ± 26.94	58.56 ± 6.77	37.21 ± 4.34
Control group	43.19 ± 4.35	72.18 ± 6.14	251.58 ± 19.74	293.69 ± 24.87	57.94 ± 6.50	45.69 ± 5.28
t	0.711	8.934	0.426	4.388	0.472	8.860
P	0.479	<0.001	0.671	<0.001	0.638	<0.001

and remifentanil in the observation group was lower than that in the control group, indicating that the dosage of anesthetics can be reduced in Dex-assisted intravenous anesthesia in open colectomy, further ameliorating gastrointestinal dysfunction caused by anesthetics. Previous evidence showed that Dex can stabilize the hemodynamic indexes of patients undergoing hepatectomy. In addition, it can also effectively relieve the stress response in laparoscopic gastrectomy and reduce the dosage of propofol and remifentanil, which is consistent with the results in this study (16, 17). The above findings confirm that Dex-assisted intravenous anesthesia can better stabilize the hemodynamic indexes of patients with CC undergoing open colectomy and effectively reduce the dosage of anesthetics with high safety.

In this study, the postoperative first exhaust time, the first defecation time, the first ambulation time, and the first feeding time in the observation group were all earlier than those in the control group, suggesting that Dex-assisted intravenous anesthesia can promote the recovery of gastrointestinal function in patients with CC after open colectomy. Due to stress, surgical trauma, and anesthetics, patients with CC undergoing open colectomy are prone to intestinal motility disorders, resulting in postoperative gastrointestinal dysfunction. Dex is able to maintain hemodynamic stability, alleviate inflammatory and stress responses, reduce the dosage of intravenous anesthetics, promote intestinal microcirculation perfusion, and protect the intestinal barrier function, contributing to the recovery of postoperative gastrointestinal motility (18, 19). Previous evidence showed that Dex-combined anesthesia exerts a protective effect on the intestinal barrier function of patients with acute intestinal obstruction, which is consistent with the results in this study, indicating that Dex-assisted intravenous anesthesia can facilitate the recovery of gastrointestinal function in patients with CC after open colectomy. Besides, GAS, MTL, and CCK are all important gastrointestinal hormones. GAS can promote gastric emptying through stimulating gastric acid secretion, MTL can enhance gastrointestinal motility, and CCK can suppress gastric emptying by inhibiting the contraction of the esophageal sphincter (20). In this Study, the observation group had higher levels of GAS and MTL but had a lower level of CCK than the control group after the operation, demonstrating that Dex can regulate the levels of gastrointestinal hormones in patients with CC after open colectomy, thereby improving the gastrointestinal function. In addition, the incidence rate of gastrointestinal complications (abdominal distension, abdominal pain, nausea, and intestinal obstruction) in the observation group was lower than that in the control group, further confirming that Dex-assisted intravenous anesthesia can boost the recovery of gastrointestinal motility with high safety in patients with CC after open colectomy.

CONCLUSIONS

In conclusion, Dex-assisted intravenous anesthesia can facilitate the recovery of gastrointestinal motility, stabilize the levels of hemodynamic indexes, and regulate the levels of gastrointestinal hormones in patients with CC after open colectomy, with high safety. However, there were deficiencies in this study. For example, the sample size was limited, and the effect of non-effect dose of Dex on gastrointestinal motility in patients with CC after open colectomy was not explored and analyzed. Therefore, the sample size remains to be expanded for validation in the future.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Sun Yat-sen University Cancer Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CO, SK, and YZ designed the study and prepared the manuscript. CO, SK, and RX collected the data. YZ and JL analyzed the data. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Otani K, Kawai K, Hata K, Tanaka T, Nishikawa T, Sasaki K, et al. Colon cancer with perforation. *Surg Today.* (2019) 49:15–20. doi: 10.1007/s00595-018-1661-8
2. Ruan H, Leibowitz BJ, Zhang L, Yu J. Immunogenic cell death in colon cancer prevention and therapy. *Mol Carcinog.* (2020) 59:783–93. doi: 10.1002/mc.23183
3. Akyüz M, Topal U, Kültüroğlu M, Sozuer E, Dal F, Talih T, et al. Comparison of rarely observed tumors of the colorectal region clinicopathologically. *Iran Red Crescent Med J.* (2021) 23:e1404. doi: 10.32592/ircmj.2021.23.11.1404
4. Gleason F, Chu DI, Kennedy GD, Kenzik KM. Early elective surgery after colon cancer diagnosis has higher risk of readmission and death. *Ann Surg.* (2021) 273:188–94. doi: 10.1097/SLA.0000000000004431
5. Lee S. Dexmedetomidine: present and future directions. *Korean J Anesthesiol.* (2019) 72:323–30. doi: 10.4097/kja.19259
6. Kaye AD, Chernobylsky DJ, Thakur P, Siddaiah H, Kaye RJ, Eng LK, et al. Dexmedetomidine in Enhanced Recovery After Surgery (ERAS) Protocols for Postoperative Pain. *Curr Pain Headache Rep.* (2020) 24:21. doi: 10.1007/s11916-020-00853-z
7. Grape S, Kirkham KR, Frauenknecht J, Albrecht E. Intra-operative analgesia with remifentanil vs. dexmedetomidine: a systematic review and meta-analysis with trial sequential analysis. *Anaesthesia.* (2019) 74:793–800. doi: 10.1111/anae.14657
8. Sperotto F, Mondardini MC. Dell'Oste C, Vitale F, Ferrario S, Lapi M, et al. Efficacy and Safety of Dexmedetomidine for Prolonged Sedation in the PICU: a Prospective Multicenter Study (PROSDEX). *Pediatr Crit Care Med.* (2020) 21:625–36. doi: 10.1097/PCC.0000000000002350
9. Dekker E, Tanis PJ, Vleugels J, Kasi PM, Wallace MB. Colorectal cancer. *Lancet.* (2019) 394:1467–80. doi: 10.1016/S0140-6736(19)32319-0
10. Wang C, Wang B, Aili M, Huo S, Han MT, Aibai S, et al. Effect of Artemisia rupestris L. Extract on gastrointestinal hormones and brain-gut peptides in functional dyspepsia rats. *Evid Based Complement Alternat Med.* (2020) 2020:2528617. doi: 10.1155/2020/2528617
11. Kobayashi T, Masaki T, Kogawa K, Matsuoka H, Sugiyama M. Efficacy of gum chewing on bowel movement after open colectomy for left-sided colorectal cancer: a randomized clinical trial. *Dis Colon Rectum.* (2015) 58:1058–63. doi: 10.1097/DCR.0000000000000452
12. Argiles G, Tabernero J, Labianca R, Hochhauser D, Salazar R, Iveson T, et al. Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* (2020) 31:1291–305. doi: 10.1016/j.annonc.2020.06.022
13. Langarizadeh M, Sayadi M. Machine learning techniques for diagnosis of lower gastrointestinal cancer: a systematic review. *Iran Red Crescent Med J.* (2021) 23:e436. doi: 10.32592/ircmj.2021.23.7.436
14. Yuan D, Liu Z, Kaindl J, Maeda S, Zhao J, Sun X, et al. Activation of the alpha2B adrenoceptor by the sedative sympatholytic dexmedetomidine. *Nat Chem Biol.* (2020) 16:507–12. doi: 10.1038/s41589-020-0492-2
15. Mei B, Li J, Zuo Z. Dexmedetomidine attenuates sepsis-associated inflammation and encephalopathy via central alpha2A adrenoceptor. *Brain Behav Immun.* (2021) 91:296–314. doi: 10.1016/j.bbi.2020.10.008
16. Chamadia S, Pedemonte JC, Hobbs LE, Deng H, Nguyen S, Cortinez LI, et al. A Pharmacokinetic and pharmacodynamic study of oral dexmedetomidine. *Anesthesiology.* (2020) 133:1223–33. doi: 10.1097/ALN.0000000000003568
17. Nair AS, Saifuddin MS, Naik V, Rayani BK. Dexmedetomidine in cancer surgeries: Present status and consequences with its use. *Indian J Cancer.* (2020) 57:234–8. doi: 10.4103/ijc.IJC_376_19
18. Zhang T, Yu Y, Zhang W, Zhu J. Comparison of dexmedetomidine and sufentanil as adjuvants to local anesthetic for epidural labor analgesia: a randomized controlled trial. *Drug Des Devel Ther.* (2019) 13:1171–5. doi: 10.2147/DDDT.S197431
19. Wang K, Wu M, Xu J, Wu C, Zhang B, Wang G, et al. Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: systematic review and meta-analysis. *Br J Anaesth.* (2019) 123:777–94. doi: 10.1016/j.bja.2019.07.027
20. Rehfeld JF. Premises for cholecystokinin and gastrin peptides in diabetes therapy. *Clin Med Insights Endocrinol Diabetes.* (2019) 12:1218420648. doi: 10.1177/1179551419883608

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Ou, Kang, Xue, Lai and Zhang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 25 February 2022
doi: 10.3389/fsurg.2022.842292

hsa_circ_0072309 Expression Profiling in Non-small-Cell Lung Carcinoma and Its Implications for Diagnosis and Prognosis

Yong Zhou[1,2†], *Zhongkai Tong*[1,2†], *Xiaoxiao Zhu*[1,2], *Shaoqing Huang*[1,2], *Zhaoxing Dong*[1,2*] *and Zhenyue Ye*[1,2*]

[1] *Respiratory Department, HwaMei Hospital, University of Chinese Academy of Sciences, Ningbo, China,* [2] *Ningbo Institute of Life and Health Industry, University of Chinese Academy of Sciences, Ningbo, China*

Circular RNAs (circRNAs), which fall into the category of endogenous ncRNAs, are linked to disease progression of neoplastic diseases. Whereas, it remains uncharacterized regarding hsa_circ_0072309's function and implications in lung carcinoma (LC). Gene Expression Omnibus (GEO) database was utilized for identifying circRNAs with aberrantly expression in LC. qRT-PCR was responsible for determining hsa_circ_0072309 levels in lung adenocarcinoma (LAC). Also, its involvement in LC cell progression was investigated. Experimentally, hsa_circ_0072309 was identified as one of the most aberrantly down-regulated circRNAs in the GEO database (GSE101684 and GSE112214). qRT-PCR revealed notably down-regulated hsa_circ_0072309 in LAC tissue, which had a close association with adverse 3-year survival, as well as LNM and advanced TNM stage. Based on ROC, the AUC of hsa_circ_0072309 was determined to be 0.887, and its specificity and susceptibility can be improved by combined detection of either CYFRA21-1 or CEA. In a word, hsa_circ_0072309 is lowly expressed in lung cancer patients and the survival rate of lowly expressed patients is significantly lower, a candidate marker with prognostic utility for the disease.

Keywords: hsa_circ_0072309, NSCLC, diagnosis, prognosis, GEO

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Xiaming Pei,
Hunan Cancer Hospital, China
Jianhua Xiao,
University of South China, China

***Correspondence:**
Zhaoxing Dong
2538287311@qq.com
Zhenyue Ye
yezhenyue2021@163.com

[†] *These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *23 December 2021*
Accepted: *20 January 2022*
Published: *25 February 2022*

Citation:
Zhou Y, Tong Z, Zhu X, Huang S, Dong Z and Ye Z (2022) hsa_circ_0072309 Expression Profiling in Non-small-Cell Lung Carcinoma and Its Implications for Diagnosis and Prognosis. Front. Surg. 9:842292. doi: 10.3389/fsurg.2022.842292

INTRODUCTION

Lung carcinoma (LC), as a prevalent respiratory malignancy (1). Epidemiological statistics reveal 4.3 million new cancer cases and an associated death toll of 2.9 million in 2018 in China, including 770,000 new LC cases and 690,000 associated deaths (2). Therefore, in the future, not only will the number of LC patients increase, but also the number of elderly patients (3). The predisposing factors of LC in the elderly include smoking, environmental exposure, ionizing radiation, and vocational diseases, heredity (4). However, due to the relatively concealed pathogenesis, the non-specific initial clinical manifestation, and the lack of good clinical diagnostic indicators, the disease has developed into the mid-late stage in some patients when they are hospitalized, resulting in losing the optimal time for operation (5). In addition, the long-term treatment cycle and dim outcomes of advanced LC aggravate the pressure of sufferers and the family economical load (6). Therefore, searching for a diagnostic index with high specificity and sensitivity is pressing to address this problem.

Recent evidence has indicated that non-coding RNAs (ncRNAs), closely linked to human life process, are vital in modulating a wide spectrum of illnesses, especially neoplastic diseases (7). As vital members of ncRNAs, miRNAs and lncRNAs have always been the focus of research (8). circRNAs, on the other hand, are recently found RNAs capable of forming loops that are covalently closed and continuous, with 3′ and 5′RNA ends binded, more favorable stability than linear types, and no polyadenosinic acid counterpart (9). hsa_circ_0072309, or LIFR, is located on chr5:38523520-38530768 (10), with its expression profiling being found in LC (11). But there is no research to prove its connection with patient prognosis and its diagnostic implications in non-small-cell lung carcinoma (NSCLC). Herein, we screened GSE101684 and GSE112214 microarrays and found that hsa_circ_0072309 had high levels in LC, suggesting its role of a candidate target for NSCLC.

Therefore, we have experimentally analyzed the expression of hsa_circ_0072309 in NSCLC patients and its diagnostic significance, providing a new potential target for clinical diagnosis and paving the way for our subsequent studies.

METHODS AND MATERIALS

Microarray (GEO-Chip) Analysis

From GEO database (URL: https://www.ncbi.nlm.nih.gov/gds/), two microarrays (GSE101684 and GSE112214) were obtained. In the GSE101123 microarray, we found 4 tumor samples and 4 normal counterparts. And three tumor samples and three normal counterparts were found in the GSE112214 microarray. Then Series Matrix File(s) was downloaded, and GPL21825 and GPL19978 were sorted out into a matrix file. VLOOKUP function was utilized to correct the circRNA name and limma package to identify the circRNAs with differences (logFC $= 1$, $P < 0.05$). Volcano plots and heat maps were drawn.

Clinical Data

Between February 2017 and February 2019, 46 NSCLC patients who received treatment in our hospital were included, with their peripheral blood samples collected before treatment. Meanwhile, peripheral blood specimens of 40 healthy people with concurrent physical examinations were used as control samples. Informed consents were got before patient enrollment. This study, in compliance with the Helsinki Declaration, has been ethically ratified by our hospital. The two arms were similar in age, sex and BMI ($P > 0.05$).

Eligibility Criteria

Inclusion criteria: Diagnosis of NSCLC by imaging and pathology; In compliance with the TNM staging standard issued by AJCC (8th Edition) (12); Treatment-naive patients who had not received surgical resection, chemoradiotherapy, immunotherapy or molecular targeted therapy before participation.

Exclusion criteria: Other tumors; Estimated survival < 3 months; No follow-up data; Incomplete case date.

qRT-PCR Detection

Serum was analyzed in this study. TRIzol-extracted (Takara Bio, Shiga, Japan) total RNA from the collected serum was subjected to purity and concentration identification and the subsequent cDNA synthesis with use of the PrimeScript RT kit. Then the synthesized cDNA was subjected to amplification by PCR via the SYBR Premix Ex Taq kit, with the reaction system and reaction conditions configured following the instructions provided with the kit. The primers used are listed in **Table 1**. hsa_circ_0072309 expression normalized with β-actin (endogenous control) was obtained via the formula $2^{-\Delta\Delta CT}$[ΔCT(test) = CT(target, test)–CT(ref, test)ΔCT(calibrator) = CT(target, calibrator)–CT(ref, calibrator), ΔΔCT = ΔCT(test)–ΔCT(calibrator)]. In this experiment, the ABI 7500 PCR system was used for analysis.

CEA and CYFRA21-1 Detection

For all experiments, blood samples were collected from an elbow vein in the early morning on an empty stomach prior to the start of treatment. Serum tumor markers: 10 ml of blood was collected. CEA and CYFRA21-1 were measured using a Beckman Coulter AU5800 automated biochemistry analyser.

Endpoints

Primary endpoints: The differential circRNAs in GSE101684 and GSE112214 microarrays were analyzed and heat maps and volcano plots were drawn. Serum and carcinoma tissue hsa_circ_0072309 expression in cases was tested. ROC curves were drawn to visualize hsa_circ_0072309's diagnostic implications in NSCLC.

Secondary endpoints: The connection between hsa_circ_0072309 and patient clinical data was analyzed. In addition, patients were followed up for 3 years to observe the connection between hsa_circ_0072309 and patient prognosis.

Statistical Processing

The above index data were input into SPSS21.0 and GraphPad Prism 8.0 for statistical processing and plotting, respectively. Quantitative variables, described in (Mean ± SD), were analyzed via the independent samples T test. While represented by n, categorical variables were examined using the χ^2 test. ROC curves were used for assessing the diagnostic implications of serum hsa_circ_0072309. Patient survival was evaluated by the K-M algorithm. The R software limma package was used to analyse the differential genes, the library package to map the differential gene volcanoes and the heatmap package to map the differential gene heat map. Significance was set at the probability (P) level < 0.05.

RESULTS

GEO-Chip Analysis

In this study, the GSE101684 microarray was analyzed, and 249 differential circRNAs were identified, of which 157 were over-expressed and 92 were under-expressed (**Table 1**, **Figures 1A,B**). One hundred differential circRNAs were found through analyzing the GSE112214 microarray, including 11 over-expressed and 89 were under-expressed circRNAs

TABLE 1 | The top five up- down-regulated circRNAs in the GSE101684 microarray.

Symbol	logFC	AveExpr	*t*-value	*P*-Value	adj.P.Val	β
Up						
hsa_circ_0072088	2.830	10.003	5.380	4.212E-04	0.011	0.339
hsa_circ_00723098	2.828	11.026	8.856	8.780E-06	0.003	4.135
hsa_circ_0067301	2.689	9.446	7.046	5.560E-05	0.005	2.358
hsa_circ_0001806	2.571	13.307	7.611	3.010E-05	0.004	2.955
hsa_circ_0006349	2.459	12.740	9.572	4.590E-06	0.003	4.739
Down						
hsa_circ_0000317	−2.627	10.286	−5.631	3.033E-04	0.009	0.670
hsa_circ_0001640	−2.057	7.020	−4.820	9.056E-04	0.016	−0.433
hsa_circ_0013480	−2.042	8.534	−6.318	1.290E-04	0.006	1.525
hsa_circ_0000320	−2.005	9.213	−4.839	8.815E-04	0.016	−0.406
hsa_circ_0000319	−1.938	7.523	−5.343	4.430E-04	0.012	0.289

TABLE 2 | The top five up- down-regulated circRNAs in the GSE112214 microarray.

Symbol	logFC	AveExpr	*t*-value	*P*-value	adj.P.Val	β
Up						
hsa_circ_0007580	1.257	6.451	7.041	2.083E-04	1.769E-02	1.232
hsa_circ_0001998	1.223	8.145	4.843	1.894E-03	3.874E-02	−1.045
hsa_circ_0017956	1.183	7.915	4.684	2.276E-03	4.295E-02	−1.237
hsa_circ_0003028	1.132	7.414	6.669	2.911E-04	1.974E-02	0.892
hsa_circ_0008758	1.087	8.681	7.245	1.743E-04	1.568E-02	1.412
Down						
hsa_circ_0072309	−2.968	6.912	−9.212	3.770E-05	1.020E-02	2.918
hsa_circ_0008234	−2.450	9.592	−6.210	4.486E-04	2.251E-02	0.450
hsa_circ_0006677	−2.372	9.231	−11.186	1.050E-05	6.183E-03	4.104
hsa_circ_0001947	−2.293	8.022	−7.425	1.495E-04	1.568E-02	1.566
hsa_circ_0072305	−2.181	6.274	−9.070	4.170E-05	1.020E-02	2.822

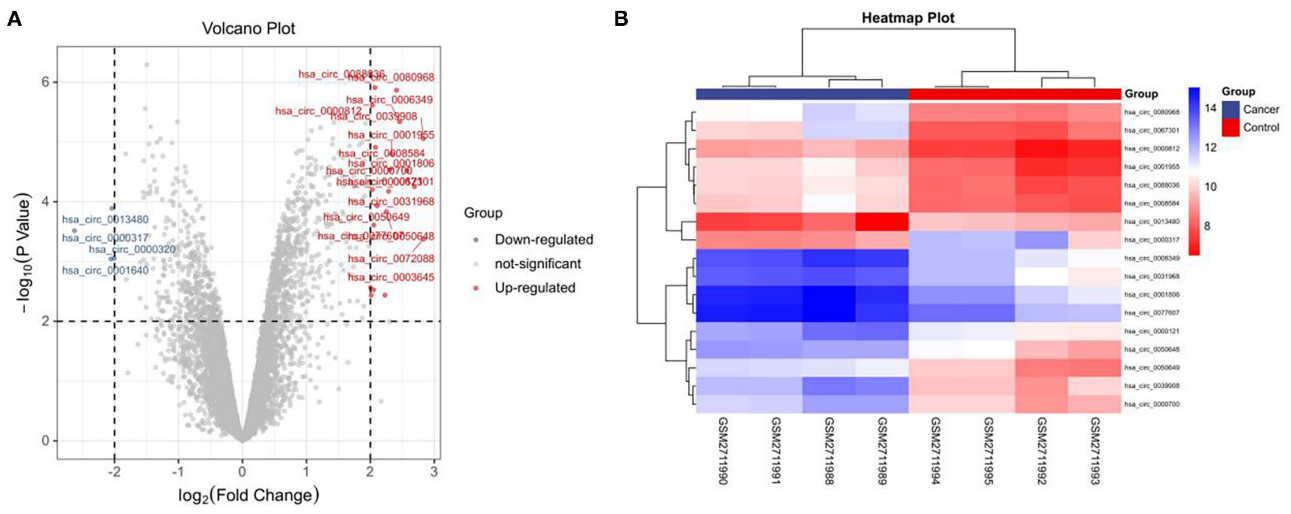


FIGURE 1 | Volcanic plot and heat map of circRNAs with aberrant expression in the GSE101684 microarray. **(A)**. Volcanic plot of circRNAs with aberrant expression in the GSE101684 microarray: Red, blue and gray represent those with high, low, and undifferential expression, respectively. **(B)**. Heat map of circRNAs with aberrant expression in the GSE101684 microarray.

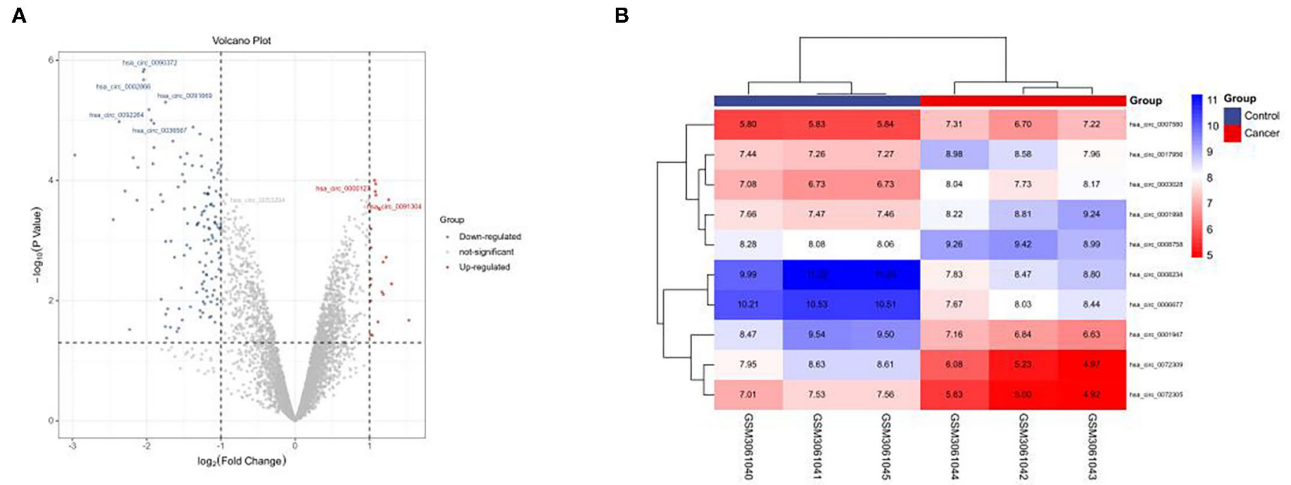


FIGURE 2 | Volcanic plot and heat map of circRNAs with aberrant expression in the GSE112214 microarray. **(A)**. Volcanic plot of differentially expressed circRNAs in the GSE112214 microarray: Red, blue and gray indicate those with high, low, and undifferential expression, respectively. **(B)**. Heat map of circRNAs with aberrant expression in the GSE112214 microarray.

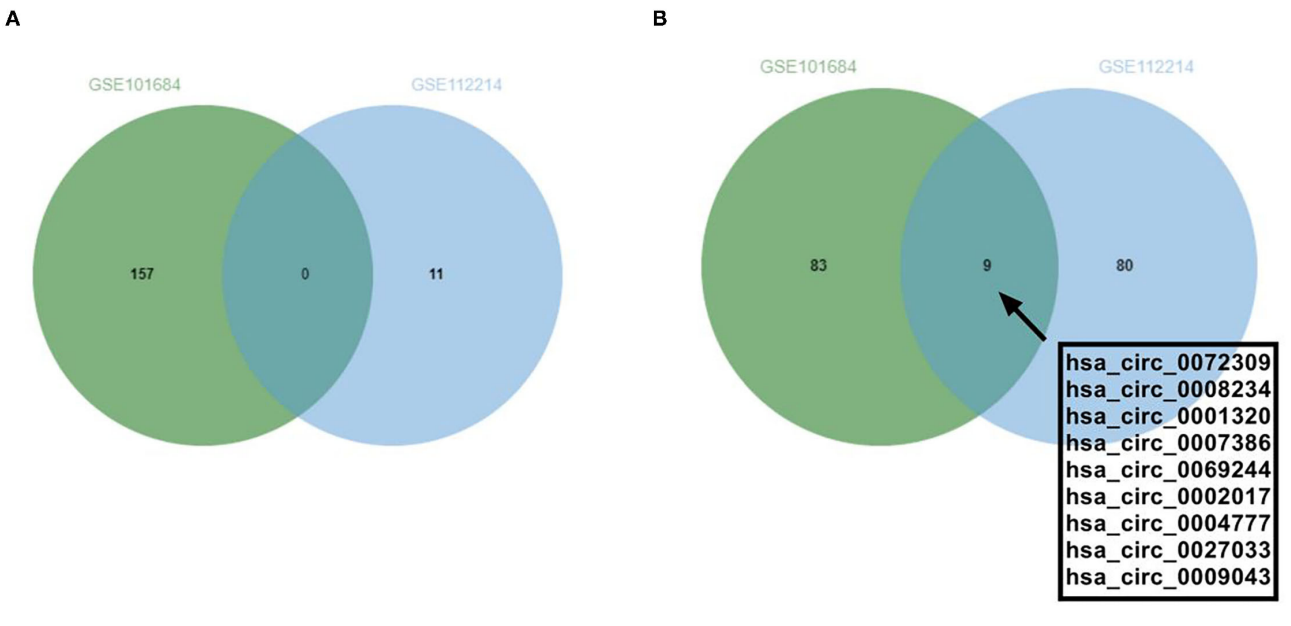


FIGURE 3 | Shared differentially expressed circRNAs in GSE101684 and GSE112214 microarrays. **(A)**. The shared highly expressed circRNAs in GSE101684 and GSE112214 microarrays. **(B)**. The shared low-expressed expressed circRNAs in GSE101684 and GSE112214 microarrays.

(**Table 2**, **Figures 2A,B**). In order to find shared differentially expressed circRNAs, we drew a Venn diagram to find zero shared highly expressed circRNAs in the two microarrays while nine common lowly expressed circRNAs (**Figures 3A,B**). hsa_circ_0072309 with the most significant difference and the largest LogFC was selected for follow-up study.

hsa_circ_0072309 in Cases

We compared serum hsa_circ_0072309 levels between cases and controls and found statistically higher hsa_circ_0072309 levels in cases (**Figure 4**, $P < 0.001$).

Connection Between hsa_circ_0072309 and Patient Clinical Data

Based on median hsa_circ_0072309 expression, cases were subgrouped (high/expression groups, 23 cases each). The comparison of clinical data revealed an evidently elevated chance of developing III-IV LC and lymph node metastasis (LNM) in patients

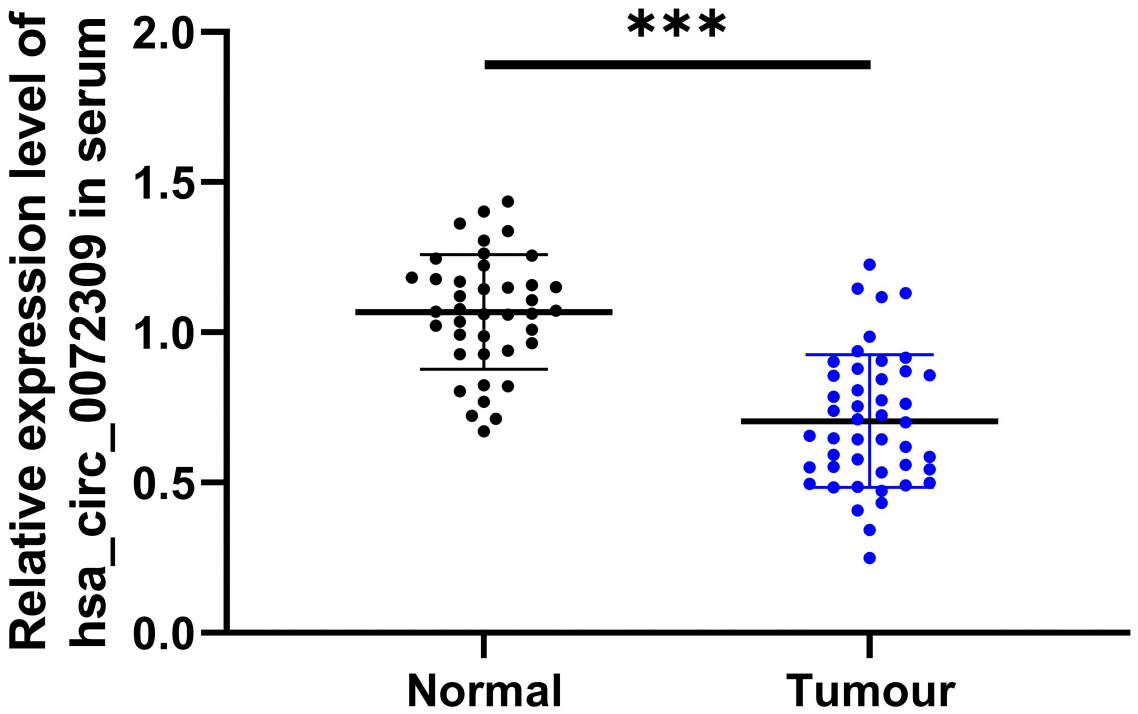


FIGURE 4 | Serum hsa_circ_0072309 in LC patients. *** $P < 0.001$.

TABLE 3 | Connection between hsa_circ_0072309 and patient clinical data.

Variables		Relative expression of hsa_circ_0072309		*P*-value
		High expression ($n = 23$)	Low expression ($n = 23$)	
Age				0.552
	≥60 ($n = 20$)	9	11	
	<60 ($n = 26$)	14	12	
Gender				0.555
	Male ($n = 22$)	12	10	
	Female ($n = 24$)	11	13	
Tumor size (cm)				0.546
	≥3 ($n = 18$)	10	8	
	<3 ($n = 28$)	13	15	
Clinical staging				0.003
	I-II ($n = 26$)	18	8	
	III-IV ($n = 20$)	5	15	
LNM				0.013
	With ($n = 16$)	4	12	
	Without ($n = 30$)	19	11	
Tumor types				0.767
	Squamous cell carcinoma ($n = 21$)	11	10	
	Adenocarcinoma ($n = 25$)	12	13	

TABLE 4 | ROC curve parameters.

Variables	AUC	95 CI%	Specificity	Sensitivity	Youden index	Cut-off
hsa_circ_0072309	0.887	0.818–0.956	82.50%	86.95%	69.45%	0.921
CEA	0.815	0.720–0.911	97.50%	63.04%	60.54%	6.001
CYFRA21-1	0.834	0.743–0.924	77.50%	84.78%	62.28%	3.128
hsa_circ_0072309+CEA	0.940	0.889–0.990	82.50%	95.65%	78.15%	0.337
hsa_circ_0072309+CYFRA21-1	0.944	0.898–0.989	90.00%	84.78%	74.78%	0.614

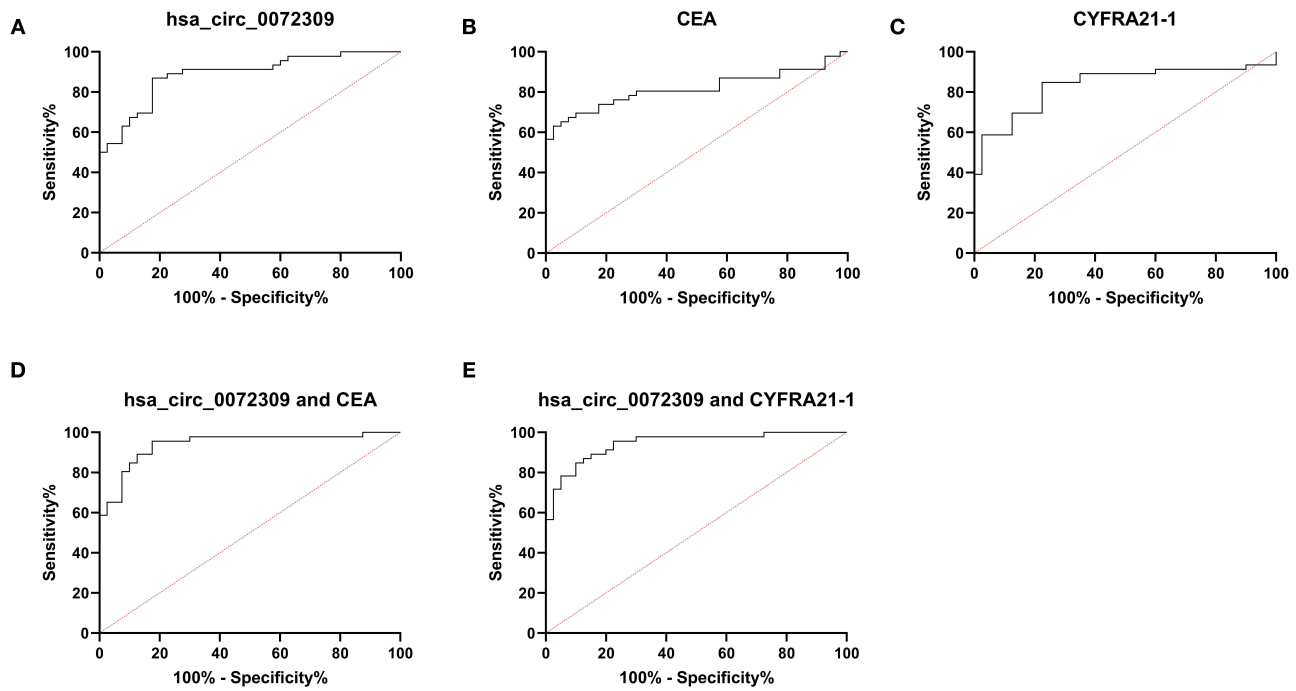


FIGURE 5 | hsa_circ_0072309 for NSCLC diagnosis by ROC analysis. **(A)**. hsa_circ_0072309's implications for NSCLC diagnosis by ROC. **(B)**. CEA's implications for NSCLC diagnosis by ROC. **(C)**. CYFRA21-1's implications for NSCLC diagnosis by ROC. **(D)**. Diagnosistic implications of hsa_circ_0072309+CEA for NSCLC by ROC. **(E)**. Diagnosistic implications of hsa_circ_0072309+CYFRA21-1 for NSCLC by ROC.

with under-expressed hsa_circ_0072309 (**Table 3**, $P < 0.05$).

Diagnostic Implications of hsa_circ_0072309 in NSCLC Patients

ROC curves were drawn to understand hsa_circ_0072309's diagnostic implications in NSCLC patients. Through analysis, hsa_circ_0072309's AUC, specificity and susceptibility were determined to be 0.887, 82.50, and 86.95%, respectively, which were evidently higher than those of CEA (0.815, 97.50, and 63.04%) and CYFRA21-1 (0.834, 77.50, and 84.78%). Further, hsa_circ_0072309 could improve the sensitivity and specificity of CEA and CYFRA21-1 through joint prediction (**Table 4**, **Figure 5**).

Cox Regression Analysis

Finally, we conducted statistics on the 3-year survival of patients and Cox regression analysis by combining patient's medical records. Univariate analysis revealed that clinical stage, LNM, hsa_circ_0072309 were prognostic factors for NSCLS patients (**Figure 6**). Furthermore, multivariate Cox regression analysis by further incorporating differentially expressed factors in univariate analysis identified the independence of LNM and hsa_circ_0072309 as prognostic factors for NSCLS (**Table 5**).

DISCUSSION

Due to the current lack of basic biological understanding of NSCLC, the feasible biomarkers for detection and effective medicines for treatment are lacking (13, 14). Relevant literature has revealed a close connection between the survival of LC patients and staging, with the 5-year survival rate decreasing from 82 to 6% as the staging (IA-IV) increases (15). However, early diagnosis is too hard given the non-specific early symptoms (16). Consequently, most cases are confirmed at the late stage when the best treatment opportunity has been missed (17).

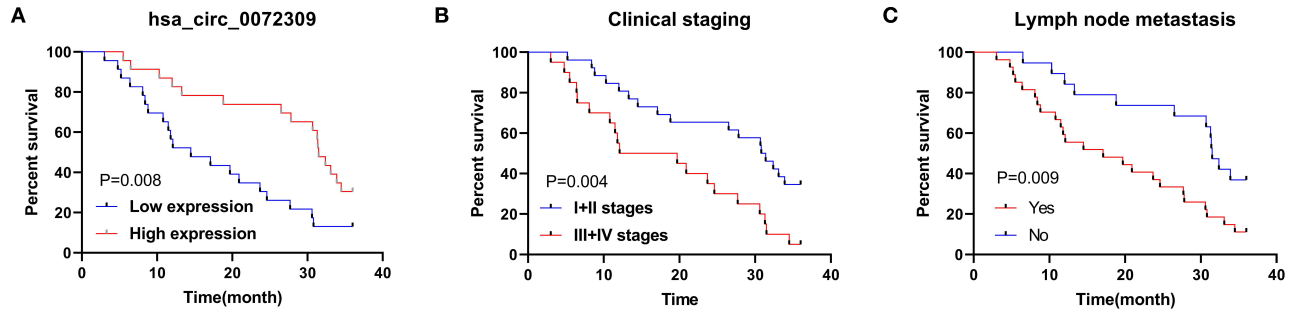


FIGURE 6 | K-M survival curve of factors with differences in univariate analysis. **(A)**. Three-year survival of NSCLC patients with up- and down-regulated hsa_circ_0072309 by K-M curves. **(B)**. Three-year survival of NSCLC patients with I-II or III-IV LC by K-M curves. **(C)**. Three-year survival of NSCLC patients with and without lymph node metastasis by K-M curves.

TABLE 5 | Cox regression.

Factors	Univariate			Multivariate		
	P-value	HR	95%CI	*P*-value	HR	95%CI
Age	0.708	0.881	0.455–1.707			
Gender	0.749	0.898	0.466–1.731			
Tumor size	0.268	1.482	0.739–2.975			
Clinical staging	0.005	2.582	1.323–5.042	0.180	1.666	0.790–3.515
Lymph node metastasis	0.004	0.364	0.185-0.719	0.010	0.399	0.198–0.804
Tumor types	0.249	1.479	0.760–2.876			
hsa_circ_0072309	0.010	2.426	1.234–4.767	0.025	2.219	1.104–4.460

Therefore, finding effective diagnostic markers is beneficial to improve patient prognosis and survival, which is also a current clinical challenge.

CircRNA are recently found endogenous ncRNAs with closed-loop structure (18). Because of their high tissue specificity and stablility in structure, they are less prone to digestion by exonuclease (RNase) (19), which also results in circRNAs being potentially favorable biomarkers for diagnosing and predicting outcomes of various illnesses (20). Earlier, research has revealed the close association between circRNA-100876 and prognosis of colorectal cancer (21). Another research identified markedly upregulated hsa_circ_0004585 in colorectal cancer and its function as a feasible biomarker for the disease (22). All these studies suggest that circRNAs are feasible biomarkers for cancer diagnosis.

For the purpose of determining the expression of circRNAs in NSCLC, GSE101684 and GSE112214 microarray datasets were retrieved through the GEO database in this study for analysis. Additionally, qRT-PCR was carried out for identifying the circRNAs with aberrant expression in clinical samples. It identified underexpressed hsa_circ_0072309 in cases, which agreed the findings of Mo et al. (11). However, their study did not further analyze hsa_circ_0072309's clinical application in NSCLC. Through analysis, we further confirmed a notably increased probability of LNM and clinical stage III-IV in patients with hsa_circ_0072309 underexpression. Therefore, it may interfere with NSCLC cell growth, progression and migration. Furthermore, we probed into hsa_circ_0072309's clinical implications in diagnosing NSCLC. As indicated by ROC curve analysis, hsa_circ_0072309's AUC was 0.887, notably higher than that of CEA and CYFRA21-1. AUC is considered to be the best index to evaluate the diagnostic value, with a value of <0.5, 0.5- <0.7, 0.7- <0.9 and ≥ 0.9 indicating no diagnostic value, lower accuracy, certain accuracy, and higher accuracy respectively. This suggests that hsa_circ_0072309 is a feasible diagnostic index for NSCLC (23). We then performed joint prediction based on Logistic regression, and found improved sensitivity of CEA and CYFRA21-1 by hsa_circ_0072309. Finally, we discussed the connection between hsa_circ_0072309 and patient prognosis. As shown by Cox regression analysis, hsa_circ_0072309 was independently linked to patient prognosis, suggesting its potential as an essential marker for adverse prognosis in NSCLC patients.

This research experimentally confirmed down-regulated_circ_0072309 in NSCLC and its potential to be a marker with diagnosis and prognosis utility for NSCLC. However, there are some limitations to be addressed. We only collected samples from LC patients, but not patients with benign lung diseases. The occurrence of LC is a long process, whether hsa_circ_0072309 can distinguish benign lung diseases from LC remains to be defined. Second, this study has a single sample type. Recent studies have found that circRNAs exist in exosomes, peripheral blood mononuclear cells and alveolar fluid. Whether hsa_circ_0072309 is more significantly differentially

expressed in other samples needs further verification. Third, this time, the mechanism of hsa_circ_0072309 has not been deeply explored, and it is hoped that the later expansion through bioinformatics analysis will lay the foundation for our follow-up basic experiments.

In conclusion, hsa_CIRC_0072309 is a candidate marker with prognostic utility in lung cancer patients with low expression and a significantly lower survival rate in patients with low expression.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

AUTHOR CONTRIBUTIONS

YZ and ZT are the mainly responsible for the writing of the article. XZ is mainly responsible for research design. SH is mainly responsible for data analysis. ZD and ZY are responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by Natural Science Foundation of Zhejiang Province (No. LQ21H160014), Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (No. 2018KY689), and Ningbo Health Branding Subject Fund (No. PPXK201805).

REFERENCES

1. Nasim F, Sabath BF, Eapen GA. Lung cancer. *Med Clin North Am.* (2019) 103:463–73. doi: 10.1016/j.mcna.2018.12.006
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2018) 68:394–424. doi: 10.3322/caac.21492
3. Schabath MB, Cote ML. Cancer progress and priorities: lung cancer. *Cancer Epidemiol Biomarkers Prev.* (2019) 28:1563–79. doi: 10.1158/1055-9965.EPI-19-0221
4. Jones GS, Baldwin DR. Recent advances in the management of lung cancer. *Clin Med.* (2018) 18:s41–6. doi: 10.7861/clinmedicine.18-2-s41
5. Hoy H, Lynch T, Beck M. Surgical treatment of lung cancer. *Crit Care Nurs Clin North Am.* (2019) 31:303–13. doi: 10.1016/j.cnc.2019.05.002
6. Ruiz-Cordero R, Devine WP. Targeted therapy and checkpoint immunotherapy in lung cancer. *Surg Pathol Clin.* (2020) 13:17–33. doi: 10.1016/j.path.2019.11.002
7. Zhu J, Zhang X, Gao W, Hu H, Wang X, Hao D. lncRNA/circRNAmiRNAmRNA ceRNA network in lumbar intervertebral disc degeneration. *Mol Med Rep.* (2019) 20:3160–74. doi: 10.3892/mmr.2019.10569
8. Bushati N, Cohen SM. microRNA functions. *Annu Rev Cell Dev Biol.* (2007) 23:175–205. doi: 10.1146/annurev.cellbio.23.090506.123406
9. Patop IL, Kadener S. circRNAs in cancer. *Curr Opin Genet Dev.* (2018) 48:121–7. doi: 10.1016/j.gde.2017.11.007
10. Yan L, Zheng M, Wang H. Circular RNA hsa_circ_0072309 inhibits proliferation and invasion of breast cancer cells via targeting miR-492. *Cancer Manag Res*. (2019) 11:1033–41. doi: 10.2147/CMAR.S186857
11. Mo WL, Deng LJ, Cheng Y, Yu WJ, Yang YH, Gu WD. Circular RNA hsa_circ_0072309 promotes tumorigenesis and invasion by regulating the miR-607/FTO axis in non-small cell lung carcinoma. *Aging*. (2021) 13:11629–45. doi: 10.18632/aging.202856
12. Koul R, Rathod S, Dubey A, Bashir B, Chowdhury A. Comparison of 7th and 8th editions of the UICC/AJCC TNM staging for non-small cell lung cancer in a non-metastatic North American cohort undergoing primary radiation treatment. *Lung Cancer.* (2018) 123:116–20. doi: 10.1016/j.lungcan.2018.06.029
13. Skrickova J, Kadlec B, Venclicek O, Merta Z. Lung cancer. *Cas Lek Cesk.* (2018) 157:226–36.
14. Duruisseaux M, Esteller M. Lung cancer epigenetics: From knowledge to applications. *Semin Cancer Biol.* (2018) 51:116–28. doi: 10.1016/j.semcancer.2017.09.005
15. Milano AF. 20-Year comparative survival and mortality of cancer of the stomach by age, sex, race, stage, grade, cohort entry time-period, disease duration & selected ICD-O-3 oncologic phenotypes: a systematic review of 157,258 cases for diagnosis years 1973-2014: (SEER*Stat 8.3.4). *J Insur Med.* (2019) 48:5–23. doi: 10.17849/insm-48-1-1-19.1
16. Alexander M, Kim SY, Cheng H. Update 2020: management of non-small cell lung cancer. *Lung.* (2020) 198:897–907. doi: 10.1007/s00408-020-00407-5
17. Oudkerk M, Liu S, Heuvelmans MA, Walter JE, Field JK. Lung cancer LDCT screening and mortality reduction - evidence, pitfalls and future perspectives. *Nat Rev Clin Oncol.* (2021) 18:135–51. doi: 10.1038/s41571-020-00432-6
18. Shi Y, Jia X, Xu J. The new function of circRNA: translation. *Clin Transl Oncol.* (2020) 22:2162–9. doi: 10.1007/s12094-020-02371-1
19. Li S, Teng S, Xu J, Su G, Zhang Y, Zhao J, et al. Microarray is an efficient tool for circRNA profiling. *Brief Bioinform.* (2019) 20:1420–33. doi: 10.1093/bib/bby006
20. Liu J, Xue N, Guo Y, Niu K, Gao L, Zhang S, et al. CircRNA_100367 regulated the radiation sensitivity of esophageal squamous cell carcinomas through miR-217/Wnt3 pathway. *Aging.* (2019) 11:12412–27. doi: 10.18632/aging.102580
21. Zhou GR, Huang DP, Sun ZF, Zhang XF. Characteristics and prognostic significance of circRNA-100876 in patients with colorectal cancer. *Eur Rev Med Pharmacol Sci.* (2020) 24:11587–93. doi: 10.26355/eurrev_202011_23801
22. Tian J, Xi X, Wang J, Yu J, Huang Q, Ma R, et al. CircRNA hsa_circ_0004585 as a potential biomarker for colorectal cancer. *Cancer Manag Res.* (2019) 11:5413–23. doi: 10.2147/CMAR.S199436
23. Kim J, Hwang IC. Drawing guidelines for receiver operating characteristic curve in preparation of manuscripts. *J Korean Med Sci.* (2020) 35:e171. doi: 10.3346/jkms.2020.35.e171

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhou, Tong, Zhu, Huang, Dong and Ye. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 28 February 2022
doi: 10.3389/fsurg.2022.848724

Observation of the Effect of Singulair Combined With Ketotifen in the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease With Airway Hyperresponsiveness and Its Influence on Th17/Treg

*Haiou Wang and Gaojie Qu**

The Third Affiliated Hospital, Department of Respiratory Medicine, Hengyang Medical School, University of South China, Hengyang, China

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Wenjun Gu,
Shanghai Jiaotong University School of Medicine, China
Liang Hui,
Hainan General Hospital, China

***Correspondence:**
Gaojie Qu
q13875706009@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *05 January 2022*
Accepted: *31 January 2022*
Published: *28 February 2022*

Citation:
Wang H and Qu G (2022) Observation of the Effect of Singulair Combined With Ketotifen in the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease With Airway Hyperresponsiveness and Its Influence on Th17/Treg. Front. Surg. 9:848724. doi: 10.3389/fsurg.2022.848724

Objective: To investigate the effect of montelukast sodium (singulair) combined with ketotifen fumarate on the acute exacerbation of chronic obstructive pulmonary disease (AECOPD) with airway hyperresponsiveness (AHR) and its effect on helper T cells 17 (Th17)/regulator T cells (Treg).

Methods: 168 patients with AECOPD and AHR diagnosed in our hospital from February 2018 to December 2019 were selected, and divided into the observation group ($n = 84$) and the control group ($n = 84$). Both groups were given anti infection, bronchodilator, glucocorticoid, phosphodiesterase inhibitor, cough and expectorant. The observation group was additionally treated with singulair tablets and ketotifen tablets for 14 days. The curative effect were observed after treatment. The first second forced expiratory volume (FEV1), forced vital capacity (FVC) and FEV1 as percentage of predicted value (FEV1% pred), blood oxygen pressure (PaO_2) and blood carbon dioxide pressure ($PaCO_2$), high-sensitivity C-reactive protein (hs-CRP) and procalcitonin (PCT), Th17 and Treg levels were measured in both groups before and after treatment.

Results: Compared with the control group, the total effective rate after treatment in the observation group was increased (94.05 vs. 75.00%, $P < 0.05$). Compared with before treatment, the FEV1, FVC and FEV1%pred levels of the two groups of patients after treatment were increased ($P < 0.05$). Compared with the control group, the FEV1, FVC and FEV1%pred levels of the observation group were increased after treatment ($P < 0.05$). Compared with before treatment, the PaCO2, hs-CRP and PCT levels of the two groups of patients were reduced after treatment, and PaO2 levels were increased ($P < 0.05$). Compared with the control group, the PaCO2, hs-CRP and PCT levels in the observation group were reduced after treatment, and the PaO2 level was increased ($P < 0.05$). Compared with before treatment, Th17 and Th17/Treg levels of the two groups of patients were reduced after treatment, and Treg levels were increased

($P < 0.05$). Compared with the control group, the Th17 and Th17/Treg levels of the observation group were reduced after treatment, and the Treg levels was increased ($P < 0.05$).

Conclusion: Singulair combined with ketotifen in the treatment of patients with AECOPD combined with AHR can significantly improve the efficacy, improve lung function, reduce inflammatory response, and improve the balance of Th17/Treg, effectively controlling the disease.

Keywords: acute exacerbation, chronic obstructive pulmonary disease, airway hyperresponsiveness, montelukast, ketotifen fumarate

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common pulmonary disease with the characteristics of airflow limitation, which develops irreversibly and progressive (1, 2). COPD is more common in middle-aged people, especially in people with a long history of smoking or long-term exposure to other harmful gases. Its clinical symptoms include chronic cough, expectoration, shortness of breath or dyspnea. In the early stage, it only appears during severe exercise, but with the aggravation of the disease, it often appears in daily life (3, 4). Acute exacerbation of COPD (AECOPD) is a severe stage in the course of COPD, in which the exacerbation of respiratory symptoms exceeds the daily level, which can be caused by bacterial infection, changes in environmental factors, and other reasons (5, 6). Airway hyper responsiveness (AHR) refers to the strong contraction response of the airway after being exposed to stimulation factors, which is often accompanied by AECOPD. In recent years, due to the aggravation of environmental pollution and the aging process of population in China, the incidence of AECOPD combined with AHR is gradually increasing (7, 8). It has become extremely important to select the appropriate and effective treatment for AECOPD combined with AHR. Montelukast sodium (singulair) is an oral leukotriene (LT) receptor antagonist that inhibits the binding of LT to its receptors in the airway, thereby rendering LT ineffective in improving airway inflammation (9, 10). Ketotifen fumarate tablets, as an allergic mediator release inhibitor for sensitized active cell mast cells or basophils, can reduce the release of allergic active mediator and have good anti-allergic effect (11, 12). T helper cell 17 (Th17) is a kind of pro-inflammatory cell that plays an important role in the body's own defense (13). T regulatory cells (Treg) are generated by thymus and can inhibit the proliferation of autoreactive T cells in the body and play a negative role in immune regulation (14). The purpose of this study was to investigate the efficacy of singulair in combination with ketotifen in the treatment of AECOPD with AHR and its effect on Th17/Treg.

MATERIALS AND METHODS

Patients

A total of 168 patients with AECOPD and AHR diagnosed in our hospital from February 2018 to December 2019 were selected. Inclusion criteria: All patients met the diagnostic guidelines for AECOPD (15); no recent oral glucocorticoid or ICS therapy; no history of bronchial asthma. Determination of AHR by bronchial provocation test (16): First, the forced vital capacity curve of the subject was determined with the pulmonary function meter, and the first second forced expiratory volume (FEV1) of the three curve was taken as the basic value. The provocation test could be performed for patients with FEV1 > 70%. The lung function was measured after the subjects were inhaled with normal saline. If the FEV1 decreased by more than 10% after the normal saline was inhaled, the airway reactivity would be high and the test would not be appropriate. If FEV1 decreased by no more than 10%, subjects were given histamine at an increasing dose of 5% beginning with the lower dose, and pulmonary ventilation was measured after inhalation until FEV1 decreased by more than 20% from baseline or symptoms appeared, or the maximum dose of histamine was inhaled. After histamine stimulation, albuterol was routinely inhaled, and the positive person would be AHR. Exclusion criteria: patients combined with severe cardiac insufficiency and arrhythmia; patients with severe cerebrovascular diseases; patients combined with severe hyperthyroidism, patients with pulmonary infection; patients who smoke. A total of 168 AECOPD patients complicated with AHR were randomly divided into the observation group ($n = 84$) and the control group ($n = 84$). There was no significant difference in general data between the two groups ($P < 0.05$).

Research Methods

The control group received sensitive antibiotics to fight infection according to the sputum culture drug sensitivity test, aminophylline, salbutamol, budesonide solution to relieve asthma, ambroxol expectorant, oxygen inhalation, etc., and systemic use of glucocorticoid (methylprednisolone), which was discontinued after infection control. On this basis, the observation group was additionally treated with singulair tablets (Hangzhou MSD Pharmaceutical Co., LTD.) 10 mg orally, once a day, every night before bedtime. Ketotifen tablets (Jiangsu Pengrier Pharmaceutical Co., LTD.) were orally taken at 1 mg, twice a day. The treatment course was 14 days. Evaluation criteria for therapeutic effects: Excellent: The symptoms such as cough and wheeze disappeared, and the dry and wet rales in the lung disappeared. Effective: cough and wheeze are reduced, and pulmonary dry and wet rales are reduced; Ineffective: cough and wheeze were not improved obviously, and pulmonary dry and wet rales recurred. Pulmonary function tests were carried out,

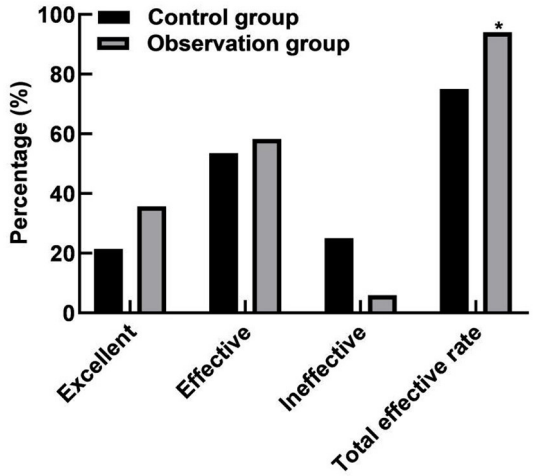


FIGURE 1 | Comparison of clinical effects between the two groups. Compared with the control group, *$P < 0.05$.

respectively, and the PowerCube spirometer of German Kangxun Company was used to check the FEV1, FVC, and FEV1%pred before and after treatment in the two groups. Each inspection is determined by a professional technician. The ABL90 blood gas analyzer provided by Radiometer Medical Equipment (Shanghai) Co., Ltd. was used to analyze the blood gas of the patient's blood to determine the PaO_2 and $PaCO_2$. The venous blood of the two groups of patients was drawn, and the hs-CRP and PCT were determined by ELISA. The percentage contents of Th17 and Treg cells in the venous blood of patients were detected by flow cytometry.

Statistical Methods

All data were processed with SPSS 22.0 statistical software. The enumeration data were examined by X^2 test and expressed by [n (%)], the measurement data were examined by t-test and expressed by ($x \pm$ s). The difference is statistically significant when $P < 0.05$.

RESULTS

Comparison of Clinical Effects Between the Two Groups

Compared with the control group, the total effective rate after treatment in the observation group was increased (94.05 vs. 75.00%, $P < 0.05$). As shown in **Figure 1**.

Comparison of Lung Function Between the Two Groups

Compared with before treatment, the FEV1, FVC, and FEV1%pred levels of the two groups of patients were increased after treatment ($P < 0.05$). Compared with the control group, the FEV1, FVC, and FEV1%pred levels of the observation group increased after treatment ($P < 0.05$). As shown in **Figure 2**.

Comparison of Blood Gas Indicators and Inflammation Indicators Between the Two Groups

Compared with before treatment, the $PaCO_2$, hs-CRP and PCT levels of the two groups of patients were reduced after treatment, and PaO_2 levels were increased ($P<0.05$). Compared with the control group, the $PaCO_2$, hs-CRP and PCT levels in the observation group were reduced after treatment, and the PaO_2 level was increased ($P < 0.05$). As shown in **Figure 3**.

Comparison of Th17 and Treg Between the Two Groups

Compared with before treatment, Th17 and Th17/Treg levels of the two groups of patients were reduced after treatment, and Treg levels were increased ($P < 0.05$). Compared with the control group, the Th17 and Th17/Treg levels of the observation group were reduced after treatment, and the Treg levels was increased ($P < 0.05$). As shown in **Figure 4**.

DISCUSSION

COPD is a common chronic lung disease, and its pathogenesis is abnormal inflammatory reaction caused by lung infection due to long-term smoking or external environmental factors such as respiratory tract infection, which causes excessive mucus secretion to narrow the airway and aggravate the obstruction (17–19). AECOPD is a serious stage in the course of COPD, in which the inflammatory response is aggravated, resulting in the increase of eosinophils and basophils in the body, and the release of more neutrophil chemokines and proteolytic enzymes to participate in the inflammatory response, and the persistent inflammatory response may even lead to the death of the patient (20, 21). AHR is often associated with COPD, and it is caused by narrowing and obstruction of the airway in patients with COPD that the mucosal epithelium of the airway is damaged, resulting in the enhanced response of the airway to non-specific stimuli, further triggering inflammation (22, 23). Therefore, selecting treatment that is effective in alleviating AHR is one of the main strategies for preventing and treating the progression of COPD.

The results of this study showed that compared with the control group, the total effective rate of the observation group was higher after treatment. The reason for this was analyzed as LT is an inflammatory response substance different from glucocorticoid-sensitive mediators, which has a high biological activity and always exists in the occurrence and development of COPD. Singulair is a specific cysteine LT receptor antagonist, which can effectively inhibit the pro-maturation effect of peptide growth factor on eosinophilic and basophilic stem cells, and reduce the eosinophils in the airway and surrounding blood, thereby reducing airway inflammation, relaxing smooth muscle, and reducing pulmonary hypertension (24, 25). Ketotifen is an allergy-inducing medium release inhibitor of mast cells or basophils, which can protect the membrane of mast cells or basophils, reduce the membrane allosterism under the attack of allergens, and prevent the release of allergic reaction medium. At the same time, it has strong antihistamine H1 receptor

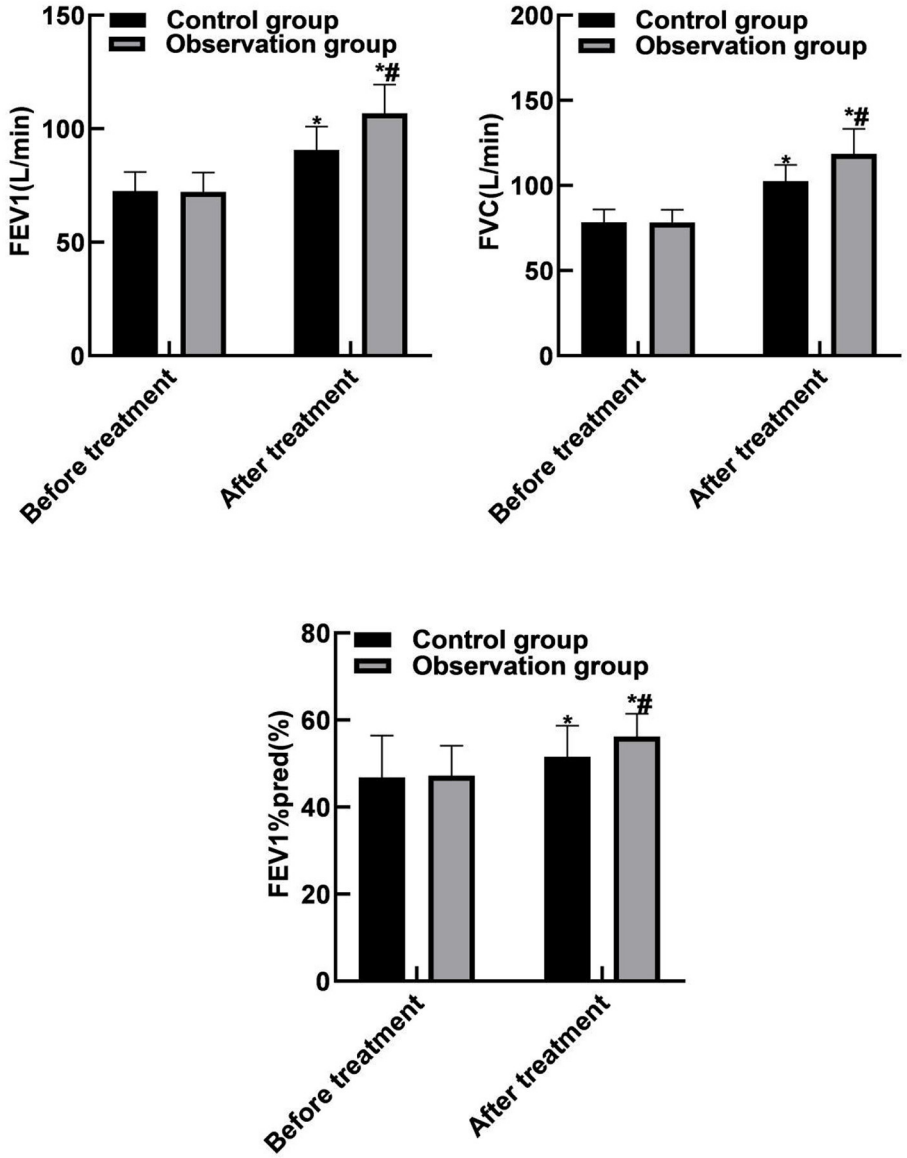


FIGURE 2 | Comparison of lung function between the two groups. Compared with before treatment, $^{*}P < 0.05$. Compared with the control group, $^{\#}P < 0.05$.

antagonism, which can effectively inhibit the release of histamine by bronchial submucosal mast cells to avoid the occurrence of respiratory tract non-specific inflammation, and thus reduce AHR (26, 27).

The results of this study showed that compared with before treatment, the levels of FEV1, FVC, and FEV1%pred in the two groups were increased after treatment. Compared with the control group, the FEV1, FVC, and FEV1%pred levels of the observation group increased after treatment. These results indicated that the combination therapy of singulair and ketotifen could effectively improve the lung function of patients. LT is the medium that causes increased mucus secretion. Singulair can prevent the adhesion of white blood cells and endothelial cells, reduce the production of inflammatory mediators, various proteases and oxygen free radicals, thereby inhibiting airway inflammation, reducing mucus secretion, reducing airway hyperresponsiveness and relieving airway spasm. The results of this study showed that compared with before treatment, the $PaCO_2$, hs-CRP and PCT levels of the two groups of patients were reduced after treatment, and PaO_2 levels were increased. Compared with the control group, the $PaCO_2$, hs-CRP and PCT levels of the observation group were reduced after treatment, and the PaO_2 level was increased. The reason was analyzed as follows: Singulair could effectively inhibit the binding of LT to its receptor in airway and make it unable to play a role, thus reducing the permeability of capillaries,

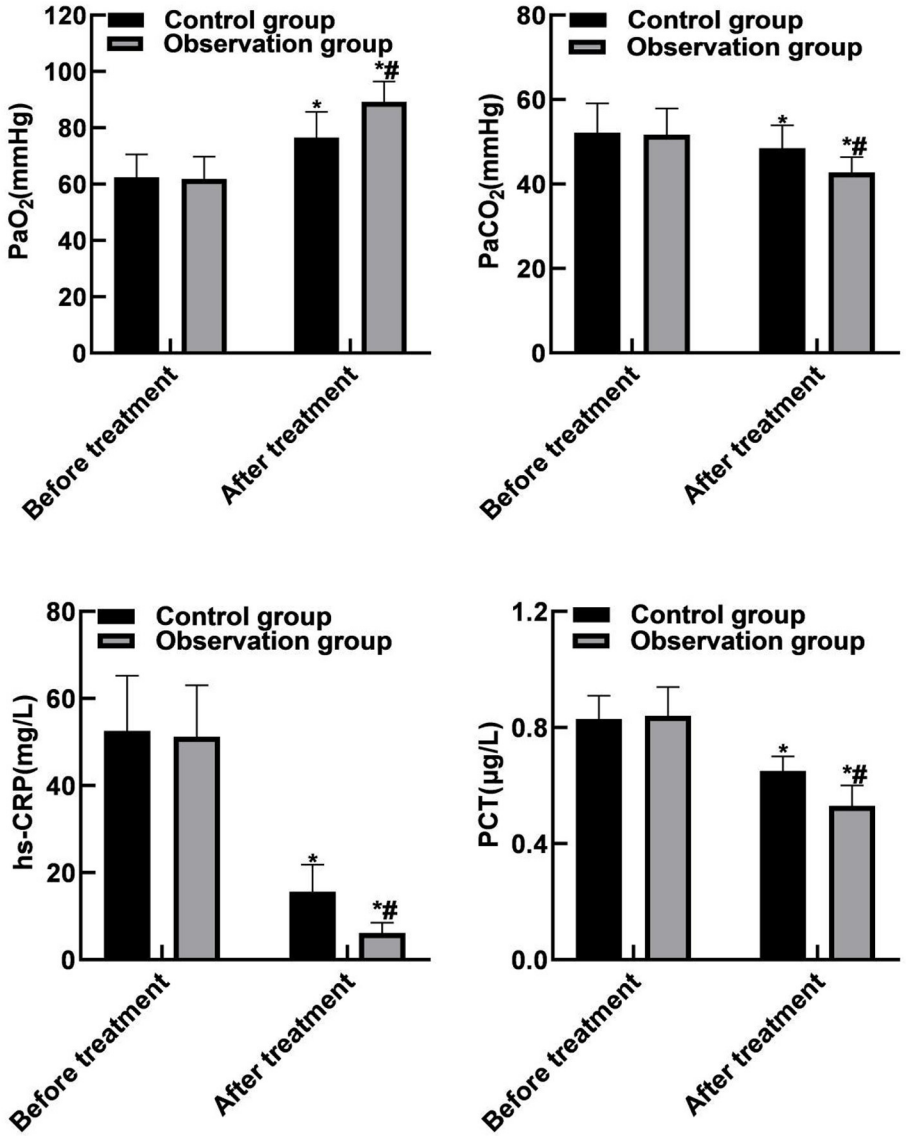


FIGURE 3 | Comparison of blood gas indicators and inflammation indicators between the two groups. Compared with before treatment, $^{*}P < 0.05$. Compared with the control group, $^{\#}P < 0.05$.

reducing mucus secretion, relieving airway inflammation and improving the ventilatory function and inflammatory reaction of patients.

Th17 cells are a subpopulation of Th cells and are named after their ability to produce IL-17. As a pre-inflammatory factor, IL-17 is involved in many inflammatory responses and in a variety of autoimmune diseases. Activated Th17 cells can secrete IL-17, which combines with inflammatory cell surface receptors to induce the release of a large number of inflammatory factors that act on the airway mucus glands to produce a large amount of mucus, increase airway responsiveness, and further promote airway remodeling (28, 29). Treg cells, as important regulatory cells in the body, can negatively regulate T cells and reduce body damage caused by over-immunity of antigen and antibody. Treg cells are related to the immune function of patients, and can indirectly reflect the degree of inflammation in the lungs and airways. The increase of Treg cells causes immune imbalance, and then inhibits the increase of Th17 cell activity, weakening the inflammatory response in the lungs, which may induce lung cancer. However, the mechanism needs further research and discovery. Similar to the balance between T helper 1 cell (Th1) and T helper 2 cell (Th2), there is also an important balance between Th17 and Treg cells. The imbalance will lead to local or systemic abnormal immune responses, such as autoimmune diseases, tumors, persistent infections and other diseases. At present, more and more pulmonary diseases have been found to

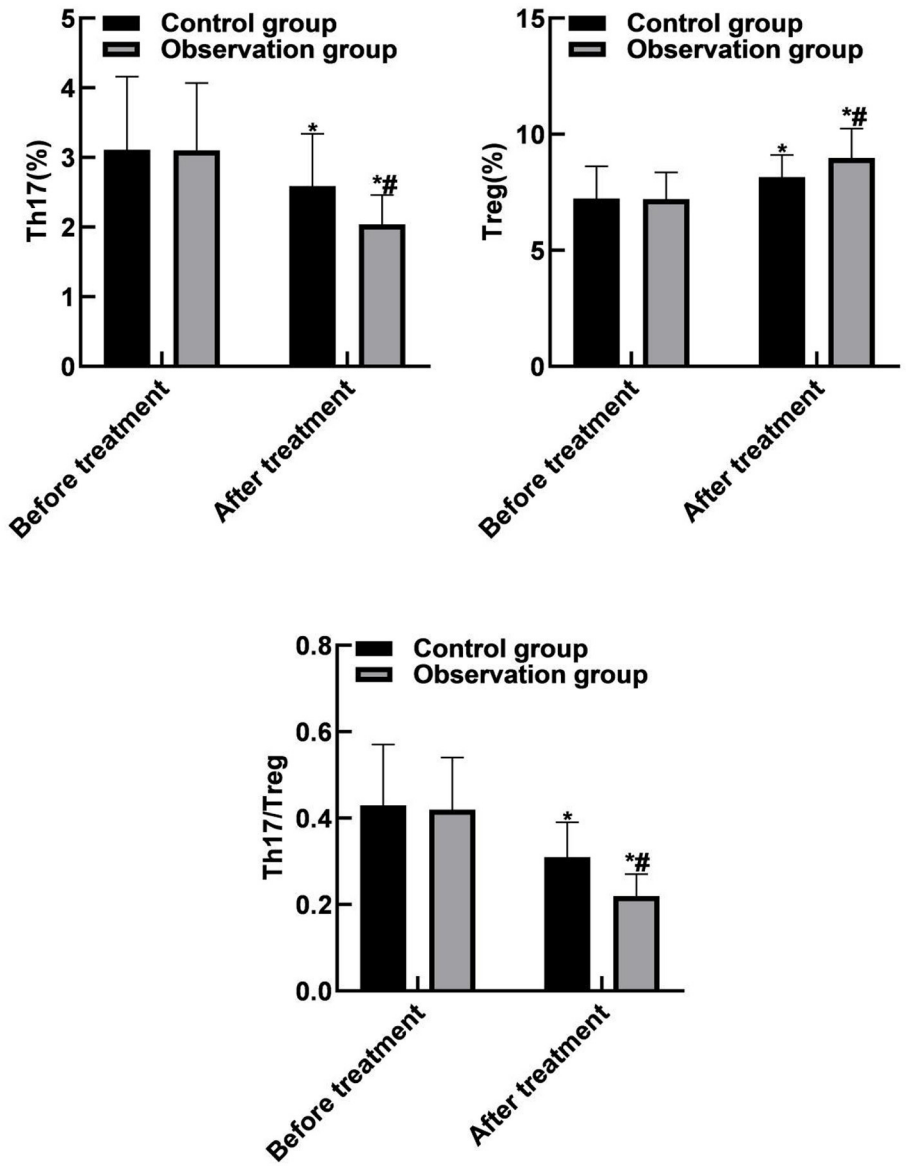


FIGURE 4 | Comparison of Th17 and Treg between the two groups. Compared with before treatment, $^{*}P < 0.05$. Compared with the control group, $^{\#}P < 0.05$.

be related to immune disorders, especially the role of Th17/Treg cells in the pathogenesis of pulmonary diseases has received increasing attention (30, 31). The results of this study showed that compared with before treatment, Th17 and Th17/Treg levels of the two groups of patients were reduced after treatment, and Treg levels were increased. Compared with the control group, the Th17 and Th17/Treg levels of the observation group were reduced after treatment, and the Treg levels was increased. These results indicated that the combination therapy of singulair and ketotifen could improve the Th17/Treg balance and maintain the immune balance of the body, thereby effectively improving the disease condition.

In summary, singulair combined with ketotifen in the treatment of patients with AECOPD combined with AHR can significantly improve the curative effect, improve the lung function of patients, reduce the inflammatory response, and improve the Th17/Treg balance, and effectively control the disease.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Third Affiliated Hospital of South China University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Both authors have made equal contributions and participated in the design of the study, the search for literature, the analysis of the data, and the writing and revision of the paper. Both authors contributed to the article and approved the submitted version.

REFERENCES

1. Labaki WW, Rosenberg SR. Chronic obstructive pulmonary disease. *Ann Intern Med.* (2020) 173:C17–32. doi: 10.7326/AITC202008040
2. Segal LN, Martinez FJ. Chronic obstructive pulmonary disease subpopulations and phenotyping. *J Allergy Clin Immunol.* (2018) 141:1961–71. doi: 10.1016/j.jaci.2018.02.035
3. Leo F, Menger H. Exacerbations of chronic obstructive pulmonary disease - diagnostic approach, management and follow-up care. *Dtsch Med Wochenschr.* (2019) 144:21–7. doi: 10.1055/a-0723-4172
4. Zhou HX, Ou XM, Tang YJ, Wang L, Feng YL. Advanced chronic obstructive pulmonary disease: innovative and integrated management approaches. *Chin Med J.* (2015) 128:2952–9. doi: 10.4103/0366-6999.168073
5. Abdulai RM, Jensen TJ, Patel NR, Polkey MI, Jansson P, Celli BR, et al. Deterioration of limb muscle function during acute exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* (2018) 197:433–49. doi: 10.1164/rccm.201703-0615CI
6. Wang Y, Lyu X, Wu X, Yu L, Hu K. Long non-coding RNA PVT1, a novel biomarker for chronic obstructive pulmonary disease progression surveillance and acute exacerbation prediction potentially through interaction with microRNA-146a. *J Clin Lab Anal.* (2020) 34:e23346. doi: 10.1002/jcla.23346
7. Plantier L, Pradel A, Delclaux C. Mechanisms of non-specific airway hyperresponsiveness: methacholine-induced alterations in airway architecture. *Rev Mal Respir.* (2016) 33:735–43. doi: 10.1016/j.rmr.2015.10.742
8. Maarsingh H, Bidan CM, Brook BS, Zuidhof AB, Elzinga CR, Smit M, et al. Small airway hyperresponsiveness in COPD: relationship between structure and function in lung slices. *Am J Physiol Lung Cell Mol Physiol.* (2019) 316:L537–46. doi: 10.1152/ajplung.00325.2018
9. Hoxha M, Rovati GE, Cavanillas AB. The leukotriene receptor antagonist montelukast and its possible role in the cardiovascular field. *Eur J Clin Pharmacol.* (2017) 73:799–809. doi: 10.1007/s00228-017-2242-2
10. Kolm G, Zappe H, Schmid R, Riedelberger K, Hoven RV. Efficacy of montelukast in the treatment of chronic obstructive pulmonary disease in five horses. *Vet Rec.* (2003) 152:804–6. doi: 10.1136/vr.152.26.804
11. Schwarzer G, Bassler D, Mitra A, Ducharme FM, Forster J. Ketotifen alone or as additional medication for long-term control of asthma and wheeze in children. *Cochrane Database Syst Rev.* (2004) 2004:D1384. doi: 10.1002/14651858.CD001384.pub2
12. Feng F, Fawcett JP, Zhang H, Tucher IG. Cell-based, animal and H(1) receptor binding studies relative to the sedative effects of ketotifen and norketotifen atropisomers. *J Pharm Pharmacol.* (2020) 72:507–18. doi: 10.1111/jphp.13220
13. Iman M, Rezaei R, Azimzadeh JS, Shariati P, Kheradmand F, Salimian J. Th17/Treg immunoregulation and implications in treatment of sulfur mustard gas-induced lung diseases. *Expert Rev Clin Immunol.* (2017) 13:1173–88. doi: 10.1080/1744666X.2017.1389646
14. Xu YQ, Lv W, Wu HJ, Shi SF. Ginsenoside regulates Treg/Th17 cell ratio and inhibits inflammation to treat COPD. *Pharmazie.* (2020) 75:590–4. doi: 10.1691/ph.2020.0696
15. Ko FW, Chan KP, Hui DS, Goddard JR, Shaw JG, Reid DW, et al. Acute exacerbation of COPD. *Respirology.* (2016) 21:1152–65. doi: 10.1111/resp.12780
16. Guan W, Zheng J, Gao Y, Jiang C, An J, Yu X, et al. Leukotriene D4 bronchial provocation test: methodology and diagnostic value. *Curr Med Res Opin.* (2012) 28:797–803. doi: 10.1185/03007995.2012.678936
17. Duffy SP, Criner GJ. Chronic obstructive pulmonary disease: evaluation and management. *Med Clin North Am.* (2019) 103:453–61. doi: 10.1016/j.mcna.2018.12.005
18. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med.* (2008) 359:2355–65. doi: 10.1056/NEJMra0800353
19. Osthoff M, Leuppi JD. Management of chronic obstructive pulmonary disease patients after hospitalization for acute exacerbation. *Respiration.* (2010) 79:255–61. doi: 10.1159/000235721
20. Baqdunes MW, Leap J, Young M, Kaura A, Cheema T. Acute exacerbation of chronic obstructive pulmonary disease. *Crit Care Nurs Q.* (2021) 44:74–90. doi: 10.1097/CNQ.0000000000000341
21. Friege B, Friege L, Pelz J, Weber M, von Spiegel T, Schroder S. Bronchial asthma and chronic obstructive pulmonary disease with acute exacerbation: preclinical differential diagnostic and emergency treatment. *Anaesthesist.* (2009) 58:611–22. doi: 10.1007/s00101-009-1536-x
22. Gazzola M, Flamand N, Bosse Y. Extracellular molecules controlling the contraction of airway smooth muscle and their potential contribution to bronchial hyperresponsiveness. *Rev Mal Respir.* (2020) 37:462–73. doi: 10.1016/j.rmr.2020.03.009
23. Calzetta L, Ritondo BL, Matera MG, Facciolo F, Rogliani P. Targeting IL-5 pathway against airway hyperresponsiveness: a comparison between benralizumab and mepolizumab. *Br J Pharmacol.* (2020) 177:4750–65. doi: 10.1111/bph.15240
24. Abdel KH. Montelukast versus dexamethasone treatment in a guinea pig model of chronic pulmonary neutrophilic inflammation. *COPD.* (2016) 13:455–63. doi: 10.3109/15412555.2015.1046041
25. Fogli S, Stefanelli F, Martelli A, Daniele S, Testai L, Calderone V, et al. Protective effect of high-dose montelukast on salbutamol-induced homologous desensitisation in airway smooth muscle. *Pulm Pharmacol Ther.* (2013) 26:693–9. doi: 10.1016/j.pupt.2013.06.006
26. Triantafillou V, Maina IW, Patel NN, Tong CC, Papagiannopoulos P, Kohanski MA, et al. *In vitro* safety of ketotifen as a topical nasal rinse. *Int Forum Allergy Rhinol.* (2020) 10:265–70. doi: 10.1002/alr.22461
27. Blackwell W, Cruz PJ. Ketotifen in over-the-counter products is a contact allergen. *Dermatitis.* (2020) 31:e39–40. doi: 10.1097/DER.0000000000000586
28. Imani S, Salimian J, Bozorgmehr M, Vahedi E, Ghazvini A, Ghanei M, et al. Assessment of Treg/Th17 axis role in immunopathogenesis of chronic injuries of mustard lung disease. *J Recept Signal Transduct Res.* (2016) 36:531–41. doi: 10.3109/10799893.2016.1141953
29. Imani S, Salimian J, Fu J, Ghanei M, Panahi Y. Th17/Treg-related cytokine imbalance in sulfur mustard exposed and stable chronic obstructive pulmonary (COPD) patients: correlation with disease activity. *Immunopharmacol Immunotoxicol.* (2016) 38:270–80. doi: 10.1080/08923973.2016.1188402
30. Silva L, Lourenco JD, Silva KR, Santana F, Kohler JB, Moreira AR, et al. Th17/Treg imbalance in COPD development: suppressors of cytokine signaling and signal transducers and activators of transcription proteins. *Sci Rep.* (2020) 10:15287. doi: 10.1038/s41598-020-72305-y
31. Ito JT, Cervilha D, Lourenco JD, Goncalves NG, Volpini RA, Caldini EG, et al. Th17/Treg imbalance in COPD progression: a

temporal analysis using a CS-induced model. *PLoS ONE.* (2019) 14:e209351. doi: 10.1371/journal.pone.0209351

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Wang and Qu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 28 February 2022
doi: 10.3389/fsurg.2022.851657

Application of Preoperative Ultrasonography in the Diagnosis of Cervical Lymph Node Metastasis in Thyroid Papillary Carcinoma

Ailong Zhang[1]*, *Shenglan Wu*[2], *Zhenhui You*[1] and *Wenkai Liu*[1]

[1] Department of General Surgery, Fujian Provincial Hospital, Fuzhou, China, [2] Department of Ultrasonography, Jingzhou City Women and Children Hospital, Jingzhou, China

Background: The clinical value and application of preoperative ultrasound contrast in the diagnosis of cervical lymph node metastasis in thyroid papillary carcinoma is investigated.

Methods: In total, 126 cases of thyroid papillary carcinoma were selected, the sensitivity and accuracy of color ultrasound and ultrasound contrast were analyzed by comparing preoperative gray-scale ultrasound, color ultrasound, and ultrasound contrast.

Results: The accuracies of preoperative color ultrasound and ultrasound contrast in detecting lymph node metastasis were 74 and 82%, respectively, and their sensitivities were 80 and 94%, respectively. Lymph node metastasis was significantly more severe when the tumor diameter was >4 cm. The lymphatic metastatic rate of the patients with multifocal papillary carcinoma was 96.4%, whereas the lymphatic metastatic rate of the patients with thyroid gland lesions was 87.7%. The central foci of cervical lymph node metastasis included the following pathological subtypes: diffuse sclerosis type (89.3%, 25/28), high-cell type (72.2%, 8/11), and papillary type (40.0%, 4/10).

Conclusion: Ultrasound contrast is more sensitive than color ultrasound in the diagnosis of cervical lymph node metastasis. Primary lesions ≥4 cm, lesion involvement, outer membrane, and high-risk pathologic subtypes and lesions were considered as the criteria for ultrasound contrast application.

Keywords: lymph node metastasis, contrast-enhanced ultrasonography, ultrasonic examination, thyroid tumor, preoperative

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Changfu Qin,
Shihezi University, China
Pengyun Wang,
Xian Hospital of Traditional Chinese Medicine, China

***Correspondence:**
Ailong Zhang
ailongzhfjsl@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *10 January 2022*
Accepted: *25 January 2022*
Published: *28 February 2022*

Citation:
Zhang A, Wu S, You Z and Liu W (2022) Application of Preoperative Ultrasonography in the Diagnosis of Cervical Lymph Node Metastasis in Thyroid Papillary Carcinoma. Front. Surg. 9:851657. doi: 10.3389/fsurg.2022.851657

INTRODUCTION

Papillary thyroid carcinoma is the most common type of thyroid malignancy and accounts for over 80%. Most patients with this malignancy experience slow disease progress and have a good prognosis, but 30–80% of them might experience potential cervical lymph node metastasis (1, 2). However, whether cervical lymph node metastasis affects the prognosis of papillary thyroid carcinoma remains controversial. Some factors might influence the lymph node metastasis of papillary thyroid carcinoma. It was reported that vascular invasion, multifocality, large tumor diameter, young age, and male sex were positively correlated with central lymph node metastasis in the cervical region in papillary thyroid carcinoma patients (3). In papillary thyroid cancer patients, Hashimoto's thyroiditis has a protective effect on central lymph node metastasis and a risk effect on lateral lymph node metastasis (4).

The standard surgical treatment for this disease is cervical lymphatic dissection, but excessive or insufficient neck cleaning is common in clinics because of the difficulty in accurately diagnosing cervical lymph node metastasis before operation (1). Lymph node biopsy is a pathological analytical method with high diagnostic accuracy, which is yet to be widely applied in China (5). Although ultrasound, CT, and MRI have significantly increased the diagnostic rate for this disease, several deficiencies still remain (6). Thus, ultrasound contrast has shown potential application value in diagnosing diseases.

In this study, we analyzed the factors influencing the sensitivity of this technique and discussed the value and application of preoperative ultrasonography in diagnosing cervical lymph node metastasis from thyroid papillary carcinoma patients. The diagnostic sensitivity and accuracy of color ultrasound and ultrasound contrast for thyroid papillary carcinoma patients were analyzed.

TABLE 1 | Distribution of thyroid lesion sites and regional lymph nodes (cases).

Thyroid lesions	II	III	IV	V	VI
Upper level	23	29	44	2	10
Medium level	18	23	20	3	13
Low level	6	9	6	7	66
Total	47	61	50	11	89

TABLE 2 | Pathological subtype invasion and metastasis of thyroid papillary carcinoma (cases).

Pathological subtype		Lymph node metastasis in the cervical area	Invasion of the outer glands
Diffuse sclerosis type	28	25	28
High cell type	11	8	11
Diffuse follicular type	3	3	2
Columnar cell type	3	2	3
Follicular type	10	7	3
Solid variant type	9	7	3
Fascia type	9	6	3
Hyaline cell type	10	7	4
Eosinophilic cell type	7	6	3
Typical papillary carcinoma	25	19	12
Papillary microcancer	10	4	1
Large follicular type	1	1	0
Total	126	95	73

MATERIALS AND METHODS

General Materials

In total, 126 thyroid papillary carcinoma cases were enrolled in our department from November 2015 to November 2020. This study was approved by the Institutional Animal Care and Use Committee (approval number: 2015-36). Oral informed consent was obtained from subjects. All experiment procedures are in accord with the Declaration of Helsinki. These cases included 28 thyroid papillary carcinoma cases, but clinical palpation or imaging examination revealed that these cases were enlarged with neck lymph nodes. Grayscale ultrasound, color ultrasound, and ultrasound contrast were conducted before operation. The patients included 31 men and 95 women. The ages ranged from 19 to 77 years with a median age of 46 years. Among the cases, 68 cases were $\geq$45 years and 58 cases were $<$45 years. The sizes of their thyroid nodules ranged from 4 to 42 mm and the median was 20 mm. The following conditions were observed: unilateral carcinoma in 98 cases, bilateral carcinoma in 17 cases, and multicentral carcinoma in 11 cases.

Ultrasonic Examination

Philips ultrasonic diagnostic equipment with a frequency range of 8–13 MHz, a mechanical index (MZ) of 0.05–0.08, and a compressed range of 33–35, dynamic shear rheometer (DSR) (Middle) was used in this study. An ultrasound contrast agent (Sonovue; Bracco, Milan, Italy) was combined with 5 ml saline and shaken for 30 s. A $2 \times 10^8/mm^3$ microbubble suspension was formed by intravenously injecting each contrast agent into the elbow before the vein with a 2.4 ml static push and 5 ml saline was used for flushing tubes. At the same time, the timer was pressed and the characteristics of the lymph node perfusion and the intensity changes in echo were observed using a double-image model. Automatic tracking radiography analysis software (ACQ) was used. The morphological characteristics, aspect ratio, internal echo, and the lymphatic gate of the lymph nodes were observed through conventional 2D ultrasonography. The pattern of vascular distribution in the lymph nodes was examined with color ultrasound. Contrast-enhanced ultrasound showed the characteristics of "uneven enhancement" and "fast forward and slow backward" that indicated cancer metastasis. All images and other dynamic images were stored in this machine or in a universal serial bus (USB) disk for retrospective analysis. Two individuals were designated to analyze the image data. In cases of inconsistencies in qualitative data, they agreed to include data after consultation.

Operation Method

In routine neck incision or original incision, the primary lesion was limited to the side of lateral and isthmic resections. The primary lesion invaded by the membrane or involved two lobes, routine sending rapid pathological examination report thyroid papillary carcinoma and the incision was extended after the ipsilateral sternocleidomastoid muscle was freed in the middle and lower parts of the posterior margin. The initial lesion was located on the upper lobe of the glandular leaves the first sweep of III, IV, and VI regionsof the lymphoid adipose tissue. The primary lesion was located on the anterior pituitary

TABLE 3 | Diagnosis by color ultrasound and contrast-enhanced ultrasonography.

	Sensitivity	Positive predictive value	Negative predictive value	Accuracy
Color ultrasound	(76/95) 80%	(76/90) 84.4%	(17/36) 47.2%	(93/126) 74%
Ultrasound contrast	(88/95) 94%	(89/106) 83.9%	(14/20) 70%	(103/126) 82%
P-value	0.102	0.974	0.449	0.158

gland, the first sweep of the VI area of the lymphoid adipose tissue. The results of the frozen pathological examination were transported for detecting cancer metastasis and the entire neck sweep of the lateral area. The postoperative patients with thyroid papillary carcinoma were treated with standard side necks II–V zone sweeping.

Pathological Examination

The pathological report of each paraffin section was used as the diagnostic criterion for patients. After surgery, the paraffin was sent to the pathology department, and according to II–V groups of lymph node packet, the size of the tumor was recorded, and invasion of the thyroid gland membrane was determined. Neck lymph node area, sweeping amount, metastasis number, lymph node shape, size, aspect ratio, and calcification were determined. Lymph node micrometastasis was continuously sliced and examined by two pathological experts. For the patients with thyroid papillary carcinoma, the paraffin sections of the thyroid lesion were reviewed. The sections were then classified into the following pathological subtypes: large follicular type (1 case), papillary microcancer (10 cases), follicular type (10 cases), eosinophilic cell type (7 cases), solid variant type (9 cases), fascia type (9 cases), hyaline cell type (10 cases), high cell type (11 cases), diffuse follicular type (3 cases), columnar cell type (11 cases), diffuse sclerosis type (28 cases), and typical papillary carcinoma (25 cases).

Statistical Analysis

Data were statistically analyzed using Statistical Product and Service Solutions (SPSS) 18.0 (SPSS Inc., Chicago, IL, USA). The counted data for the different groups were compared with X^2 test, and a multivariate analysis was conducted through logistic regression analysis. $p < 0.05$ was considered statistically significant.

RESULTS

General Material Analysis

In total, 95 patients had lateral cervical lymph node metastasis (total metastatic rate: 75.4%), 89 patients had central region lymph node metastasis (total metastatic rate: 70.6%), 47 patients had group II lymph node metastasis (total metastatic rate: 37.3%), 61 patients had group III lymph node metastasis (total metastatic rate: 48.4%), 50 patients had group IV lymph node metastasis (total metastatic rate: 39.7%), and 11 patients had group V lymph node metastasis (total metastatic rate: 8.7%).

No significant difference was observed as for the age and gender of patients with cervical lymph node metastasis of papillary thyroid carcinoma. Lymph node metastasis was significantly more severe if tumor diameter was >4 cm ($X^2 = 8.3$, $p < 0.05$). The lymphatic metastatic rate of multiple central papillary carcinomas reached 96.4% (27/28). The lymph node metastatic rate was 87.7% (64/73) in the patients with thyroid gland membrane invasion, whereas the cervical lymph node metastasis was 58.5% (31/53) in the patients with the thyroid gland membrane, and the difference was significant. The primary lesion was located on the surface of the gland leaves in zones II–IV lymph node metastases (39, 49.5, and 41.9%, respectively), but the primary lesion was located at the bottom of gland leaves in the main VI regional lymph node metastasis (62.8%). The central lesions of cervical lymph node metastasis were classified under the following pathologically subtypes: diffuse sclerosis type (89.3%, 25/28) and high cell type (72.2%, 8/11). These values are significantly higher than those of the papillary micro-carcinoma type (40%, 4/10; **Tables 1**, **2**).

Preoperative color ultrasound and ultrasound contrast detected 74 and 82% patients with total lymph node metastasis, respectively ($X^2 = 16.457$, $p = 0.158$). The sensitivity of ultrasound contrast was 94%, the positive predictive value was 83.9%, and the negative predictive value was 70% (**Table 3**).

Analysis and Comparison of Sensitivity Between Color Ultrasound and Contrast-Enhanced Ultrasonography in Diagnosing Cervical Lymph Node Metastasis

We examined the positive rate of ultrasonography and the total number of regional lymph node metastasis in terms of diagnostic sensitivity. The sensitivity of color ultrasound in detecting cervical lymph node metastasis was 80%. A total of 13 cases of cervical lymph node metastasis were detected through color ultrasound and contrast echocardiography. The clinical and histological subtypes of the patients with lymph node metastasis were compared through color ultrasonography, and the results revealed that 10.3% of the patients were diagnosed with small calcification (68%). The sensitivity of contrast-enhanced ultrasonography used in the detection of cervical lymph node metastasis was 94% ($X^2 = 2.5002$, $p = 0.102$). Such a high sensitivity might be associated with the unique microcirculation of lymph node metastasis. Logistic regression analysis showed that lymph node calcification was correlated with color ultrasonic diagnostic sensitivity in the following parameters: age, tumor size, histologic subtype, lymph node calcification, aspect ratio, necrosis, and blood flow signal richness [odds ratio (OR) = 8.723, $p = 0.007$]. The abundance of blood flow signals was correlated with the diagnostic sensitivity of ultrasound angiography (OR = 3.481, $p = 0.029$). Color ultrasound was significantly different from contrast-enhanced ultrasonography in terms of the diagnosis of lymph node metastasis.

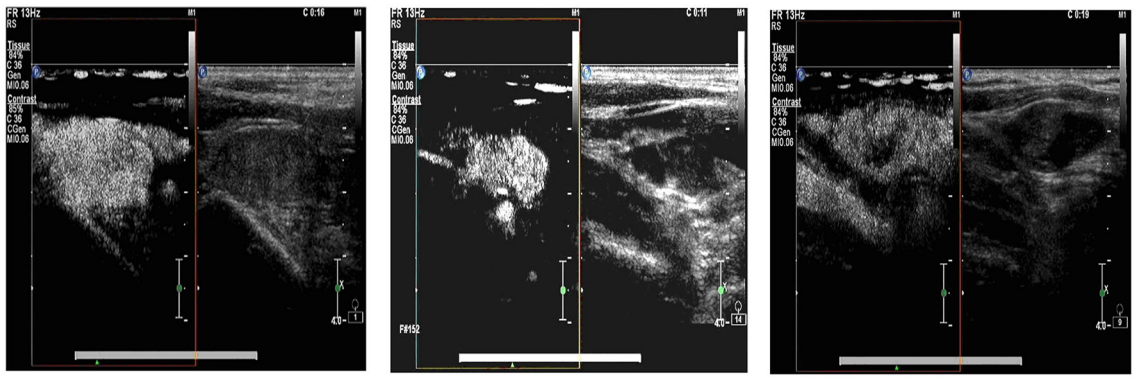


FIGURE 1 | The ultrasonography image of cervical lymph nodes in comparison with ultrasound contrast and color ultrasound images. The images produced by color ultrasound are used for the evaluation of the nature of lymph node lesions. The characteristics of "uneven enhancement" and "fast forward and slow backward" are observed after ultrasound contrast. Postoperative pathological analysis confirms lymph node metastasis.

DISCUSSION

Ultrasonography is the most widely used method for the preoperative diagnosis of thyroid carcinoma and cervical lymph node metastasis (7). CT, MRI, and 2-deoxy-2-[fluorine-18]fluoro-D-glucose (18-FDG) PET are not recommended by the latest domestic and international guidelines for routine examination (1). Ultrasonography is the first method utilized for the evaluation of lymph node metastasis in thyroid carcinoma and cervical region and an accuracy rate of 72% is reported in the literature (8, 9). In this study, the accuracy of color ultrasound in the diagnosis of cervical lymph nodes was 74%, which is consistent with the reported value. Our results also found that ultrasound contrast was accurate (82%) and highly sensitive, suggesting that ultrasound contrast has an enhanced clinical application value.

Some studies have shown that the calcification of lymph nodes, the delineation of the medulla, an aspect ratio of >1, the disappearance of the lymphatic gate, central liquefaction necrosis, and peripheral enhancement are the criteria for determining lymph node metastasis (10). However, this standard has limitations. Small lymph nodes with normal morphological sizes are common, whereas lymph node calcification, fluid necrosis, and peripheral enhancement do not rarely indicate metastasis (11). Moreover, cervical lymph node inflammation is also visible (12). Some researchers found that the lymph node metastatic rate of thyroid papillary carcinoma (CN0) was 60% when the cervical lymph node was swept during operation (13). In other reports, patients with chronic lymphocytic thyroiditis often exhibit neck lymph node enlargement, lymph node echo heterogeneity reduction, and lymphatic door disappearance (14, 15). We used ultrasound contrast technology to address these deficiencies. The diagnosis of positive lymph nodes can reveal not only their morphological characteristics but also the "uneven reinforcement" and "fast forward slow backward" behavior of local blood supply in ultrasound contrast. In typical cases, as shown in **Figure 1**, the morphological structure of lymph nodes in grayscale and color ultrasound images is generally normal. "Uneven enhancement" and "fast forward slow backward" are only observed after ultrasound contrasts and are consistent with the pathological examination results. However, for the regional lymph nodes in grayscale, the color ultrasound performance of typical audio-visual transfer, especially low degree of calcification, the aspect ratio of >1, the abundance of blood flow signal, and the overall accuracy of ultrasound contrast was 86% compared with that of the other technique (84%), but the difference between these techniques was not significant. This result suggested that ultrasound contrast was advantageous over other ultrasound methods in terms of the diagnosis of patients with capability in diagnosing suspected lymph node metastasis.

At present, the pathogenesis of cervical lymph node metastasis in papillary thyroid carcinoma is not established. Some studies reported that thyroid papillary carcinoma invades the membrane or the surrounding tissues or organs, and the metastatic rate in cervical lymph nodes was 46.9% (13). In the present study, the patients with membranous invasion were more prone to lymph node metastasis than those without invasion, and the normal grayscale and color ultrasound results were not transferred. The lesions were located on the upper-medium lobe of the gland mainly in the IIA, III, and IV regional lymph node metastases (39, 49.5, and 41.9%, respectively). The primary lesion was found at the low level mainly in the zone VI regional lymph node metastasis (62.8%). Cancer lesions detected at the upper-medium level are likely to be transferred to zones II and III. Most of the lower-level lesions are transferred to the VI area, which should be targeted to "focus" on the key areas of lymph nodes.

In the present study, the pathological subtypes of primary thyroid tumor were combined with ultrasound contrast. The lymph node metastatic rates were 89.3, 72.2, and 66.7% in the cervical regions with diffuse-type, high-cell-type, and columnar-cell-type pathologies. The cervical lymph node metastatic rate was 96.4%. Under the following conditions, ultrasound contrast

examination should be actively performed: (1) maximum diameter of the primary lesion $\geq$40 mm; (2) lesions are involved in the membrane or invading the surrounding tissues or organs; (3) diffuse type, high cell type, columnar cell type, and other high-risk groups; and (4) multicentric primary lesion. The reoperation rate should be reduced, and a precise direction of neck-selective area sweeping should be followed.

The study has several limitations. This research is a retrospective analysis and may be limited by potential selective bias. Moreover, the research is limited by case group, the absence of benign thyroid tumor, and the presence of cervical lymph node enlargement of the case for comparison. The diagnostic specificity of ultrasound contrast was also difficult to compare. Further studies should be performed to achieve objective observations.

CONCLUSION

In conclusion, the study showed that ultrasound contrast is more sensitive and accurate than color ultrasound in the diagnosis of cervical lymph node metastasis, especially recessive lymph node metastasis, of thyroid papillary carcinoma. Ultrasound contrast also has several of the following advantages. For example, it does not cause trauma, emit radiation, and elicit toxic effects. Furthermore, it requires simple operation and provides good clinical value.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Fujian Provincial Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AZ and SW designed the study. SW and ZY collected the data. ZY and WL analyzed the data. AZ prepared the manuscript. All authors read and approved the final manuscript.

FUNDING

This work was supported by the Science Foundation of the Fujian Province, China (grant no. 2016J1494).

REFERENCES

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: the american thyroid association guidelines task force on thyroid nodules and differentiated thyroid cancer. *Thyroid.* (2016) 26:1–133. doi: 10.1089/thy.2015.0020
2. Song Y, Fu LJ, Li HT, Qiu XG. Evaluation of MEDAG gene expression in papillary thyroid microcarcinoma: associations with histological features, regional lymph node metastasis and prognosis. *Sci Rep.* (2019) 9:5800. doi: 10.1038/s41598-019-41701-4
3. Li X, Zhang H, Zhou Y, Cheng R. Risk factors for central lymph node metastasis in the cervical region in papillary thyroid carcinoma: a retrospective study. *World J Surg Oncol.* (2021) 19:138. doi: 10.1186/s12957-021-02247-w
4. Zhou L, Chen G, Sheng L, Liu N, Zhang B, Zeng Q, et al. Influence factors for lymph node metastasis in papillary thyroid carcinoma: hashimoto's thyroiditis has a weak effect on central or lateral lymph node metastasis. *Cancer Manag Res.* (2021) 13:3953–61. doi: 10.2147/CMAR.S310773
5. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. *CA Cancer J Clin.* (2013) 63:374–94. doi: 10.3322/caac.21195
6. Boland PW, Watt-Smith SR, Pataridis K, Alvey C, Golding SJ. Evaluating lingual carcinoma for surgical management: what does volumetric measurement with MRI offer? *Br J Radiol.* (2010) 83:927–33. doi: 10.1259/bjr/28782452
7. Jin LX, Moley JF. Surgery for lymph node metastases of medullary thyroid carcinoma: a review. *Cancer.* (2016) 122:358–66. doi: 10.1002/cncr.29761
8. Ying M, Bhatia KS, Lee YP, Yuen HY, Ahuja AT. Review of ultrasonography of malignant neck nodes: greyscale, doppler, contrast enhancement and elastography. *Cancer Imaging.* (2014) 13:658–69. doi: 10.1102/1470-7330.2013.0056
9. Xiang D, Hong Y, Zhang B, Huang P, Li G, Wang P, et al. Contrast-enhanced ultrasound (CEUS) facilitated US in detecting lateral neck lymph node metastasis of thyroid cancer patients: diagnosis value and enhancement patterns of malignant lymph nodes. *Eur Radiol.* (2014) 24:2513–9. doi: 10.1007/s00330-014-3288-5
10. Liu Z, Zeng W, Liu C, Wang S, Xiong Y, Guo Y, et al. Diagnostic accuracy of ultrasonographic features for lymph node metastasis in papillary thyroid microcarcinoma: a single-center retrospective study. *World J Surg Oncol.* (2017) 15:32. doi: 10.1186/s12957-017-1099-2
11. Fenesan DI, Lenghel M, Baciut G, Vacaras S, Botar-Jid C, Vasilescu D, et al. Ultrasound and CT imaging features in a patient with salivary duct carcinoma of the parotid gland: a case report with literature review. *Med Ultrason.* (2015) 17:119–22. doi: 10.11152/mu.2013.2066.171.dif
12. Gray HJ. Primary management of early stage cervical cancer (IA1-IB) and appropriate selection of adjuvant therapy. *J Natl Compr Canc Netw.* (2008) 6:47–52. doi: 10.6004/jnccn.2008.0005
13. Lang BH, Ng SH, Lau LL, Cowling BJ, Wong KP, Wan KY, et al. Systematic review and meta-analysis of prophylactic central neck dissection on short-term locoregional recurrence in papillary thyroid carcinoma after total thyroidectomy. *Thyroid.* (2013) 23:1087–98. doi: 10.1089/thy.2012.0608
14. Jones MR, Mohamed H, Catlin J, April D, Al-Qurayshi Z, Kandil E. The presentation of lymph nodes in Hashimoto's thyroiditis on ultrasound. *Gland Surg.* (2015) 4:301–6. doi: 10.3978/j.issn.2227-684X.2015.05.11
15. Okani CO, Otene B, Nyaga T, Ngbea J, Eke A, Edegbe F, et al. Report of a case of papillary thyroid carcinoma in association with Hashimoto's

thyroiditis. *Niger Med J.* (2015) 56:433–5. doi: 10.4103/0300-1652.171612

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhang, Wu, You and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 02 March 2022
doi: 10.3389/fsurg.2022.837177

Temporal and Spatial Characterization of Mononuclear Phagocytes in Circulating, Pulmonary Alveolar, and Interstitial Compartments in LPS-Induced Acute Lung Injury

Qi Li[1], *Guoan Xiang*[2], *Shouchun Peng*[3] *and Wenjie Ji*[4]*

[1] Department of Tuberculosis, Beijing Chest Hospital, Capital Medical University, Beijing, China, [2] Department of Respiratory, The Third Medical Center of Chinese People's Liberation Army General Hospital, Beijing, China, [3] Department of Respiratory, Affiliated Hospital of Armed Police Logistic College, Tianjin, China, [4] Institute of Cardiovascular Disease and Heart Center, Pingjin Hospital, Tianjin, China

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Wenjie Song,
Fourth Military Medical University, China
Xiaming Pei,
Hunan Cancer Hospital, China

***Correspondence:**
Wenjie Ji
ji_wenjie1213@126.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: 16 December 2021
Accepted: 24 January 2022
Published: 02 March 2022

Citation:
Li Q, Xiang G, Peng S and Ji W (2022) Temporal and Spatial Characterization of Mononuclear Phagocytes in Circulating, Pulmonary Alveolar, and Interstitial Compartments in LPS-Induced Acute Lung Injury. Front. Surg. 9:837177. doi: 10.3389/fsurg.2022.837177

Peripheral circulating monocytes and resident macrophages are heterogeneous effector cells that play a critical role in the maintenance and restoration of pulmonary integrity. However, their detailed dynamic changes in lipopolysaccharide (LPS)-induced acute lung injury (ALI) remain unclear. Here, we investigated the impact of mononuclear phagocyte cells in the development of LPS-induced ALI/Acute respiratory distress syndrome (ARDS) and described the relations between the dynamic phenotypic changes and pulmonary pathological evolution. In this study, mice were divided into two groups and intraperitoneally injected with normal saline (NS) or LPS, respectively. A series of flow cytometry assay was performed for the quantification of peripheral circulating monocyte subpopulations, detection of the polarization state of bronchoalveolar lavage fluid (BALF)-isolated alveolar macrophages (AMϕ) and pulmonary interstitial macrophages (IMϕ) separated from lung tissues. Circulating Ly6C^{lo} monocytes expanded rapidly after the LPS challenge on day 1 and then decreased to day 7, while Ly6C^{hi} monocytes gradually increased and returned to normal level on the 7th day. Furthermore, the expansion of M2-like AMϕ (CD64^{+}CD206^{+}) was peaked on day 1 and remained high on the third day, while the polarization state of IMϕ (CD64^{+} CD11b^{+}) was not influenced by the LPS challenge at all the time points. Taken together, our findings show that Ly6C^{lo} monocytes and M2-like AMϕ form the major peripheral circulation and pulmonary immune cell populations, respectively. The dynamic changes of mononuclear phagocyte in three compartments after the LPS challenge may provide novel protective strategies for mononuclear phagocytes.

Keywords: acute lung injury, lipopolysaccharide, Ly6C, alveolar macrophages, interstitial macrophages

INTRODUCTION

Acute lung injury (ALI) is a pulmonary injury of alveolar epithelial cells and capillary endothelial cells, characterized by neutrophilic inflammation, diffuse pulmonary interstitial, and alveolar edema resulting in acute hypoxic respiratory insufficiency. Clinical manifestations of ALI include progressive hypoxemia, respiratory distress, and heterogeneous exudative lesions on lung imaging. ALI and its more severe stage acute respiratory distress syndrome (ARDS) occur in one-third of the patients with sepsis and have a high mortality rate of up to 40% (1, 2). However, there is no effective treatment for ALI, and the mechanisms of ALI/ARDS in sepsis remain unclear. Studies have shown that the main cause of ALI/ARDS is pulmonary vascular injury, which may lead to an increase in pulmonary vascular permeability (3–5). Lipopolysaccharide (LPS), a major component of the outer membrane of Gram-negative bacteria, is one of the most important pathogen-associated molecules of sepsis. LPS stimulation leads to a cascade of inflammatory responses resulting in lung injury. Therefore, inhibition of inflammatory cytokines is a potential treatment for ALI/ARDS.

The activation of innate and adaptive immunity leads to the aggravation of lung injury by releasing a large number of cytokines and inflammatory mediators. Monocytic phagocyte system cells are derived from immature myeloid cells and consist of a heterogeneous population of cells, providing circulating monocytes and resident recruited macrophages (Mϕ) that play an important role in innate pulmonary immune response (6, 7). Tam et al. reported that Ly6G–CD11b+Ly6Chi monocytes exhibited protective and immunosuppressive properties in inflammation (8). Our previous studies have revealed that there was a rapid expansion of circulating $Ly6C^{hi}$ monocytes and M2-like AMϕ rather than the subsets of IMϕ in the bleomycin-induced pulmonary injury model (9). These results support the theory that there is an $Ly6C^{hi}$-monocyte-directed pulmonary AMϕ alternative activation. Although studies have shown that subpopulations of mononuclear phagocytes have been recognized for their critical role in antimicrobial defense, the detailed temporal kinetic changes of mononuclear phagocytes in the circulating, pulmonary alveolar. Moreover, interstitial compartments in LPS-induced ALI/ARDS have not been described. In this study, we established an LPS-induced ALI mouse model and performed serial flow cytometry assays to investigate their association with the pathological evolution of pulmonary disease.

MATERIALS AND METHODS

Reagents

Lipopolysaccharide (0111:B4 from *Escherichia coli*) was purchased from Sigma-Aldrich (St. Louis, MO, USA). 7-amino-actinomycin D (7-AAD) viability staining solution, PerCP/Cy5.5 anti-mouse Ly6G (clone 1A8), fluorescein isothiocyanate (FITC)-conjugated anti-mouse Ly6C (clone HK1.4), phycoerythrin (PE)-conjugated anti-mouse CD11b (clone M1/70), PE-conjugated anti-mouse CD206 (clone C068C2), PerCP/Cy5.5 anti-mouse CD64 (clone X54-5/7.1), and their respective isotype controls (PerCP/Cy5.5 Rat IgG2a, FITC Rat IgG2c, PE Rat IgG2b, PE Rat IgG2a, and PerCP/Cy5.5 Mouse IgG1) were purchased from Biolegend (San Diego, CA, USA).

Animals

Male C57BL/6 mice at 8–10 weeks of age with body weights of 16–18 grams were purchased from the Laboratory Animal Center of the Academy of Military Medical Sciences (Beijing, China). All mice received human care in compliance with the Regulations for Management of Experimental Animals (Tianjin Municipal Science and Technology Commission, revised June 2004), which was in accordance with Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (NIH Pub. No.85-23, revised 1996). All procedures involving animals were approved by the Animal Use and Care Committee of the Pingjin Hospital.

LPS-Induced ALI Mouse Model

In total, 60 mice were randomly divided into two groups: the LPS group ($n = 30$) and the normal saline (NS) group ($n = 30$). Mice were anesthetized by 2% isoflurane inhalation for 60–90 s followed by intraperitoneal (i.p.) injection of LPS (5 mg/kg) in 100 μl of sterile saline or an equal volume of NS. All mice had free access to food and water after the operation. On days 1, 3, and 7 after the LPS/saline challenge, mice were sacrificed under an overdose of pentobarbital sodium (100 mg/kg, $n = 10$ for each group at each time point). The blood samples were treated with ethylene diamine tetraacetic acid disodium salt (Na2-EDTA). The bronchoalveolar lavage fluid (BALF) and the lung tissues were collected for the following experiments.

Histopathological Evaluation of the Lung Tissues

The non-lavaged lungs (left lobes) were fixed with 4% paraformaldehyde in phosphate buffer saline (PBS, pH 7.2–7.4) and inflated under pressure of −20 mmHg for 24 h. The paraformaldehyde-fixed left lobes were embedded in paraffin wax and sliced into 5 μm sections then stained with hematoxylin and eosin (H&E). To evaluate morphological characteristics, five successive selected areas of each lung section were observed under a magnification of ×200 using a light microscope (Olympus, Japan). The severity of alveolitis was determined according to the morphological characteristics, such as inflammatory infiltration and the lesion areas: score 0 represents the normal tissue; scores 1, 2, or 3 represent the degree of pulmonary inflammation <20, 20–50, or more than 50%, respectively. The average score of all examined areas was calculated as the inflammation score (IS).

Bronchoalveolar Lavage Fluid Analysis

The BALF was harvested by lavage through the lung three times with 1 ml precooled saline each time *via* intratracheal cannula, and 90% of the total injected volume was consistently recovered. The BALF was centrifuged at 300 g for 15 min at 4°C. The cell-free supernatant was collected for the inflammatory cytokines assay, total protein quantification, and lactate dehydrogenase (LDH) detection (LDH Assay Kit, Jiancheng Bioengineering

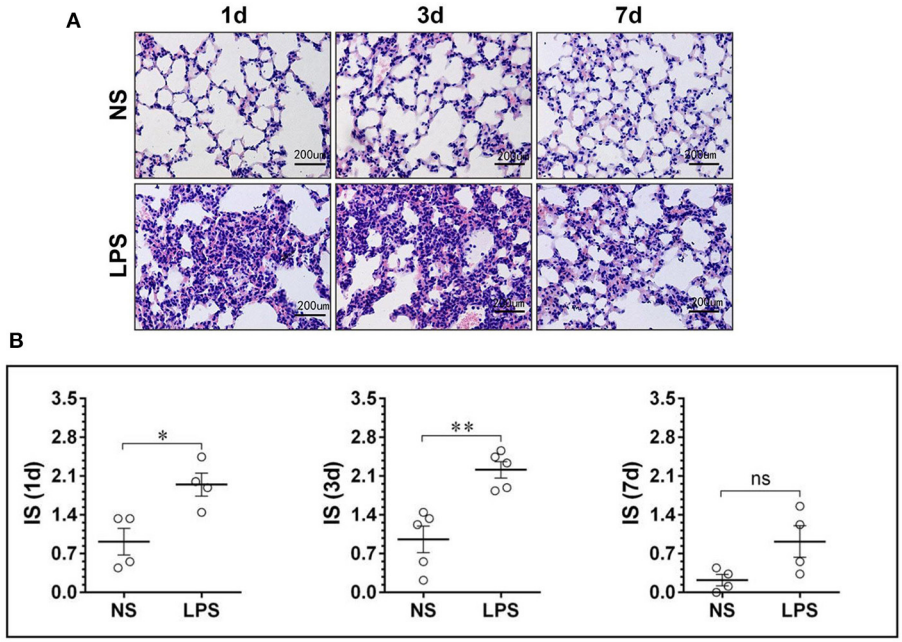


FIGURE 1 | LPS-induced massive leukocyte infiltration and alveolar structural damage. **(A)** H&E staining lung tissue sections showed alveolar edema and swelled alveolar epithelium under stimulation of LPS. **(B)** The inflammation score of the NS and LPS groups at different time points. LPS, lipopolysaccharide; NS, normal saline; HE, hematoxylin and eosin; IS, inflammation score. Scale bars correspond to 50 μm in the micrographs. $^{*}p < 0.05$, $^{**}p < 0.01$. Statistical results were an average of five animals in each group.

Institute, Nanjing, China). The cell pellets were resuspended in 0.9% sterile saline for total and differential cell counts and flow cytometry analysis.

Flow Cytometry

Flow cytometry was performed to analyze the peripheral blood, lung cell suspensions, and BALF cell suspensions using a Cytomics FC500 Flow Cytometry (Beckman Coulter Inc., CA, USA) and FlowJo software (Treestar, Ashland, OR, USA) for data analysis. In monocytes phenotypic assays, hypotonic lysis was used to deplete the red blood cells prior to FCM detection. A volume of 30 μl Na2–EDTA anti-coagulated peripheral blood was stained for 15 min in the dark at room temperature using a mixture of anti-mouse antibodies specific for Ly6G (PerCP/Cy5.5), PE-conjugated CD11b, and FITC-conjugated Ly6C to identify $Ly6C^{hi}$ and $Ly6C^{lo}$ cells. In the AMϕ phenotypic assay, 50 μl BALF cell suspension was stained using a mixture of 7-AAD viability staining solution (eBioscience, Thermo Fisher Scientific, Inc., Waltham, MA, USA), anti-mouse antibodies specific for CD64 (PerCP/Cy5.5), PE-conjugated anti-mouse CD206, and PE-conjugated anti-mouse CD11b (BioLegend, CA, USA) according to the manufacturer's instructions to identify AMϕ M1 and AMϕ M2 cells. FCM assay was carried out after incubation. In IMϕ phenotypic assay, the right lower lung tissues were digested with 0.1% type I collagenase (Sigma-Aldrich, Inc., MA, USA) at 37°C for 1 h. After washing with D-Hanks and cell viability detection, 50 μl refiltered single-cell suspensions were stained in the presence of hypotonic lysis using a mixture of 7-AAD viability staining solution (eBioscience, Thermo Fisher Scientific, Inc., Waltham, MA, USA), anti-mouse antibodies specific for CD64 (PerCP/Cy5.5), PE-conjugated anti-mouse CD11b, and PE-conjugated anti-mouse CD206 (BioLegend, CA, USA) according to the manufacturer's instructions to identify IMϕ M1 and IMϕ M2 cells. FCM measurement was performed after incubation.

Statistical Analysis

All data were expressed as means ± SEM from three replicate experiments and analyzed with one-way ANOVA using GraphPad Prism 5.0 software (GraphPad, San Diego, CA, USA) followed by the Bonferroni *post-hoc test* for statistical comparison of multiple groups. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Lung Inflammatory Response in the LPS-Mediated ALI Model

To investigate the histological changes, the H&E-stained lung tissues were examined by light microscope on days 1, 3, and 7 after the LPS or NS challenge. As shown in **Figures 1**, **2**, compared to the normal structure of lung tissue and pulmonary alveoli composed of thin septa, vascular, and connective tissue, LPS-induced ALI resulted in peribronchial and interstitial inflammatory cells significant infiltration with complications of acute congestion, edema, and alveolar wall thickening (**Figure 1**). **Figure 2** shows the degree of inflammation in LPS groups is

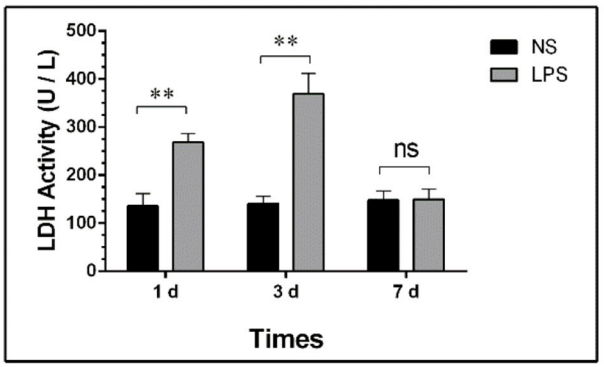


FIGURE 2 | Total protein in BALF of LPS-induced ALI. Mice were sacrificed on days 1 and 3 after LPS stimulation and BALF were collected for protein quantification. BALF, bronchoalveolar lavage fluid; LPS, lipopolysaccharide; ALI: Acute lung injury; $*p < 0.05$; $**p < 0.01$; ns, no statistical significance. Statistical results were an average of five animals in each group.

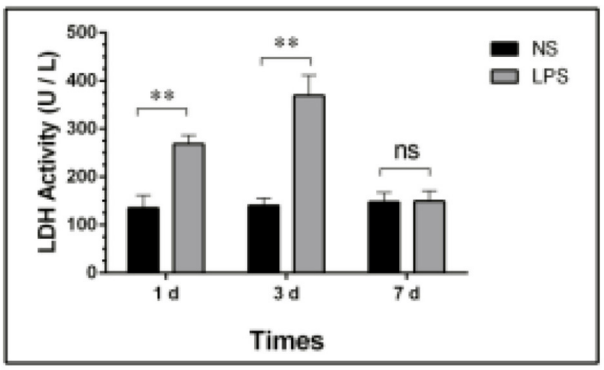


FIGURE 3 | LDH activity in BALF of LPS-induced ALI. Mice were sacrificed on days 1, 3, and 7 after LPS stimulation and BALF were collected for LDH activity detection. BALF, bronchoalveolar lavage fluid; LPS, lipopolysaccharide; ALI, Acute lung injury; $** p < 0.01$; ns, no statistical significance. Statistical results were an average of five animals in each group.

much higher than that in NS groups on days 1–3 and decreases to normal level on day 7.

Total LDH Activity of BALF

The concentration of total protein and LDH activity detection at each time point are shown in **Figure 3**.

Temporal Dynamic Changes of Peripheral Circulating Monocyte Sub-Populations

The peripheral circulating monocytes presented a dynamic expression of Ly6C after LPS stimulation (**Figures 4A,B**). Compared with the NS group, the percentage of $Ly6C^{lo}$ in the LPS group was highly increased on day 1 after the LPS challenge, then gradually declined from day 3 to day 7 ($p < 0.05$) and finally reached a level similar to that of the NS group (**Figure 4C**). In contrast with $Ly6C^{lo}$, the temporal dynamics of $Ly6C^{hi}$ remained at a lower level than that of the NS group until day 7 (**Figure 4D**).

Temporal Dynamic Changes of BALF-Isolated AMϕ

The temporal dynamic changes of BALF-isolated AMϕ and IMϕ both in NS and LPS groups were characterized by FCM. Results showed that $7\text{-AAD}^{-}\text{CD64}^{+}\text{CD206}^{-}$ cells (M1-like AMϕ) accounted for the majority of cell types of BALF-isolated AMϕ in the NS group (**Figures 5A,B**). The percentage of M1-like AMϕ in the LPS group was low on day 1, then showed an upward trend from day 3 and finally reached a level similar to that of the NS group on day 7 (**Figure 5C**). However, the level of $7\text{-AAD}^{-}\text{CD64}^{+}\text{CD206}^{+}$ cells (M2-like AMϕ) in LPS treated mice was much higher than that in the NS group on day 1 then gradually decreased to normal level (**Figure 5D**).

Temporal Dynamic Changes of BALF-Isolated IMϕ

Dynamic variations of IMϕ from digested lungs are shown in **Figure 6**. More than 92% of $7\text{-AAD}^{-}\text{CD64+CD11b}^{+}$ cells showed M1-like phenotype (CD206–) (**Figures 5A,B**). Moreover, there was no significant change in M1 and M2 compared with normal levels from day 1 to 7 after LPS stimulation (**Figures 6C,D**).

DISCUSSION

Acute lung injury is a severe symptom of ARDS, characterized by capillary hyperpermeability, interstitial, and alveolar edema and aggregation of neutrophils, macrophages, and red blood cells in the alveoli. Although a large number of technical and supportive therapies have been developed by intensive care units over the past 40 years, few effective approaches have been used to treat ALI/ARDS, which has resulted in high mortality (2). LPS has a pro-inflammatory effect, triggering pulmonary inflammatory response through N oxide-dependent redox signaling (10) in pulmonary endothelial cells and causing alteration in the airway and pulmonary circulation function in mice (11, 12). i.p. injection of LPS has been widely acknowledged as a repeatable pharmacological model of ALI. Therefore, we used a mouse model of i.p. injection of LPS to observe the dynamics of three components of the mononuclear phagocyte system.

The present work manifested the temporal and spatial characterization of circulating monocytes, pulmonary resident macrophages, which include alveolar macrophage (AM) and interstitial macrophage (IM) in an ACI rodent model induced by i.p. injection of LPS. The main findings are all around these three monocyte-macrophage subpopulations. First, there was a higher level of Ly6C subset in the LPS group than that in the NS group on day 1 after LPS administration and declined subsequently and reached the same level as NS ultimately on day 7. Of note, there is a more active $Ly6C^{lo}$ subset due to the LPS challenge, and by contrast, $Ly6C^{hi}$ remained at a lower level than that of the NS group until day 7. Second, the temporal changes of M2-like AM are almost the same as $Ly6C^{lo}$: an expansion of M2-like alveolar macrophage from day 1 and reached a similar level as that of the NS group on day 7. Third, with regard to IM, there was no significant difference between M1 and M2 compared

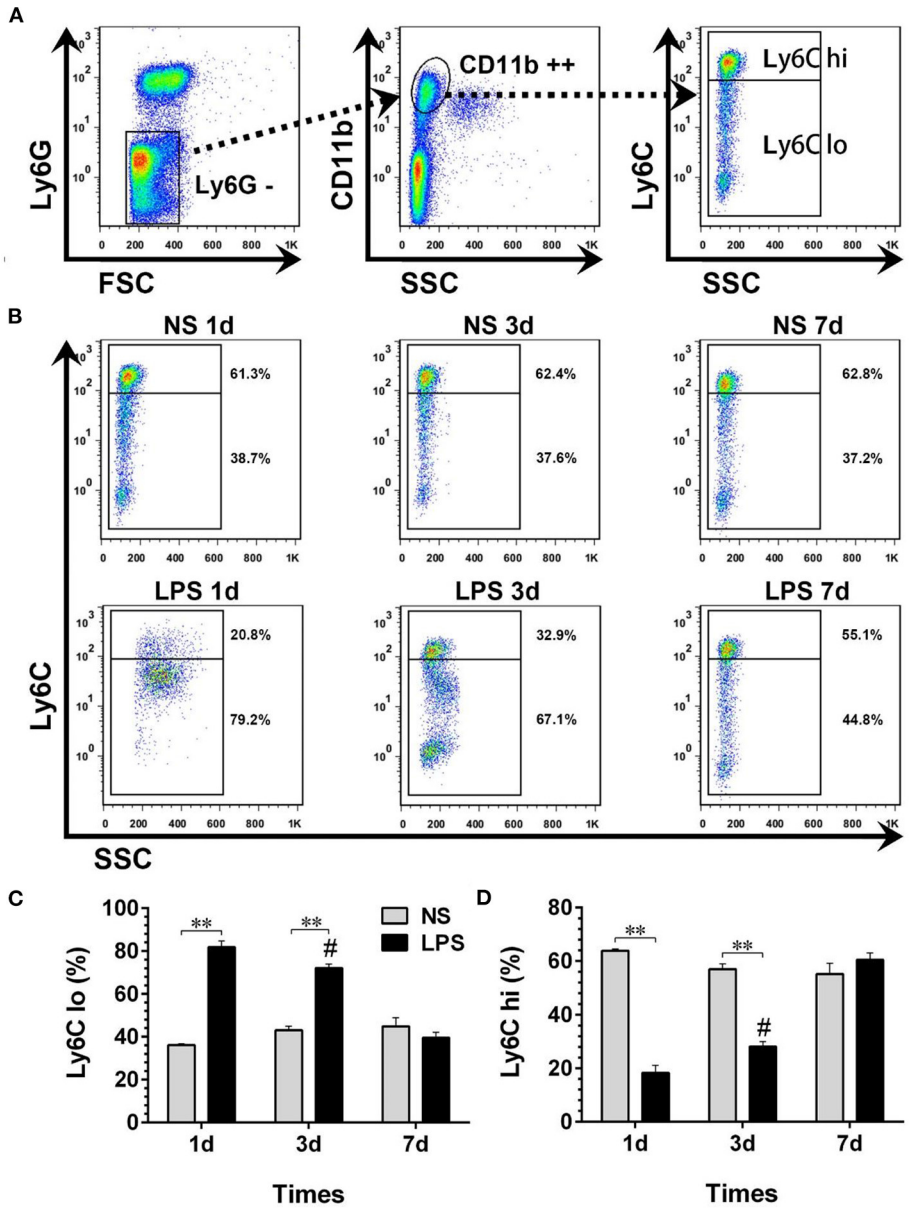


FIGURE 4 | Temporal dynamic changes of peripheral circulating monocyte subpopulations after LPS stimulation. **(A, B)** Ly6C^{hi} and Ly6C^{lo} monocytes were identified by flow cytometry. Numbers outside boxed areas indicated the percentage of cells. The gating strategies for peripheral circulating monocyte subpopulations are shown in **(A)**. The dynamic characteristics of Ly6C^{hi} and Ly6C^{lo} monocytes in NS and LPS groups are shown in **(B)**. **(C, D)** Kinetics of increase in Ly6C^{hi} and Ly6C^{lo} monocyte numbers in peripheral blood. FSC, forward-scattered light; SSC, side-scattered light. #$p < 0.05$, compared with the LPS group on day 1; **$p < 0.01$. ($n = 5$ in each group).

with normal levels from day 1 to 7 after the LPS challenge. To the best of our knowledge, the present work is the first report with regard to describing the temporal and spatial changes of mononuclear phagocytes in the LPS-induced ACI model, which may provide clues for monocyte/macrophage targeting treatment of ACI or septic-ARDS. Moreover, we prove for the first time that LPS induces increased accumulation of M2-like AMϕ in the pulmonary alveoli rather than M1-like AMϕ.

As a component of the mononuclear phagocyte system, circulating peripheral blood monocytes provide a mobile and powerful cell source for innate immune system (13). They are also precursors of macrophages and dendritic cells and involved in the maintenance and restoration of tissue integrity (14, 15). It is noteworthy that in the previous studies of dynamics of circulating monocytes, AMϕ and IMϕ in BLM-induced lung injury and fibrosis mouse model, mouse Ly6C^{hi} monocyte was a therapeutic target for many inflammatory diseases, which supported the Ly6C^{hi} directed pulmonary alternative activation mechanism (16).

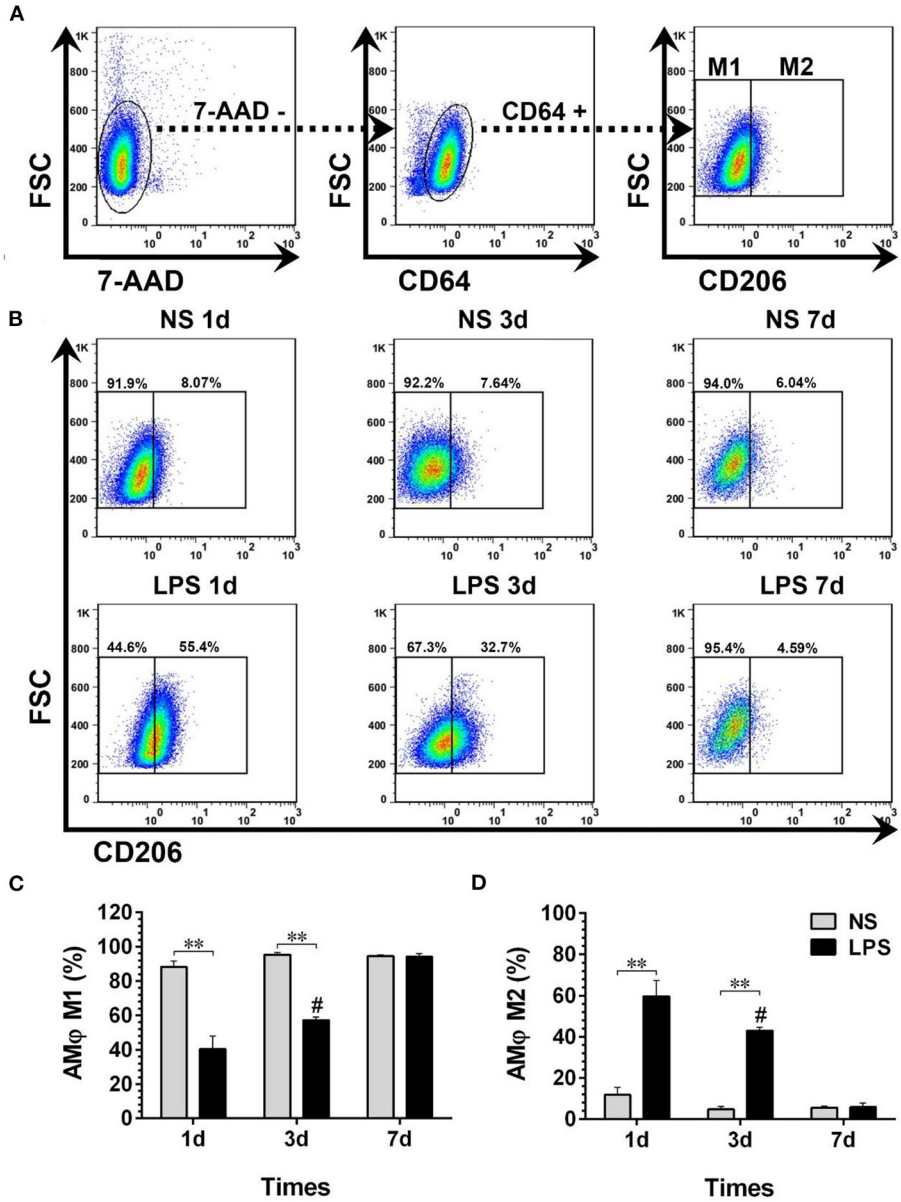


FIGURE 5 | Temporal dynamic changes of AMϕ subpopulations after LPS stimulation. **(A, B)** M1- and M2-like AMϕ were identified by flow cytometry. Numbers outside boxed areas indicate the percentage of cells. The gating strategies for pulmonary AMϕ subpopulations is shown in **(A)**. The dynamic characteristics of lung M1- and M2-like AMϕ in NS and LPS groups are shown in **(B)**. **(C, D)** Kinetics of increase in M1- and M2-like AMϕ numbers in BALF-isolated cells. FSC, forward-scattered light; SSC, side-scattered light. #$p < 0.05$, compared with the LPS group on day 1; **$p < 0.01$. ($n = 5$ in each group).

Compared to active Ly6C^{hi} in fibrosis mice, the Ly6C^{lo} subpopulation was more active after LPS exposure. The mechanism behind this phenomenon may be that when the cells are damaged, the Ly6C^{lo} subpopulation with more surface CX3CR1 expression, which can crawl or patrol in the vascular cavity faster, and can be seen as sentinel cells (27), and neutrophils can migrate to the injured site by Ly6C^{lo} cells secreting CXCL2 chemokine (28). Moreover, it is also reported that the accumulation of Ly6C^{low} monocytes was associated with the expression of adhesion molecules in vascular endothelial cells (17), and LPS-induced tumor necrosis factor α (TNF-α) release resulted in intercellular adhesion molecule (ICAM-1) and E-selectin expression as well as increased vascular cell adhesion molecule (VCAM-1) expression in supernatant-activated endothelial cells. Therefore, LPS is a trigger for the indirect activation of endothelial cells by monocytes, which plays an important role in the adhesion of breast cancer cells (18). According to these findings, we propose that LPS-induced adhesion molecules expression contributes to the accumulation of Ly6Clow monocytes in

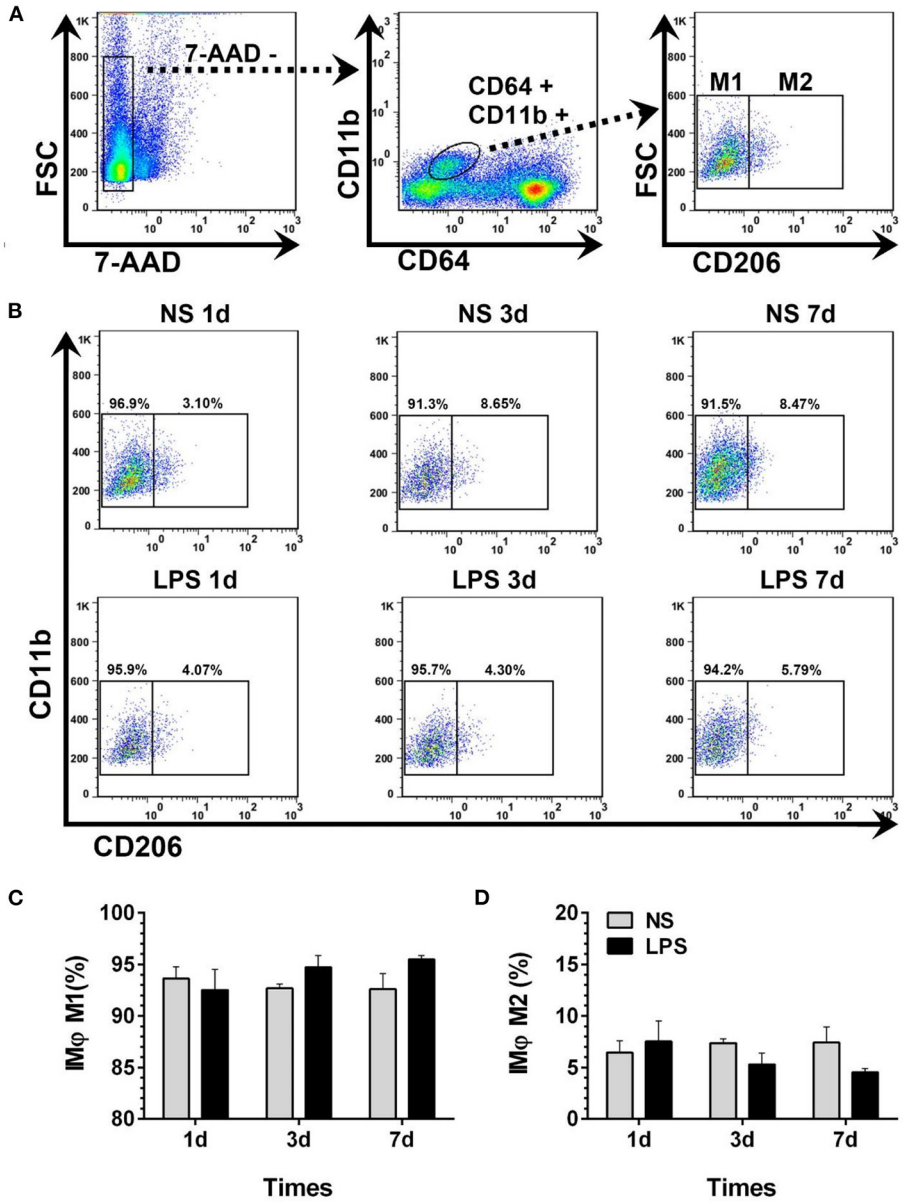


FIGURE 6 | Temporal dynamic changes of IMϕ subpopulations after LPS stimulation. **(A, B)** M1- and M2-like IMϕ were identified by flow cytometry. Numbers outside boxed areas indicated the percentage of cells. The gating strategies for pulmonary IM subpopulations is shown in **(A)**. The dynamic characteristics of lung M1- and M2-like IMϕ in NS and LPS groups are shown in **(B)**. **(C, D)** Kinetics of increase in M1- and M2-like IMϕ numbers in the lung tissue. FSC, forward-scattered light; SSC, side-scattered light. #$p < 0.05$, compared with the LPS group on day 1; **$p < 0.01$. ($n = 5$ in each group).

the peripheral circulation and local infiltrate of M2-like AMϕ in the pulmonary alveoli. Additionally, it is reported that selective depletion of Ly6C^{lo} subpopulation would lengthen the duration of inflammation absorption and regression (19), and furthermore, Shichino et al. (20) believed that Ly6C^{lo} restorative macrophage subset plays a role of candidate lung macrophages and could different into the monocyte-derived macrophages (MMs) in alveoli as a result of Ly6C^{lo} subset cells and MMs response to inflammation both in a C-C chemokine receptor type 2 (CCR2)-dependent manner (21). Although we observed the ACI in mice within 7 days, according to the comparison betweensilica-induced pulmonary fibrosis mice and LPS-induced ARDS or ALI mice, we can reasonably speculate that LPS can cause a slight rise of M2 phenotype alveolar macrophages for a short time, while it would cause secondary fibrosis change in the lung tissue later as well. The magnitude of the LPS-induced lung lesion should be less than the typical pulmonary fibrosis caused by bleomycin and silica. We believe that there is a positive correlation between M2 phenotype alveolar macrophages proportion in the early stage

with the degree of prognosis in the later stage, and it also has a certain suggestive effect on the degree of lung injury at that time.

In conclusion, this study demonstrates the dynamic changes of circulating monocytes, AMϕ and IMϕ, in the LPS-induced ALI mouse model. A rapid expansion of circulating Ly6C^{lo} monocytes and M2-like AMϕ suggests that monocyte phagocytes may be a potential therapeutic target for ALI (22).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The animal study was reviewed and approved by Animal Use and Care Committee of the Beijing Chest Hospital, Capital Medical University.

AUTHOR CONTRIBUTIONS

QL is the mainly responsible for the writing of the article. GX is mainly responsible for research design. SP is mainly responsible for data analysis. WJ is responsible for the guidance of the entire research. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

REFERENCES

1. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. *N Engl J Med.* (2005) 353:1685–93. doi: 10.1056/NEJMoa050333
2. Confalonieri M, Salton F, Fabiano F. Acute respiratory distress syndrome. *Eur Respir Rev*. (2017) 26:160116. doi: 10.1183/16000617.0116-2016
3. Dobbe L, Rahman R, Elmassry M, Paz P, Nugent K. Cardiogenic pulmonary edema. *Am J Med Sci.* (2019) 358:389–97. doi: 10.1016/j.amjms.2019.09.011
4. Olivier NB. Pulmonary edema. *Vet Clin North Am Small Anim Pract.* (1985) 15:1011–30. doi: 10.1016/S0195-5616(85)50107-2
5. Koma T, Yoshimatsu K, Nagata N, Sato Y, Shimizu K, Yasuda SP, et al. Neutrophil depletion suppresses pulmonary vascular hyperpermeability and occurrence of pulmonary edema caused by hantavirus infection in C.B-17 SCID mice. *J Virol.* (2014) 88:7178–88. doi: 10.1128/JVI.00254-14
6. Chen L, Zhang Z, Barletta KE, Burdick MD, Mehrad B. Heterogeneity of lung mononuclear phagocytes during pneumonia: contribution of chemokine receptors. *Am J Physiol Lung Cell Mol Physiol.* (2013) 305:L702–11. doi: 10.1152/ajplung.00194.2013
7. Kuznetsova T, Prange KHM, Glass CK, de Winther MPJ. Transcriptional and epigenetic regulation of macrophages in atherosclerosis. *Nat Rev Cardiol.* (2020) 17:216–28. doi: 10.1038/s41569-019-0265-3
8. Tam JW, Kullas AL, Mena P, Bliska JB, van der Velden AW. CD11b+ Ly6Chi Ly6G- immature myeloid cells recruited in response to Salmonella enterica serovar Typhimurium infection exhibit protective and immunosuppressive properties. *Infect Immun.* (2014) 82:2606–14. doi: 10.1128/IAI.01590-13
9. Ji WJ, Ma YQ, Zhou X, Zhang YD, Lu RY, Sun HY, et al. Temporal and spatial characterization of mononuclear phagocytes in circulating, lung alveolar and interstitial compartments in a mouse model of bleomycin-induced pulmonary injury. *J Immunol Methods.* (2014) 403:7–16. doi: 10.1016/j.jim.2013.11.012
10. Menden H, Tate E, Hogg N, Sampath V. LPS-mediated endothelial activation in pulmonary endothelial cells: role of Nox2-dependent IKK-β phosphorylation. *Am J Physiol Lung Cell Mol Physiol.* (2013) 304:L445–55. doi: 10.1152/ajplung.00261.2012
11. Lin MH, Chen MC, Chen TH, Chang HY, Chou TC. Magnolol ameliorates lipopolysaccharide-induced acute lung injury in rats through PPAR-γ-dependent inhibition of NF-kB activation. *Int Immunopharmacol.* (2015) 28:270–8. doi: 10.1016/j.intimp.2015.05.051
12. Tsai T, Kao CY, Chou CL, Liu LC, Chou TC. Protective effect of magnolol-loaded polyketal microparticles on lipopolysaccharide-induced acute lung injury in rats. *J Microencapsul.* (2016) 33:401–11. doi: 10.1080/02652048.2016.1202344
13. Sunderkötter C, Nikolic T, Dillon MJ, Van Rooijen N, Stehling M, Drevets DA, et al. Subpopulations of mouse blood monocytes differ in maturation stage and inflammatory response. *J Immunol.* (2004) 172:4410–7. doi: 10.4049/jimmunol.172.7.4410
14. Geissmann F, Jung S, Littman DR. Blood monocytes consist of two principal subsets with distinct migratory properties. *Immunity.* (2003) 19:71–82. doi: 10.1016/S1074-7613(03)00174-2
15. VanGundy ZC, Guerau-de-Arellano M, Baker JD, Strange HR, Olivo-Marston S, Muth DC, et al. Continuous retinoic acid induces the differentiation of mature regulatory monocytes but fails to induce regulatory dendritic cells. *BMC Immunol.* (2014) 15:8. doi: 10.1186/1471-2172-15-8
16. Shieh JM, Tseng HY, Jung F, Yang SH, Lin JC. Elevation of IL-6 and IL-33 levels in serum associated with lung fibrosis and skeletal muscle wasting in a bleomycin-induced lung injury mouse model. *Mediators Inflamm.* (2019) 2019:7947596. doi: 10.1155/2019/7947596
17. Weisheit C, Zhang Y, Faron A, Köpke O, Weisheit G, Steinsträsser A, et al. Ly6C(low) and not Ly6C(high) macrophages accumulate first in the heart in a model of murine pressure-overload. *PLoS ONE.* (2014) 9:e112710. doi: 10.1371/journal.pone.0112710
18. Chen C, Khismatullin DB. Lipopolysaccharide induces the interactions of breast cancer and endothelial cells via activated monocytes. *Cancer Lett.* (2014) 345:75–84. doi: 10.1016/j.canlet.2013.11.022
19. Ramachandran P, Pellicoro A, Vernon MA, Boulter L, Aucott RL, Ali A, et al. Differential Ly-6C expression identifies the recruited macrophage phenotype, which orchestrates the regression of murine liver fibrosis. *Proc Natl Acad Sci U S A*. (2012) 109:E3186–95. doi: 10.1073/pnas.1119964109
20. Shichino S, Abe J, Ueha S, Otsuji M, Tsukui T, Kosugi-Kanaya M, et al. Reduced supply of monocyte-derived macrophages leads to a transition from nodular to diffuse lesions and tissue cell activation in silica-induced pulmonary fibrosis in mice. *Am J Pathol.* (2015) 185:2923–38. doi: 10.1016/j.ajpath.2015.07.013
21. Mitchell C, Couton D, Couty JP, Anson M, Crain AM, Bizet V, et al. Dual role of CCR2 in the constitution and the resolution of liver fibrosis in mice. *Am J Pathol.* (2009) 174:1766–75. doi: 10.2353/ajpath.2009.080632
22. Cao C, Yu M, Chai Y. Pathological alteration and therapeutic implications of sepsis-induced immune cell apoptosis. *Cell Death Dis.* (2019) 10:782. doi: 10.1038/s41419-019-2015-1

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Li, Xiang, Peng and Ji. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 03 March 2022
doi: 10.3389/fsurg.2022.851113

Analysis of the Effect of External Counterpulsation Combined With High-Intensity Aerobic Exercise on Cardiopulmonary Function and Adverse Cardiovascular Events in Patients With Coronary Heart Disease After PCI

Shiming Zhao[1†], *Shaowen Liu*[1†], *Yuan Wen*[1], *Qiuhuan Qi*[1] *and Peng Huang*[2*]

[1] *Department of Cardiology, Wuhan Hankou Hospital, Wuhan, China,* [2] *Intensive Care Unit, Emergency Medical Department, Wuhan Hankou Hospital, WuHan, China*

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Xuefeng Yang,
University of South China, China
Wenjun Gu,
Shanghai Jiaotong University School of Medicine, China

***Correspondence:**
Peng Huang
hpp1361@163.com

[†] *These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *09 January 2022*
Accepted: *31 January 2022*
Published: *03 March 2022*

Citation:
Zhao S, Liu S, Wen Y, Qi Q and Huang P (2022) Analysis of the Effect of External Counterpulsation Combined With High-Intensity Aerobic Exercise on Cardiopulmonary Function and Adverse Cardiovascular Events in Patients With Coronary Heart Disease After PCI. Front. Surg. 9:851113. doi: 10.3389/fsurg.2022.851113

Purpose: To explore the intervention effect of external counterpulsation (ECP) combined with high-intensity aerobic exercise (HIAT) on patients with coronary heart disease (CHD) after PCI.

Methods: 124 patients with stable CHD after PCI admitted to our hospital from June 2018 to June 2021 were selected, and all patients were divided into control group and observation group using the random number table method. The control group received conventional treatment, The observation group received ECP combined with HIAT based on the control group. The cardiorespiratory function indexes, exercise endurance indexes, incidence of major cardiovascular adverse events (MACE), Barthel index of the two groups were observed.

Results: After intervention, METs $_{max}$, $VO_{2\ max}$, $VO_{2\ max}$/kg, $VO_{2\ max}$/HR, and PP, ED, AT, and Barthel score in both groups were significantly higher than before intervention, and patients in the observation group were significantly higher than those in the control group ($P < 0.05$). The incidence of MACE in the observation group (3.23%) was lower than in the control group (12.90%) ($P < 0.05$).

Conclusion: ECP combined with HIAT can improve the cardiopulmonary function of patients with CHD after PCI, and improve exercise endurance, reduce the incidence of MACE, improve patients' ability of daily living.

Keywords: coronary heart disease, external counterpulsation, high-intensity aerobic exercise, cardiopulmonary function, adverse cardiovascular events

INTRODUCTION

Coronary heart disease (CHD), a common disease among middle-aged and elderly people, has become the leading cause of hospitalization and death in China. The onset age of this disease is generally after 60 years old, and in recent years, the prevalence of CHD has been on a rapid rise (1). With the development of science and technology and medical treatment, percutaneous coronary intervention (PCI) is increasingly used in the treatment of CHD, which is a therapeutic method for patients with coronary artery stenosis to unblock the narrowed or occluded coronary artery lumen by transcatheter technique. It has the advantages of less trauma, quick recovery and high success rate (2, 3). However, PCI is not the end of treatment for patients with CHD. Although PCI can save patients' lives, the incidence of major cardiovascular adverse events (MACE) after PCI is high and the recovery of cardiopulmonary function after PCI is poor (4, 5). At present, only drug or surgical treatment can not completely relieve the risk factors of patients with CHD, and it is of great clinical significance to effectively stabilize the condition of patients with CHD, reduce the incidence of coronary complications, and improve the cardiopulmonary function of patients.

Research has shown that the key to improving the quality of life and prognosis of patients with CHD is not only conventional drug therapy, but also somato-psychological and other integrated rehabilitation measures are equally important (6). External counterpulsation (ECP) is a non-invasive assisted circulation device, which sequentially inflates the balloon during the diastolic phase of the heart to promote blood return to the lower extremity arteries and increase coronary artery perfusion, and is beneficial to improving myocardial blood supply and increasing oxygen-carrying capacity, thus affecting cardiopulmonary function, and has become the main non-drug treatment for various angina pectoris, heart failure and other cardiovascular diseases (7, 8). In addition, cardiac rehabilitation therapy with exercise training as the core content is gradually recognized and respected by clinical health care professionals and patients. High-intensity aerobic training (HIAT) can reduce the body's inflammatory reaction, improve the patient's endothelial function, promote the establishment of coronary collateral circulation and delay coronary stenosis through high-intensity effective exercise stimulation (9). HIAT not only helps to control body weight, improve patients' blood pressure and blood glucose, but also prevents cardiovascular events, promotes mental health, and controls risk factors of cardiovascular disease as a whole, thus improves patients' exercise function and survival quality, and has a positive impact on patients' prognosis (10). The aim of this study was to investigate the effect of ECP combined with HIAT on cardiopulmonary function and MACE in patients with CHD after PCI.

MATERIALS AND METHODS

Object

124 patients with stable CHD after PCI admitted to our hospital from June 2018 to June 2021 were selected, and all patients were divided into control group and observation group using the random number table method, with 62 cases each.

Inclusion Criteria

Met the diagnostic criteria of coronary heart disease (11); PCI was performed successfully for the first time within 3 months; Hemodynamics was stable after PCI; Have the condition of basic movement.

Exclusion Criteria

Accompanied by movement restriction diseases such as bone joints and muscles; Patients with severe arrhythmia and severe heart failure that affect ECP; Severe cardiopulmonary dysfunction; Those who were unable to perform cardiopulmonary exercise test for various reasons; Accompanied by systemic serious organic diseases; Complicated infectious diseases; Mental disorder, abnormal cognitive function, Unable to cooperate with training; Increase or decrease the amount of exercise if you did not follow the instructions.

Methods

The control group received conventional treatment, including drug therapy, anti-blocking rehabilitation training, and daily nursing (1). The medical staff gave the patients anti-platelet aggregation, nitrates, angiotensin-converting enzyme inhibitors, and statins (2). Integrated with the guidance of the director of our rehabilitation department, the patients performed elastic band exercises with the help of researchers to ensure that the patients did not feel any discomfort on the day of training, and instructed the patient to wear a heart rate monitor. Preparatory activities and relaxation activities were performed before exercise, relaxation movements and warm-up movements include shoulder, wrist, ankle, neck, waist, hip, knee joint activities. The patients' blood pressure and heart rate were closely monitored during exercise, and exercise was stopped immediately if symptoms such as progressive chest pain, pale complexion, ataxia, dizziness, fatigue, and shortness of breath occurred. The training forms could simply be arranged and designed according to the movement of the joint, the resistance provided by the elastic band at 100% extension was 1.7 kg. In resistance training, each isometric contraction lasted 10s, rested for 10 s, repeated 10 times as a set of training, and each training was done with 10 sets of training (3). Health education was carried out on quitting smoking and drinking, eating regularly, exercising properly, and regulating emotions.

The observation group received ECP combined with HIAT based on the control group. Patients were evaluated by cardiopulmonary exercise test before the intervention. Patients were first warmed up with a power bike for 5 min with no load and rested for 3 min with an initial power of 5 W. The power was increased at a rate of 10 W/min. Patients were kept at a speed of 50–60 r/min while pedaling training. When patients had chest pain, weakness, dyspnea and other uncomfortable symptoms, or when ECG and blood pressure monitoring reached the indications for test discontinuation, the evaluation was discontinued and peak power (PP) was recorded (1). ECP: The intervention was performed with a balloon type ECP device

(P-ECP/TM, Pushkang, Chongqing). During the treatment, the patient was lying flat on the bed, and airbags were pumped on the patient's calves and thighs as well as buttocks, which were connected to the air compressor through an air tube. Under cardiac monitoring, the balloons were inflated and deflated simultaneously with the patient's cardiac cycle, with sequential compression of the lower limbs and buttocks during diastole and rapid deflation of the three balloons during systole, with a counterpulsation balloon inflation pressure of 260–340 mmHg and a finger pulse wave showing a diastolic/systolic wave ratio >1.2. 1 time/d, 1 month was a course of treatment (2). HIAT: After 5 min of warm-up, patients were trained with power treadmill by bicycle with aerobic exercise intensity of 80% PP, 3 min for each group, with 1 min rest between groups, 10 groups for each training, a total of 40 min. The initial training could be carried out with 60% PP as exercise load for 7 days of adaptive training. The treatment lasted for 3 months, 1 time/d, and 3 times/week.

Observation Index

(1) Baseline information such as patient's age, gender, smoking history, alcohol history, combined diseases, and postoperative course of PCI were recorded.
(2) Before intervention and 3 months after intervention, the K482 cardiopulmonary exercise test training system (COSME, Italy) was used to measure the patients' cardiorespiratory function indexes. The patients' maximal METs ($METs_{max}$), maximal oxygen uptake ($VO_{2\ max}$), maximal oxygen uptake every kilogram ($VO_{2\ max}$/kg) and maximal oxygen pulse ($VO_{2\ max}$/HR) were recorded.
(3) Before intervention and 3 months after intervention, the K482 cardiopulmonary exercise test training system (COSME, Italy) was used to measure the exercise endurance indexes of the patients. The PP, exercise duration (ED) and anaerobic threshold (AT) in the patients' cardiopulmonary exercise test were recorded.
(4) The incidence of MACE such as angina pectoris, arrhythmia and heart failure was recorded in both groups within 3 months of intervention.
(5) Before intervention and 3 months after intervention, the Barthel index was used to evaluate the patients' ability of daily living. The scale had 10 items with a total score of 100 points, >60 points: in daily life, patients could basically take care of themselves; 40–60 points: in daily life, patients needed the help from others; 20–40 points: life needs a lot of help; <20 points: in daily life, patients completely needed the help from others. The higher the score, the stronger the independence and the smaller the dependence of the patient.

Statistical Methods

SPSS 22.0 software was used for analysis. The measurement data was (± s), the comparison was made by *t*-test, the count data was (%), and the comparison was made by χ^2 test. $P < 0.05$ was statistically significant.

RESULTS

Baseline Information of the Patient

There was no statistical difference in age, gender, smoking history, alcohol history, combined diseases, and postoperative course of PCI between the two groups ($P > 0.05$). As shown in **Table 1**.

Cardiopulmonary Function of Patients

After intervention, $METs_{max}$, $VO_{2\ max}$, $VO_{2\ max}$/kg, and $VO_{2\ max}$/HR in both groups were significantly higher than before intervention, and patients in the observation group were significantly higher than those in the control group ($P < 0.05$). As shown in **Figure 1**.

Exercise Endurance of Patients

After intervention, PP, ED, and AT in both groups were significantly higher than before intervention, and patients in the observation group were significantly higher than those in the control group ($P < 0.05$). As shown in **Figure 2**.

Incidence of MACE in Patients

The incidence of MACE in the observation group (3.23%) was lower than in the control group (12.90%) ($P < 0.05$). As shown in **Table 2**.

Ability of Daily Living of Patients

After intervention, the Barthel score in both groups were significantly higher than before intervention, and patients in the observation group was significantly higher than that in the control group ($P < 0.05$). As shown in **Figure 3**.

DISCUSSION

PCI is one of the common clinical treatment modalities for CHD, which can effectively improve myocardial blood perfusion, promote myocardial cell recovery and improve prognosis (12). However, after PCI, the myocardial blood supply of patients with CHD is insufficient, and the oxygen-carrying capacity of the body is reduced, which leads to the decline of cardiopulmonary function and exercise endurance, easily triggers MACEs such as angina pectoris, arrhythmia, heart failure, seriously affecting the physical and mental health and life safety of patients (13). At present, the clinic attaches great importance to the rehabilitation of patients with CHD, and the intervention model with the ultimate goal of improving cardiopulmonary function, improving quality of life and returning to society is gradually applied widely.

ECP is a non-medical, non-invasive physiotherapy method that increases cardiac perfusion by wrapping the patient's buttocks and lower extremities with segmental balloons. During the diastolic phase of the heart, the balloons are sequentially inflated to promote the return of blood from the arteries of the lower extremities to the aorta and then to the arteries at all levels, thereby increasing diastolic pressure, and during the systolic phase of the heart, the balloons are rapidly deflated to allow rapid flow of blood from the aorta to the lower extremities to reduce cardiac afterload (14). The

TABLE 1 | Baseline information of patients (n, %, $\bar{x} \pm s$).

Group	Number of cases	Age (years)		Gender		Smoking history	Alcohol history
		<60	≥60	Male	Female		
Control group	62	28 (45.16%)	34 (54.84%)	31 (50.00%)	31 (50.00%)	36 (58.06%)	35 (56.45%)
Observation group	62	30 (48.39%)	32 (51.61%)	27 (43.55%)	35 (56.45%)	37 (59.68%)	39 (62.90%)
χ^2 value		0.130		0.518		0.033	0.536
P-value		0.719		0.472		0.855	i0.464

Group	Number of cases	Combined diseases			Postoperative course of PCI (d)
		Diabetes	Hypertension	Hyperlipidemia	
Control group	62	19 (30.64%)	14 (22.58%)	13 (20.96%)	40.23 ± 8.13
Observation group	62	17 (27.42%)	16 (25.81%)	12 (19.35%)	38.85 ± 8.55
χ^2/t value			0.273		0.920
P-value			0.872		0.359

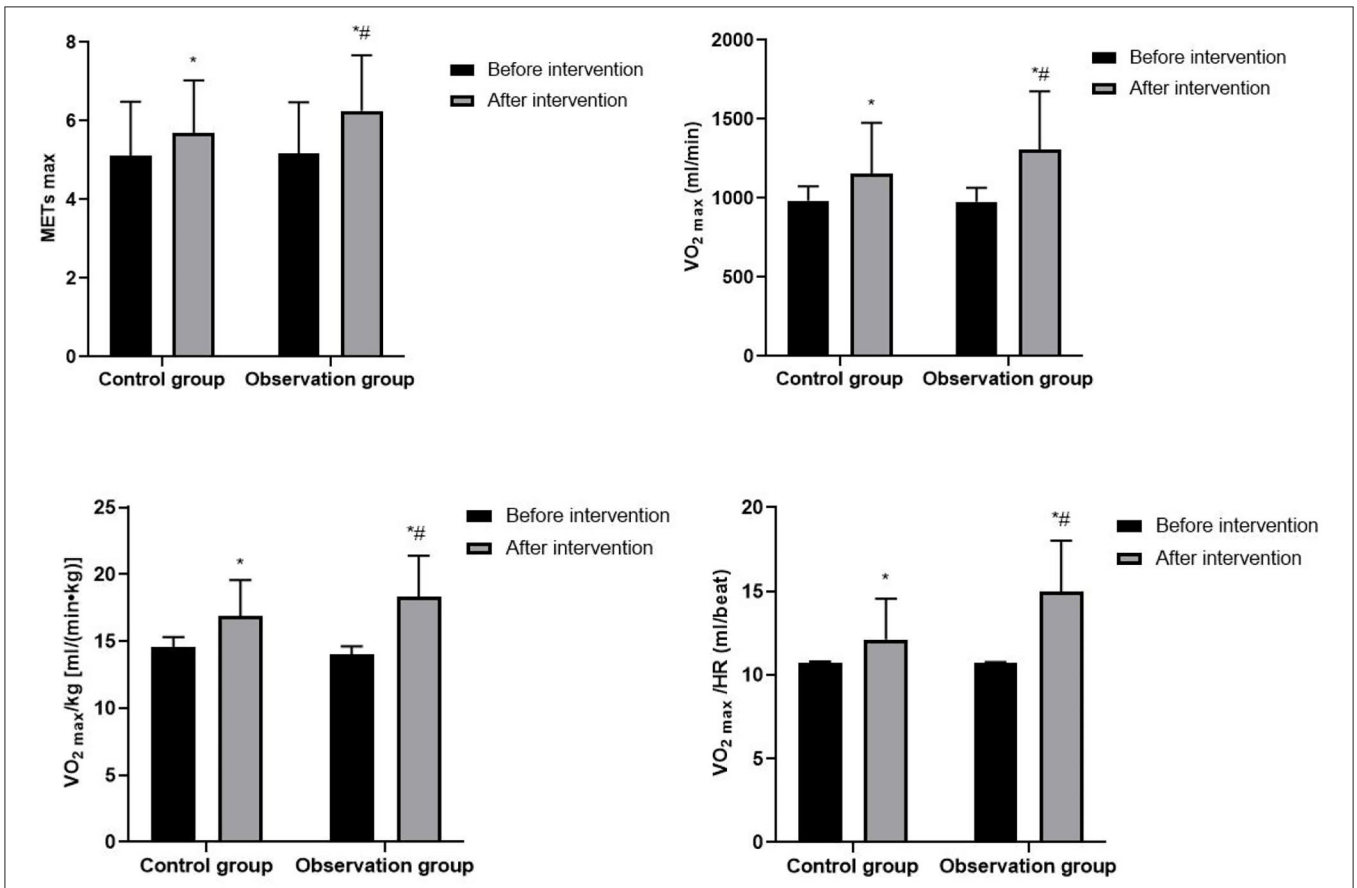


FIGURE 1 | Cardiopulmonary function of patients. Compared with before intervention, $^*P < 0.05$; compared with control group, $^{\#}P < 0.05$.

principles of ECP therapy are mainly: (1) Increase aortic diastolic pressure, increase coronary blood perfusion and improve myocardial blood supply. (2) Reduce peripheral resistance, improve blood flow, and promote the formation of coronary collateral circulation. (3) Increase the shear stress of blood flow, improve the shape and function of vascular endothelial cell, repair damaged vascular endothelium, and inhibit the development of atherosclerosis. (4) Accelerate blood flow, reduce blood viscosity, improve microcirculation while increasing the oxygen uptake capacity of the body. (5) When the balloon is

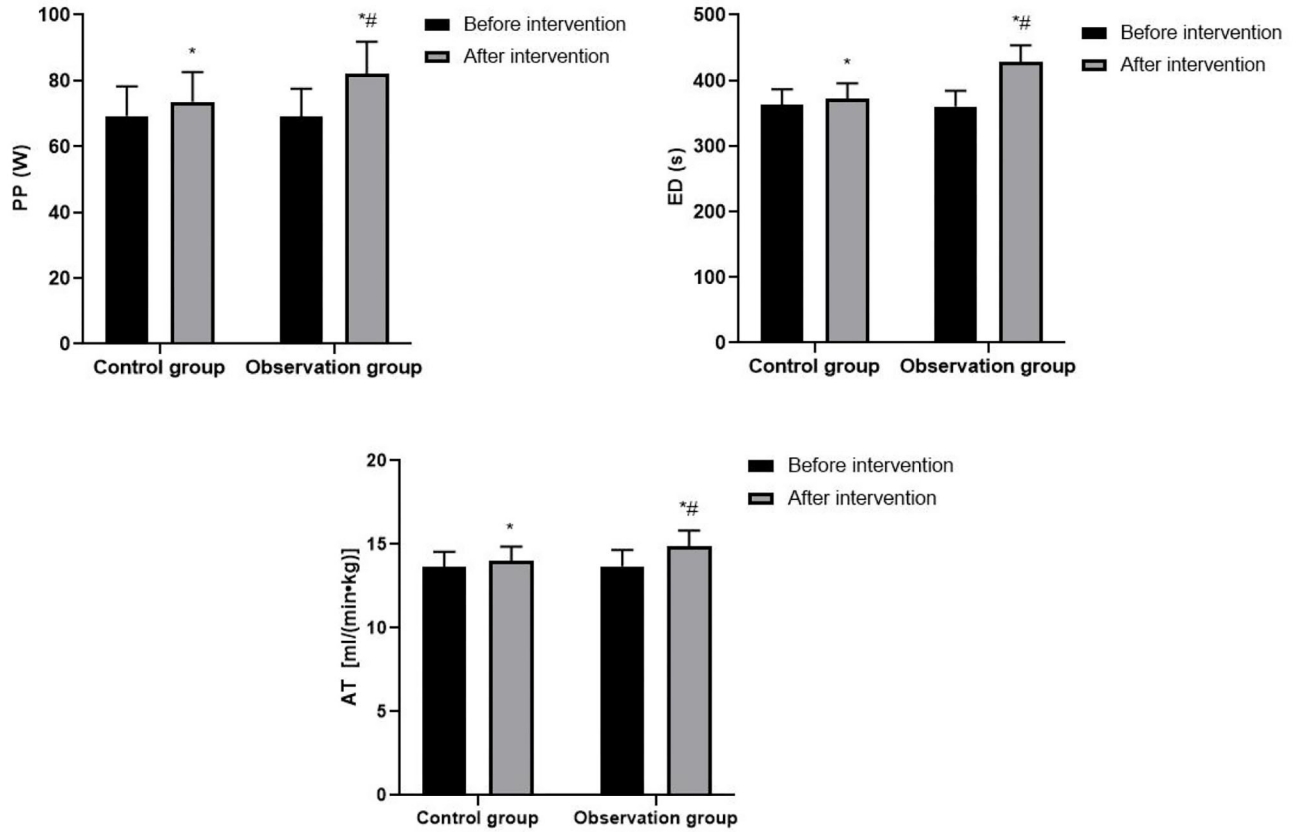


FIGURE 2 | Exercise endurance of patients. Compared with before intervention, $^{*}P<0.05$; compared with control group, $^{\#}P < 0.05$.

TABLE 2 | Incidence of MACE in patients (*n*, %).

Group	Number of cases	Angina pectoris	Arrhythmia	Heart Failure	Total incidence
Control group	62	5 (8.06%)	2 (3.23%)	1 (1.61%)	8 (12.90%)
Observation group	62	1 (1.61%)	1 (1.61%)	0 (0.00%)	2 (3.23%)
χ^2 value					3.916
P-value					0.048

constantly squeezing the lower limbs, the body's nervous system generates micro-electrical stimulation, which is conducive to relieving muscle tension and relaxing the cerebral cortex (15–17). ECP is a non-invasive, safe, effective, and inexpensive treatment device that can reduce the discomfort of patients with CHD, control the progression of the disease, and change the exercise endurance of the patient, thereby facilitating adaptation to more intense or longer exercise (18). Physical inactivity is one of the risk factors for CHD, and long-term physical inactivity may lead to a decrease in cardiorespiratory fitness, which in turn may affect the patient's quality of life. HIAT can positively affect the cardiovascular system of patients with CHD after PCI in many ways: (1) HIAT can promote the formation of cardiac collateral circulation, improve coronary artery blood supply and intrinsic myocardial contractility, increase coronary blood flow and capillary diffusion, and improve the circulation transportation capacity of the coronary artery, thereby reducing cardiac work and improving left ventricular myocardial function. (2) HIAT can promote adaptive changes in the structure, function and regulatory capacity of the cardiovascular system and skeletal muscle system, which can increase the density of skeletal muscle capillaries, increase the number of myocardial capillaries, improve the supply of peripheral blood, increase the oxygen uptake capacity of skeletal muscle, so as to meet the body's demand for oxygen and reducing the load on the heart. (3) Aerobic exercise can increase the shear stress of coronary blood flow, stimulate the production and release of nitric oxide synthase in vascular endothelial cells, improve the vasodilatory capacity of endothelial intact coronary arteries, improve the function of peripheral vascular endothelial cells,

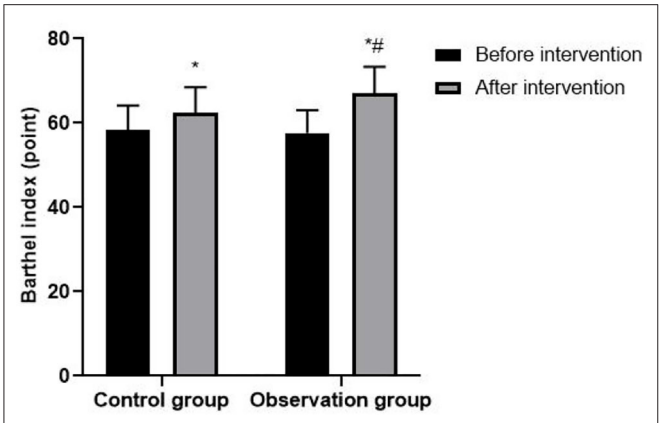


FIGURE 3 | Ability of daily living of patients. Compared with before intervention, $^{*}P < 0.05$; compared with control group, $^{\#}P < 0.05$.

and thus increase myocardial perfusion. (4) HIAT enhances the oxygen utilization capacity and aerobic metabolism of muscle groups, improves mitochondrial function of cardiomyocytes, which in turn increases cardiovascular effects, improves overall patient function, and reduces the incidence of cardiovascular events. (5) HIAT reduces coronary stent lumen loss in patients with CHD after PCI, and this may be closely related to a reduction in the patient's systemic inflammatory response (19–21). Villelabeitia-Jaureguizar have found that compared with moderate-intensity aerobic exercise, although the patients are more laborious during HIAT, the duration of HIAT is short, and interval rest can avoid excessive fatigue and discomfort, which makes the patient's tolerance higher (22). At the same time, HIAT brings stronger exercise stimulation to patients, and the higher the intensity of exercise, the higher the cardiorespiratory fitness of patients with CHD. METs $_{max}$ can reflect the level of cardiac energy metabolism and exercise capacity; $VO_{2\ max}$ indicates the body's maximum aerobic metabolic capacity, cardiac output and cardiac reserve function, and $VO_{2\ max}$ is the gold standard for evaluating cardiopulmonary function; $VO_{2\ max}$/kg corrects the effect of body weight on oxygen uptake and was a predictor of cardiovascular events; $VO_{2\ max}$/HR can reflect the oxygen intake capacity of the heart's stroke volume. PP is the maximum exercise load that the patient can tolerate in the cardiopulmonary exercise test; ED is the exercise time that the patient lasted from the beginning to the end of the cardiopulmonary exercise test evaluation; AT is the critical value of the transition from aerobic metabolism to anaerobic metabolism when the body performs increasing load exercise, which can reflect the body's maximum aerobic exercise capacity. In this study, METs $_{max}$, $VO_{2\ max}$, $VO_{2\ max}$/kg, $VO_{2\ max}$/HR, PP, ED, and AT of patients in the observation group were significantly higher than those in the control group, suggesting that ECP combined with HIAT can improve the cardiopulmonary function and exercise endurance of patients with CHD after PCI.

In addition, we found that patients with CHD after PCI had a lower incidence of MACE and better daily living ability after interventions. The traditional single rehabilitation training model cannot provide sufficient training volume to resist the patient's physical strength loss and cannot achieve the goal of motor learning optimization through sufficient repetitive activities, so the therapeutic effect is limited. In contrast, ECP and HIAT can improve myocardial oxygen supply, enhance the physical performance of patients, and relieve or even reduce the occurrence of angina pectoris and arrhythmias. The combined application of the two methods will eliminate obesity and bad mood and other risk factors of cardiovascular and cerebrovascular diseases, help patients gradually recover their ability to perform activities of daily living and improve the quality of survival (23, 24). It is worth mentioning that patients with contraindications to exercise can also be treated with ECP. Clinicians can give ECP to patients with CHD first, and then start HIAT when the patient's condition is stable and there is no discomfort, which is safe and effective in the field of CHD rehabilitation.

CONCLUSION

In conclusion, ECP combined with HIAT can improve the cardiopulmonary function of patients with CHD after PCI, and improve exercise endurance, reduce the incidence of MACE, improve patients' ability of daily living. This intervention brings a new model for cardiac rehabilitation. In this study, in order to ensure the uniformity of aerobic exercise intervention intensity for patients, we only used one form of exercise to train patients. In addition, when performing cardiopulmonary exercise test, due to insufficient exercise cooperation and subjective exercise effort of patients, this may affect the research results. At the same time, cardiopulmonary exercise test also require relatively high operation requirements for professional technicians. Therefore, this study needs to expand the sample size, prolong the observation time, and choose the exercise form according to the patient's personal interests in the future, so as to further prove the long-term efficacy of ECP combined with HIAT.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the WuHan HanKou Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PH was the director of the entire study. All authors of this study made equal contributions, mainly including the design of the study, the inclusion of cases, the detection of results, the statistics of the data, and the writing of the paper.

REFERENCES

1. Chiarito M, Mehilli J. Left main coronary artery disease: when and how to perform PCI?. *Minerva Cardioangiol*. (2020) 68:405–14. doi: 10.23736/S0026-4725.20.05198-1
2. Al-Lamee RK, Nowbar AN, Francis DP. Percutaneous coronary intervention for stable coronary artery disease. *Heart*. (2019) 105:11–9. doi: 10.1136/heartjnl-2017-312755
3. Burzotta F, Lassen JF, Banning AP, Lefèvre T, Hildick-Smith D, Chieffo A, et al. Percutaneous coronary intervention in left main coronary artery disease: the 13th consensus document from the European bifurcation club. *Euro Interven*. (2018) 14:112–20. doi: 10.4244/EIJ-D-18-00357
4. Sattar S, Hussain S, Aijaz S, Khan G, Akhter Z, Malik R, et al. Major adverse cardiovascular events in patients undergoing percutaneous coronary intervention or coronary artery bypass graft with underlying chronic kidney disease. *J Pak Med Assoc*. (2020) 70:1901–7. doi: 10.5455/JPMA.22790
5. Berger A, Simpson A, Leeper NJ, Murphy B, Nordstrom B, Ting W, et al. Real-world predictors of major adverse cardiovascular events and major adverse limb events among patients with chronic coronary artery disease and/or peripheral arterial disease. *Adv Ther*. (2020) 37:240–52. doi: 10.1007/s12325-019-01132-z
6. Salzwedel A, Jensen K, Rauch B, Doherty P, Metzendorf MI, Hackbusch M, et al. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: update of the cardiac rehabilitation outcome study (CROS-II). *Eur J Prev Cardiol*. (2020) 27:1756–74. doi: 10.1177/2047487320905719
7. Raza A, Steinberg K, Tartaglia J, Frishman WH, Gupta T. enhanced external counterpulsation therapy: past, present, and future. *Cardiol Rev*. (2017) 25:59–67. doi: 10.1097/CRD.0000000000000122
8. Li B, Chen S, Qi X, Wang W, Mao B, Du J, et al. The numerical study on specialized treatment strategies of enhanced external counterpulsation for cardiovascular and cerebrovascular disease. *Med Biol Eng Comput*. (2018) 56:1959–71. doi: 10.1007/s11517-018-1834-z
9. Ellingsen Ø, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, et al. High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circ*. (2017) 135:839–49. doi: 10.1161/CIRCULATIONAHA.116.022924
10. Gomes Neto M, Durães AR, Conceição LSR, Saquetto MB, Ellingsen Ø, Carvalho VO. High intensity interval training vs. moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: a systematic review and meta-analysis. *Int J Cardiol*. (2018) 261:134–41. doi: 10.1016/j.ijcard.2018.02.076
11. Joseph J, Velasco A, Hage FG, Reyes E. Guidelines in review: comparison of ESC and ACC/AHA guidelines for the diagnosis and management of patients with stable coronary artery disease. *J Nucl Cardiol*. (2018) 25:509–15. doi: 10.1007/s12350-017-1055-0
12. Fortier JH, Ferrari G, Glineur D, Gaudino M, Shaw RE, Ruel M, et al. Implications of coronary artery bypass grafting and percutaneous coronary intervention on disease progression and the resulting changes to the physiology and pathology of the native coronary arteries. *Eur J Cardiothorac Surg*. (2018) 54:809–16. doi: 10.1093/ejcts/ezy171
13. Ma L, Deng L, Yu H. The effects of a comprehensive rehabilitation and intensive education program on anxiety, depression, quality of life, and major adverse cardiac and cerebrovascular events in unprotected left main coronary artery disease patients who underwent coronary artery bypass grafting. *Ir J Med Sci*. (2020) 189:477–88. doi: 10.1007/s11845-019-02129-x
14. Kulchitskaya DB, Shovkun TV, Yarnykh EV, Konchugova TV, Knyazeva TA, Gushchina NV, et al. Impact of external counterpulsation on microcirculation in patients with coronary heart disease complicated by chronic heart failure after surgical and endovascular myocardial revascularization. *Vopr Kurortol Fizioter Lech Fiz Kult*. (2019) 96:5–10. doi: 10.17116/kurort2019960515
15. Tan S, Hadinoto K, Ebrahimi A, Langrish T. Fabrication of novel casein gel with controlled release property via acidification, spray drying and tableting approach. *Colloids Surf B Biointer*. (2019) 177:329–37. doi: 10.1016/j.colsurfb.2019.02.019
16. Zhou ZF, Wang DJ, Li XM, Zhang CL, Wu CY. Effects of enhanced external counterpulsation on exercise capacity and quality of life in patients with chronic heart failure: a meta-analysis. *Med*. (2021) 100:e26536. doi: 10.1097/MD.0000000000026536
17. Sardari A, Hosseini SK, Bozorgi A, Lotfi-Tokaldany M, Sadeghian H, Nejatian M. Effects of enhanced external counterpulsation on heart rate recovery in patients with coronary artery disease. *J Tehran Heart Cent*. (2018) 13:13–7.
18. Xu L, Chen X, Cui M, Ren C, Yu H, Gao W, et al. The improvement of the shear stress and oscillatory shear index of coronary arteries during enhanced external counterpulsation in patients with coronary heart disease. *PLoS ONE*. (2020) 15:e0230144. doi: 10.1371/journal.pone.0230144
19. Villelabeitia-Jaureguizar K, Vicente-Campos D, Senen AB, Jiménez VH, Garrido-Lestache MEB, Chicharro JL. Effects of high-intensity interval vs. continuous exercise training on post-exercise heart rate recovery in coronary heart-disease patients. *Int J Cardiol*. (2017) 244:17–23. doi: 10.1016/j.ijcard.2017.06.067
20. Quindry JC, Franklin BA, Chapman M, Humphrey R, Mathis S. Benefits and risks of high-intensity interval training in patients with coronary artery disease. *Am J Cardiol*. (2019) 123:1370–7. doi: 10.1016/j.amjcard.2019.01.008
21. Hollings M, Mavros Y, Freeston J, Fiatarone Singh M. The effect of progressive resistance training on aerobic fitness and strength in adults with coronary heart disease: a systematic review and meta-analysis of randomised controlled trials. *Eur J Prev Cardiol*. (2017) 24:1242–59. doi: 10.1177/2047487317713329
22. Villelabeitia-Jaureguizar K, Vicente-Campos D, Berenguel Senen A, Hernández Jiménez V, Ruiz Bautista L, Barrios Garrido-Lestache ME, et al. Mechanical efficiency of high vs. moderate intensity aerobic exercise in coronary heart disease patients: a randomized clinical trial. *Cardiol J*. (2019) 26:130–7. doi: 10.5603/CJ.a2018.0052
23. Li B, Wang W, Mao B, Yang H, Niu H, Du J, et al. Long-term hemodynamic mechanism of enhanced external counterpulsation in the treatment of coronary heart disease: a geometric multiscale simulation. *Med Biol Eng Comput*. (2019) 57:2417–33. doi: 10.1007/s11517-019-02028-4
24. Dun Y, Smith JR, Liu S, Olson TP. High-Intensity Interval Training in Cardiac Rehabilitation. *Clin Geriatr Med*. (2019) 35:469–87. doi: 10.1016/j.cger.2019.07.011

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhao, Liu, Wen, Qi and Huang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 04 March 2022
doi: 10.3389/fsurg.2022.841645

Rectal Signet Ring Cell Carcinoma: Post-Chemoradiotherapy Evaluation by MRI and Corresponding to Pathology

Yin Zhou[1†], *Qingshu Li*[2†] *and Yun Mao*[1*]

[1] *Department of Radiology, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China,* [2] *Department of Pathology, School of Basic Medicine, Chongqing Medical University, Chongqing, China*

Background: Signet ring cell carcinoma (SRCC) is recognized as an uncommon subtype of colorectal carcinoma (CRC). It showed characteristic magnetic resonance imaging (MRI) manifestations. However, the MRI features post-chemoradiotherapy (CRT) were not reported, and it is unknown whether the current tumor regression grade (TRG) system by MRI (mrTRG) is applicable to SRCC.

Purpose: To summarize the image features of rectal SRCC on post-CRT images corresponding to the pathology, and to determine the predicting value of mrTRG compared with TRG by pathology (pTRG).

Methods: We retrospectively enrolled seven patients (male: female = 3:4; mean age, 45.1 years) with biopsy-pathology proved SRCC, who underwent pre- and post-CRT MR imaging followed by surgery. An experienced gastrointestinal radiologist accessed mrTRG using a 5-point grading system by mandard standard on T2 weighted image (T2WI) and then added diffusion weighted image (DWI) in a 1-month interval. Additionally, MRI features were recorded on pre- and post-CRT images as follows: pattern (target sign) and main signal intensity of T2WI, characterized manifestation of DWI, and mean Apparent Diffusion Coefficient (ADC)values. The mrTRG and all MR image features were compared to the post-operative pathology.

Results: At post-CRT histology, five patients got a good response (TRG 1, n = 4; TRG 2, n = 1), one patient got a partial response, and one patient got a poor response. The accuracy of MRI predicted the pathology response by mandard standard was 14% and increased to 71.4% when added DWI. After CRT, different degrees of homogeneous high SI without enhancement representing acellular mucin were observed in all patients, and the thick-ring high SI turned into a thin-target sign in most good responders. Moreover, the tumor volume decreased or slightly increased in good responders, while it markedly increased in the partial and poor responder by 57% and 73.8%, respectively.

Conclusion: Homogeneous high SI on T2WI and thin target sigh on DWI were the main MRI changes of RSRCC, which was corresponding to the mucinous regression and represents for good response post-CRT. The mrTRG and tumor volume was not a reliable indicator to the pathology response. We considered that DWI should be added to T2WI to evaluate RSRCC response to CRT.

Keywords: signet ring cell carcinoma, colorectal carcinoma, magnetic resonance imaging, chemoradiotherapy, pathology

OPEN ACCESS

Edited by:
Weiguo Li,
Harbin Institute of Technology, China

Reviewed by:
Xinjiang Cui,
Affiliated Hospital of Weifang Medical University, China
Pinhua Pan,
Central South University, China

***Correspondence:**
Yun Mao
mao1540547925@126.com

[†] *These authors have contributed equally to this work*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *22 December 2021*
Accepted: *17 January 2022*
Published: *04 March 2022*

Citation:
Zhou Y, Li Q and Mao Y (2022) Rectal Signet Ring Cell Carcinoma: Post-Chemoradiotherapy Evaluation by MRI and Corresponding to Pathology. Front. Surg. 9:841645. doi: 10.3389/fsurg.2022.841645

INTRODUCTION

Signet ring cell carcinoma (SRCC) is defined as a carcinoma composed of >50% of signet ring cells (SRCs) by the World Health Organization (WHO) (1). In comparison, cases with ≤50% presence of SRCs are noted to be carcinomas with SRCs. SRCC shows more aggressive behavior and a worse clinical outcome than adenocarcinoma (AC) and mucinous adenocarcinoma (MAC) (2–4), even than MAC with SRCs (5, 6). Rectal SRCC (RSRCC) patients presented more frequently with Stage III or IV disease than other subtypes. Pre-operative chemoradiotherapy (CRT) followed by total mesorectal excision (TME) has become a standard treatment for patients with locally advanced rectal cancer. The patients with stage III RSRCC treated with pre-operative radiotherapy followed by surgery had better cause-special survival than that with surgery alone (7). In addition, Bratland et al. (8) reported that half of six patients with RSRCC turned into complete pathological response (pCR), and half had no response after radiotherapy. So the precise evaluation of the tumor regression post-CRT is required to determine further therapeutic strategies.

MRI is routinely applied for assessing the pre-operative stage and treatment response to pre-operative CRT. However, the previous studies almost focused on the AC or MAC (9–11). AC manifested as an isointense solid mass with diffusion restriction. The tumor regression was recognized as tumor mainly replacing by fibrosis, which showed hypointensity on T2WI, with markedly volume shrinkage and without diffusion restriction (12, 13). MAC manifested as a high signal intensity mass with multiple isointense tumor foci, corresponding to large extracellular mucin lined by columns of malignant cells, cords, and vessels. The tumor regression of MAC depended on the tumor foci pattern, which showed similar changes with AC. Disappearance of the tumor foci manifests homogeneous high SI without enhancement, which indicated good response. And only minimal volume shrinkage was observed due to the constancy existing of the extracellular mucin. However, few case reports depicted SRCC as concentric wall thickening with target sign and low SI on T2WI due to extensive scatter malignant cells, with intracellular mucin separating the anatomical layers of the rectal wall (14). It shows a big difference in histopathology and imaging features from AC and MAC. Its MR manifestations of post-CRT had not been reported, so it is unknown whether the current mrTRG system is applicable to SRCC.

In this retrospective study, we attempted to reveal the MR characteristics changes of RSRCC post-CRT, corresponding to post-operative pathology, and obtain a preliminary evaluation of association MR features to pathology tumor regression.

MATERIALS AND METHODS

Patients and Clinical Information

This retrospective study was approved by ethics committee of the first affiliated hospital of Chongqing Medical University. Thirty-one consecutive patients with pathology proved rectal carcinoma with an SRC component were identified from the electronic clinical database in our hospital between January 2012 and March 2021. The patients were included by the following criteria: (a) patients who had locally advanced rectal cancer and underwent neoadjuvant CRT followed by surgery within 6 weeks; (b) patients who underwent pelvic MR scanning pre- and post-CRT. Exclusion criteria: (a) patients with secondary rectal SRCC ($n = 1$, from gastric SRCC); (b) patients with primary rectal cancer did not undergo surgery in our hospital ($n = 9$) or neoadjuvant CRT ($n = 9$); (c) the pre or post-CRT MRI was unavailable ($n = 3$); (d) the biopsy pathology patients did not meet the SRCC criteria by WHO ($n = 2$). Finally, seven patients were enrolled.

The clinical data of the enrolled patients were also recorded, including age, sex, colonoscopy and biopsy result, and CRT strategies.

MR Imaging Method

MRI was performed with a 3.0-T MR imager (Signa HDxT, GE) and a pelvic phased-array coil. The same protocol was used in every time MR examination in all patients, which included the following sequences at least: an oblique axial, coronal, and sagittal T2 weighted fast spin-echo sequence without fat suppression (TR, 2,320–3,120 ms; TE, 85–110 ms; flip angle, 90°; matrix, 512 × 512; NEX, 2; slice thickness, 3 mm); an oblique axial diffusion-weighted sequence with fat suppression (TR, 4,925–6,200 ms; TE, 64–71 ms; flip angle, 90°; matrix, 256 × 256; NEX, 4–5; slice thickness, 4 mm; $b = 0$, 600); an axial, coronal, and sagittal LAVA sequence after contrast was injected (TR, 4.27–4.66 ms; TE, 2.08–2.22 ms; flip angle, 15°; matrix, 512 × 512; slice thickness, 4 mm). The Gadopentetate Dimeglumine (Magnevist; Bayer Schering Pharma AG, Germany) was injected into the elbow vein as a contrast agent.

Imaging Analysis

A gastrointestinal radiologist with 12 years of experience in abdominal MR imaging (Mao Yun, an associate professor), who was aware of biopsy results and treatment protocol but blind to the post-operative histopathology and other clinical information analyzed all images independently, firstly for T2WI of pre and post-CRT, 1 month later for T2WI with DWI. MR image features were recorded on pre and post-CRT images as follows: pattern (target sign or non-target sign) and main signal intensity (low, intermediate high, or high) of T2WI, characterized manifestation of DWI, mean ADC value, MR T stage, MRF involvement, and EMVI. Patterns of T2WI were evaluated on oblique axial images. Low SI was defined as lower or similar to the skeletal muscle, intermediate high SI as slightly higher than skeletal muscle, and high SI as markedly higher than skeletal muscle. On DWI, the thin-target sign was defined as a thick concentric mural characterized by high SI of thin inner and outer layers (<5 mm) and low SI of the middle layer, which was assumed non-tumor mural. A thick ring sign was noted in if the middle layer showed high SI or if the high SI layer thickened above 5 mm, which was hypothesized mural with tumor infiltrated (**Figure 1**). The ROI on the ADC map was drawn along the contour of the tumor area on each slice on the workstation, and the mean ADC value was finally recorded. The change of ADC value (δ ADC) was calculated as $_{post}$ADC

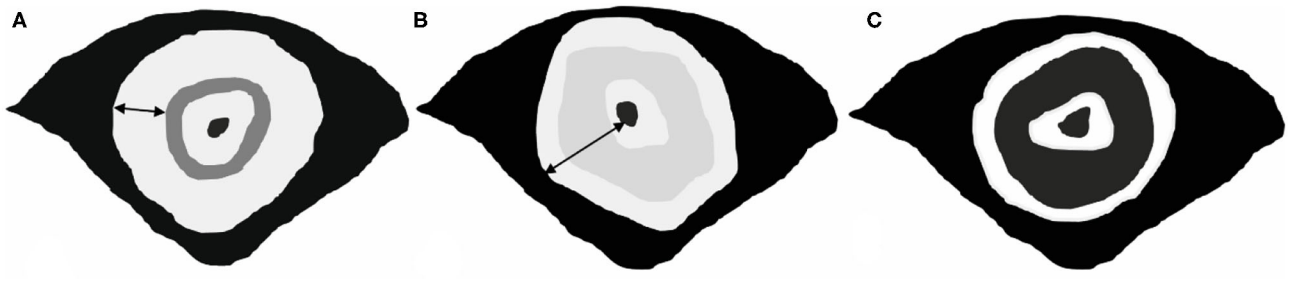


FIGURE 1 | Patterns of SRCC on DWI. **(A,B)** Definition of thick-ring signs. The wide of the high-SI ring is above 5 mm, which represents tumor tissue infiltrated all mural layers. **(C)** Definition of a thin-target sign. The thick concentric mural with high SI of thin inner and outer layers (<5 mm) and low SI of the middle layer, which was assumed non-tumor mural.

value-$_{post}$ADC value. The T stage accessed at MR imaging based on the depth of tumor or mucin involving: T2, confined to muscularis propria; T3, extended to peripheral adipose tissue; T4, involved the peritoneal reflection (T4a)/extended to adjacent organs (T4b). Negative MRF was defined as the interval between the outermost tumor tissue and MRF above 1 mm. Otherwise, it recorded positive MRF. The EMVI was defined as either intermediate or high SI was observed within vessels outside the tumor, or the contours of these vessels appeared irregular. ymrTRG was evaluated post-CRT using the 5-point-grade system on T2WI (mandard standard): Grade 1, no evidence of treated tumor; Grade 2, dense hypointense fibrosis or acellular mucin with minimal residual tumor; Grade 3, >50% fibrosis or mucin with an intermediate tumor signal representing residual tumor (fibrosis and mucin > tumor); Grade 4, minimal fibrosis or mucinous degeneration, but mostly tumor (15); and Grade 5, the tumor that has a similar appearance as the baseline. We assumed the low, intermediate high, and high T2-weighted SI representing fibrosis, tumor, and mucin, respectively, while high SI without enhancement indicated the acellular mucin. After 1 month, DWI patterns were added to access the ymrTRG compared to pre-CRT images; the area of diffused high SI through the mucosa to the out layer was assumed as residue tumor, and the stratified pattern with low SI in the middle layer was defined as tumor regression completely.

Tumor volumes were computationally calculated by adding the ROI of consecutive images, and the ROI of the tumor area was drawn along the border of the tumor on each slice of oblique axial T2WI. The reductive ratio was calculated as [(volume$_{pre}$-volume$_{post}$)/volume$_{pre}$] × 100%.

Histopathology and Evaluation of Tumor Regression

HE stain was applied for all the pathology specimens, and the samples contained all tumor and regression tissue we suspected. A pathologist with 10 years of experience (Qingshu Li, an associate professor) in gastrointestinal pathology who was aware of the biopsy results but blind to the ymrMR result evaluated the tumor regression grade by mandard standard (16). The distribution of tumor or regression tissue in the mural, resection margin, LN involvement, extramural venous invasion, and invasion to other organs was also evaluated. TRG 1 and 2 scores were considered good responses, the TRG 3 score was a partial response, and TRG 4 and 5 scores were poor responses.

RESULTS

Patients and Clinical and Histological Information

All enrolled seven patients included three men and four women (median age, 45.1 years; age range, 37–63 years). The percentage of SRC among the tumor of biopsy specimens was all above 50% (87%, 55–100%). They all accepted pelvic radiotherapy and synchronal chemotherapy due to locally advanced rectal cancer and positive CRM evaluated by MRI. A total dose of 50–56 Gy was administered to the pelvis in 25–28 daily fractions during 5 weeks (2 Gy/day, 5 days/week). Chemotherapy was applied with XELOX ($n = 6$) or FOFIRI ($n = 1$) regimen for 2–5 cycles. The mean interval between completed CRT and post-MRI was 4–6 weeks (34.5 ± 5.4 days). The interval between post-MRI and surgery was 11.7 ± 13.2 days. Surgical procedures included Dixon ($n = 3$), Miles ($n = 3$), and TME with partial bladder resection and lateral lymph node resection ($n = 1$), based on the post-CRT MRI evaluation of a tumor site and extension.

At post-CRT histology, most tumors of the rectal mural met complete pathological response ($n = 4$, TRG 1), and one patient showed few residue tumors (TRG 2). They were considered good responders. The poor and partial responders with positive MRF were noted in one case, respectively. Mucinous regression occurred in all tumors, and numerous inflammatory cells, especially lymphocytes and some collagen fiber, coexisted in the submucosa or outer membrane of only two patients. Fibrous tissue containing extensive scatter SRCs with little mucin was observed in the poor responder with low SI of T2WI. Three (43%) of seven patients did not show inflammatory and desmoplastic reactions. Five (71.4%) of seven cases showed a concentric thickening mural with its layers widened by the infiltrated tumor cells or regressed tissue without losing the rough contour. The submucosa and muscularis proporia were mainly

involved. The circular muscle (inner muscularis) predominately widened, followed by longitudinal muscle (outer muscularis), which resulted in the muscle bundles detached and fence-like form, while a lot of mass-like mucin pool in pathology was observed in the two patients showed MAC-like form on MRI.

Tumor Characteristics Pre- and Post-CRT on MRI

All cases manifested circular thickened rectal mural, and the mean volume before CRT was 56.8 ± 30.6 cm^3. After CRT, tumor volume decreased or slightly increased in good responders, while it markedly increased in the partial responder and the poor responder by 57 and 73.8%, respectively. The tumor shrank most in the patients with a much poorly differentiated adenoma component.

The majority of cases presented the target sign with multiple discontinuous rings on T2WI (five of seven), but different SI was observed among the cases (high SI, $n = 2$; moderate SI, $n = 2$; low SI, $n = 1$) pre CRT; they showed diffused or partial thick-ring-high SI on DWI. However, the other two patients mimicked mucinous adenocarcinoma without a target sign on T2WI and scattered-high SI on DWI. The mean pre-ADC value of all tumors was $1.37 \pm 0.18 \times 10^{-3}$ mm^2/s. After CRT, the targetoid patterns of tumor on T2WI did not change, but different levels of the homogeneous high-SI area without enhancement, which represented a mucin pool, (**Figure 2**) was observed in all the patients. The low T2-SI of the poor responder turned into intermediate-high tumor SI. On post-CRT DWI, almost all good responders (4/5) turned into a thin target sign, and the ADC value increased, while one good responder and the partial/poor responder showed almost the same, comparing to pre CRT (**Figure 3**), and the ADC value changed slightly. The δADC value of good responders ($0.346 \pm 0.201 \times 10^{-3}$ mm^2/s) was higher than partial/poor responders ($-0.100 \pm 0.028 \times 10^{-3}$ mm^2/s). The pre- and post-CRT MRI features and pathology changes of all cases are shown in **Table 1**.

All cases were considered locally advanced tumors on pre-CRT MR images (T3a, $n = 2$; T3c, $n = 1$; T3, $n = 1$; T4a, $n = 3$); most of them were with regional lymph node metastasis ($n = 5$) and MRF involvement ($n = 5$), while a few cases with EMVI involvement ($n = 3$). However, the post-CRT T-stage, EMVI, and MRF involvement of all the patients post-CRT were classified at the same level as the pre CRT on MR images.

Comparison of MR Evaluation and Pathology TRG

MRI by a mandard standard only correctly evaluated for one good responder of pTRG 2 (accuracy, 14%), overestimated the tumor residue for all the patients of pCR, and underestimated the partial and poor responders. The accuracy of DWI was 71.4% (three good responders, one partial responder, and one poor responder), but DWI overestimated tumor residue for two good responders, shown in **Table 2**.

DISCUSSION

The RSRCC, also called linitis plastica, is due to diffuse infiltrating of SRC and numerous desmoplastic reactions, especially in the gastric. However, two histology patterns of infiltration in rectal or colonal SRCC were described by WHO (1): (a) signet ring cells floating in copious pools of extracellular mucin; and (b) signet ring cells with a diffuse pattern of infiltration with minimal extracellular mucin, similar to diffuse-type, poorly cohesive carcinomas encountered in the stomach. In previous studies (14), circumferential thickening of the rectal mural with a concentric ring pattern (a target sign) with low SI on T2WI was considered a characteristic of rectal SRCC (corresponds to WHO Type b). In this study, classical targeted circumferential thickening of the rectal mural was noted in 71.4% (five of seven) patients. Slightly high SI with a thick-ring sign on DWI was also a characteristic sign of these SRCCs, and it corresponded to the diffuse distribution of SRCs in the entire mural. Multiple disconnected rings of low SI showed in the thickened mural either on T2WI or on enhanced phases were also the features, which correspond to separated mural layers and detached muscle bundles by infiltrated tumor tissue in histology, especially circular muscle. Besides, 28.1% (two of seven) patients mimicked mucinous adenocarcinoma without a target sign in our cohort, which was reported in only one case by the previous studies (17). Additionally, diffuse high SI and intermediate-high SI were more frequently showing rather than low SI on T2WI.

Hartman et al. (18) identified that mucin-poor signet ring cell carcinoma has a dismal prognosis with an aggressive clinical course, comparing to the mucin-rich SRCC in rectum. Similarly, in our study, the patient with low T2 SI, which represented mucin-poor tumor, showed worse CRT response than others. Three of four patients with high SI got a good response. It inferred that pre-treatment MRI might have the capacity to predict the CRT response and prognosis of SRCC, and it needs further study to confirm.

Mucinous degeneration was the dominant response to the CRT of SRCC, and it can be observed in all patients, especially the tumor with high SI on pre-CRT T2WI. It manifested as homogeneous high SI without enhancement, similarly as the form of MAC degeneration. However, the proportion of poorly differentiated adenocarcinoma components took place by extensive fibrosis, resulted in the moderated SI on pre-CRT T2WI, decreased markedly. At post-CRT DWI, most patients with good response showed thin-target signs due to the diffused tumor cell disappearance and cellular density decrease. Additionally, the mucin maintained made the mural remaining thickened, and even pCR was presented. Moreover, the ADC value of good responders increased more than partial/poor responders.

Tumor volume change is an important indicator of tumor treatment response. Our findings indicated that a significant increase in volume might indicate that the tumor is not responding well. The partial and poor responders showed more increase in tumor volume than the good responders, although tumor volume of the good responders did not show

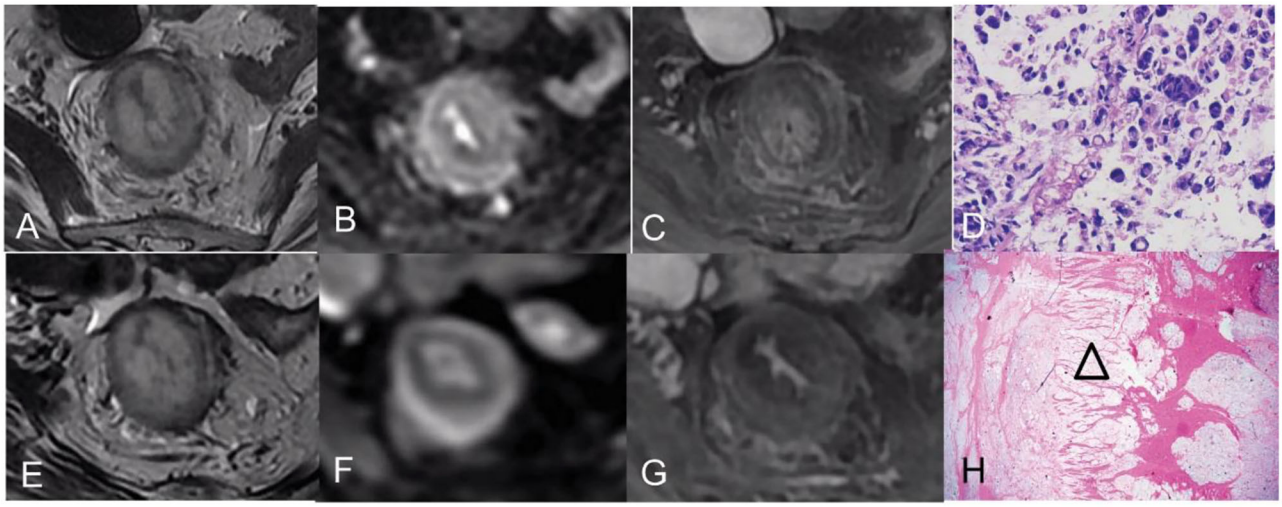


FIGURE 2 | Pre- and post-CRT rectal MR images and pathology images of a 46-year-old woman [good responder (1) with RSRCC]. **(A–C)** axial T2WI, DWI, and contrast-enhanced T1WI pre CRT, the rectal mural showed a target sign with high SI on T2WI **(A)**, a thick ring sign with slightly high SI on DWI **(B)**, and persistent enhancement of the entire mural layers **(C)**. **(D)** The biopsy showed 100% of SRCs (Hematoxylin and eosin staining, × 400). **(E–G)** Axial T2WI, DWI, and delayed contrast-enhanced T1WI post-CRT, the lesion showed similarly to that of pre CRT on T2WI **(E)**, which resulted in mrTRG 5 in the evaluation of CRT response. However, the thin target sign on DWI indicated complete response **(F)**, and the decreased enhancement of the mural also indicated a good response **(G)**. **(H)** An extensive mucin pool infiltrated the mural layers with detached muscular bands (an empty triangle) (Hematoxylin and eosin staining, × 20).

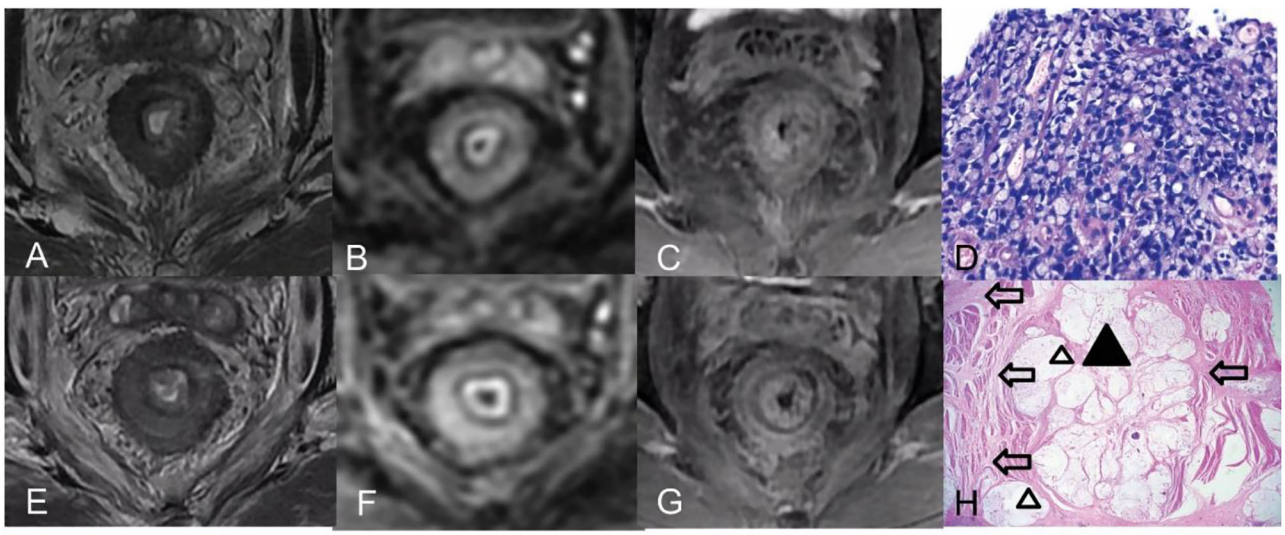


FIGURE 3 | Pre- and post-CRT rectal MR images and pathology images of a 42-year-old man (a poor responder) with RSRCC. **(A–C)** Axial T2WI, DWI, and contrast-enhanced T1WI pre CRT, the rectal mural showed a target sign with low SI on T2WI **(A)**, a thick ring sign with high SI on DWI **(B)**, and persistent enhancement of the entire mural layers **(C)**. **(D)** of the biopsy showed 100% of SRCs (Hematoxylin and eosin staining, × 400). **(E–G)** Axial T2WI, DWI, and delayed contrast-enhanced T1WI post-CRT, the lesion showed a target sign with moderate SI on T2WI with a little mucin pool on T2WI **(E)**, which resulted in mrTRG 4 in the evaluation of CRT response. **(F,G)** DWI and an enhancement pattern showed similar to the pre CRT, which indicated poor response. **(H)** Extensive SRCs (a black triangle) infiltrated the mural layers with detached muscular bands with fibrosis (empty arrows) and mucinous degeneration (empty triangles) (Hematoxylin and eosin staining, × 20).

a marked reduction. We found that SRC was mostly mucus degeneration without markedly volume reduction. In contrast, the volume reduction of the adenocarcinoma component post-CRT was more apparent due to the tumor cell disappearance and fiber shrinkage. The study of Park et al. about the CRT of MAC had a similar result (11). Meanwhile, a large number of inflammatory cell infiltration in the submucosa of the lesion may attribute a slight increase of volume. However, we cannot evaluate the accuracy degeneration of SRCCs based on the volume change.

TABLE 1 | The main clinical, image features, and pathology information pre and post-CRT.

		Good-responder1	Good-responder2	Good-responder3	Good-responder4	Good-responder5	Partial-responder	Poor-responder
Age/sex		46/F	46/M	41/F	41/M	63/F	37/F	42/M
Pre-CRT pathology and MRI	Biopsy pathology (SRCs %)	100	100	60, with poorly differentiated AC	95, with poorly differentiated AC	55, with MAC	100	100
	T2-pattern/SI	Target sign/high	Target sign/high	Target sign/intermediate high	Target sign/intermediate high	Non-target sign/high	Non-target sign/high	Target sign/low
	Enhanced pattern	Diffused enhancement	Diffused enhancement	Diffused enhancement	Diffused enhancement	Diffused enhancement	Diffused enhancement	Diffused enhancement
	DWI pattern	Diffuse/Thick ring sign/slightly high	Diffuse /Thick ring sign/slightly high	Partial/thick ring sign/high	Partial/thick ring sign/slightly high	Scatter high	Scatter high	Thick ring sign/ high
Post-CRT MRI	T2-SI	No change	Extensive acellular mucin pool	Partial fibrosis and acellular mucin pool	Partial acellular mucin pool	Partial acellular mucin pool	Partial acellular mucin pool and fibrosis	Focal acellular mucin pool
	Enhanced pattern	Markedly decrease	Markedly decrease	Partial decrease	Partial decrease	Markedly decrease	Partial decrease	No change
	DWI pattern	Thin targetoid	Thin targetoid	thin targetoid with little scatter high	Partial/thick ring sign/slightly high	Thin targetoid	Thin targetoid with little scatter high	Thick ring sign/ high
	δVolume (%)	−27%	+6.4%	−66%	+18.3%	−35.6%	+57%	+73.8%
	δADC ($\times 10^{-3}$ mm^2/s)	+0.46	+0.39	+0.43	−0.01	+0.46	−0.03	+0.01
Post-CRT pathology	Main detached layers	Propria muscularis	Submucosa and propria muscularis	Submucosa and propria muscularis	Circular muscle	Circular muscle	Submucosa and propria muscularis	propria muscularis
	Regression tissue	Mucin	Mucin	Little mucin and extensive fibrosis	Mucin and lymphoceles	Mucin, fibrosis, and lymphocytes	Mucin	Mucin and fibrosis

TABLE 2 | Comparision of mrTRG (T2WI or T2WI + DWI) and pTRG.

Patient	pTRG (score)	T2WI (score)	T2WI+DWI (score)
Good-responsder1	1	5	1
Good-responsder2	2	2	1
Good-responsder3	1	4	2
Good-responsder4	1	3	5
Good-responsder5	1	3	1
Partial-responder	3	2	3
Poor-responder	5	4	5

It seems that the TRG by mandard was also not satisfactory to evaluate the RSRCCs. It almost overestimated all tumors with good responses. Because either the stretched or broken muscle bundles or a large number of inflammatory reactions with lymphocyte proliferation and fibrosis were an equal and low signal on T2WI, which mimicked residue tumor floating in the mucin pools, so it was also challenging to evaluate CR. A previous study (11) of rectal mucinous adenocarcinoma mentioned that floating iso-signal tumor components could be distinguished in high-signal mucus lakes, and the regression of tumor components can be assessed separately. Its accuracy is about 40.7%, and this result was better than our result of SRCC. Because comparing to clustered with tumor cells of mucinous adenocarcinoma, SRCs are diffusely distributed, and it is more difficult to distinguish the tumor components from their mimickers mentioned above. However, the mimickers on T2WI did not show high SI on DWI, and it was easier to identify that the thick-ring sign turned into a thin-target sign on DWI in the good responders. Hence, it explains that T2WI with DWI has more accuracy than TRG by mandard in evaluating tumor response. However, a small number of scattered residual tumors have low cell density, which resulted in low/isointense on DWI, so one patient of pTRG Grade 2 tumors was underestimated as CR. Additionally, a good responder of CR on post-CRT pathology was estimated as a lot of residual tumor on both post-CRT T2WI and DWI. We thought the long interval (36 days) between post-CRT MRI and surgery might cause the mismatch of post-CRT MRI to pathology.

MRI staging post-CRT did not decrease in all patients on T2WI because of the inaccuracy of TRG.

Limitations

There are several limitations in our study. Firstly, the cases enrolled were too few, and only one tumor showed classical image features as low SI on T2WI, while most tumors showed high SI. That may result in the bias of the better CRT response than previous pieces of research. Secondly, we did not use OS as the observation endpoint because two of seven patients were lost to follow-up.

CONCLUSION

Circumferential thickening of the rectal mural with a target sign on T2WI and a thick-ring sign on DWI was the characteristic of rectal SRCC. Homogeneous high SI on T2WI and thin target sigh on DWI were the main MRI changes of RSRCC, which was corresponding to the mucinous regression and represented good response post-CRT. The mrTRG and tumor volume was not a reliable indicator to the pathology response. We considered that DWI should be added to T2WI to evaluate RSRCC response to CRT.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YZ and QL: designed the study. YZ and YM: collected the data. QL and YM: analyzed the data. YZ, QL, and YM: prepared the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Bosman F, Carneiro F, Hruban R, Theise ND. *WHO Classification of Tumours of the Digestive System, 4th Edn* (2010).
2. Chew MH, Yeo SA, Ng ZP, Lim KH, Koh PK, Ng KH, et al. Critical analysis of mucin and signet ring cell as prognostic factors in an Asian population of 2,764 sporadic colorectal cancers. *Int J Colorectal Dis.* (2010) 25:1221–9. doi: 10.1007/s00384-010-1033-3
3. Kang H, O'Connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes evaluation of mucinous and signet-ring cell carcinoma of the colon and rectum. *Dis Colon Rectum.* (2005) 48:1161–8. doi: 10.1007/s10350-004-0932-1
4. Zhu L, Ling C, Xu T, Zhang J, Zhang Y, Liu Y, et al. Clinicopathological features and survival of signet-ring cell carcinoma and mucinous adenocarcinoma of right colon, left colon, and rectum. *Pathol Oncol Res.* (2021) 27:1609800. doi: 10.3389/pore.2021.1609800
5. Pozos-Ochoa LI, Lino-Silva LS, Leon-Takahashi AM, Salcedo-Hernandez RA. Prognosis of signet ring cell carcinoma of the colon and rectum and their distinction of mucinous adenocarcinoma with signet ring cells. A comparative study. *Pathol Oncol Res.* (2018) 24:609–16. doi: 10.1007/s12253-017-0283-6
6. Song IH, Hong S-M, Yu E, Yoon YS, Park IJ, Lim S-B, et al. Signet ring cell component predicts aggressive behaviour in colorectal mucinous adenocarcinoma. *Pathology.* (2019) 51:384–91. doi: 10.1016/j.pathol.2019.03.001
7. Ling CR, Wang R, Wang MJ, Ping J, Zhuang W. Prognosis and value of preoperative radiotherapy in locally advanced rectal signet-ring cell carcinoma. *Sci Rep.* (2017) 7:45334. doi: 10.1038/srep45334
8. Bratland A, Vetrhus T, Groholt KK, Ree AH. Preoperative radiotherapy in rectal signet-ring cell carcinoma - magnetic resonance imaging and treatment outcome: report of six cases. *Acta Oncol.* (2010) 49:42–9. doi: 10.3109/02841860903081897
9. Hotker AM, Garcia-Aguilar J, Gollub MJ. Multiparametric MRI of rectal cancer in the assessment of response to therapy: a systematic review. *Dis Colon Rectum.* (2014) 57:790–9. doi: 10.1097/DCR.0000000000000127
10. Kim NK, Baik SH, Min BS, Pyo HR, Choi YJ, Kim H, et al. A comparative study of volumetric analysis, histopathologic downstaging, and tumor regression grade in evaluating tumor response in locally advanced rectal cancer following preoperative chemoradiation. *Int J Radiat Oncol Biol Phys.* (2007) 67:204–10. doi: 10.1016/j.ijrobp.2006.08.020
11. Park SH, Lim JS, Lee J, Kim HY, Koom WS, Hur H, et al. Rectal mucinous adenocarcinoma: MR imaging assessment of response to concurrent chemotherapy and radiation therapy-A hypothesis-generating study. *Radiology.* (2017) 285:124–33. doi: 10.1148/radiol.2017162657
12. Neri E, Guidi E, Pancrazi F, Castagna M, Castelluccio E, Balestri R, et al. MRI tumor volume reduction rate vs tumor regression grade in the pre-operative re-staging of locally advanced rectal cancer after chemo-radiotherapy. *Eur J Radiol.* (2015) 84:2438–43. doi: 10.1016/j.ejrad.2015.08.008
13. Fujii S, Nougaret S, Escal L, Azria D, Assenat E, Rouanet P, et al. MR imaging of locally advanced low rectal cancer: relationships between imaging findings and the pathological tumor regression grade. *J Magn Reson Imaging.* (2015) 42:421–6. doi: 10.1002/jmri.24783
14. Rudralingam V, Dobson MJ, Pitt M, Stewart DJ, Hearn A, Susnerwala S. MR imaging of linitis plastica of the rectum. *AJR Am J Roentgenol.* (2003) 181:428–30. doi: 10.2214/ajr.181.2.1810428
15. Allen SD, Padhani AR, Dzik-Jurasz AS, Glynne-Jones R. Rectal carcinoma: MRI with histologic correlation before and after chemoradiation therapy. *AJR Am J Roentgenol.* (2007) 188:442–51. doi: 10.2214/AJR.05.1967
16. Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer.* (1994) 73:2680–6. doi: 10.1002/1097-0142(19940601)73:11<2680::AID-CNCR2820731105>3.0.CO;2-C
17. Boustani J, Kim S, Lescut N, Lakkis Z, de Billy M, Arbez-Gindre F, et al. Primary linitis plastica of the rectum: focus on magnetic resonance imaging patterns and treatment options. *Am J Case Rep.* (2015) 16:581–5. doi: 10.12659/AJCR.893830
18. Hartman DJ, Nikiforova MN, Chang DT, Chu E, Bahary N, Brand RE, et al. Signet ring cell colorectal carcinoma: a distinct subset

of mucin-poor microsatellite-stable signet ring cell carcinoma associated with dismal prognosis. *Am J Surg Pathol.* (2013) 37:969–77. doi: 10.1097/PAS.0b013e3182851e2b

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhou, Li and Mao. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 07 March 2022
doi: 10.3389/fsurg.2022.857218

Value of CRP, PCT, and NLR in Prediction of Severity and Prognosis of Patients With Bloodstream Infections and Sepsis

*Peipei Liang and Feng Yu**

Department of Emergency Intensive Care Unit, The First Affiliated Hospital of AnHui Medical University, Hefei, China

Objective: To investigate the value of C-reactive protein (CRP), procalcitonin (PCT), and neutrophil to lymphocyte ratio (NLR) in assessing the severity of disease in patients with bloodstream infection and sepsis, and to analyze the relationship between the levels of three inflammatory factors and the prognosis of patients.

Methods: The clinical data of 146 patients with bloodstream infection and sepsis admitted to our intensive care unit (ICU) from October 2016 to May 2020 were retrospectively analyzed. The differences in the levels of inflammatory indicators such as CRP, PCT, and NLR within 24 h in patients with bloodstream infection sepsis with different conditions (critical group, non-critical group) and the correlation between these factors and the condition (acute physiology and chronic health evaluation II, APACHE II score) were analyzed. In addition, the prognosis of all patients within 28 days was counted, and the patients were divided into death and survival groups according to their mortality, and the risk factors affecting their death were analyzed by logistic regression, and the receiver operating characteristic (ROC) curve was used to analyze the value of the relevant indicators in assessing the prognosis of patients.

Results: The levels of NLR, CRP, PCT, total bilirubin (TBIL), glutamic oxaloacetic transaminase (AST), and serum creatinine (Scr) were significantly higher in the critically ill group than in the non-critically ill group, where correlation analysis revealed a positive correlation between CRP, PCT, and NLR and APACHE II scores ($P < 0.05$). Univariate logistic regression analysis revealed that CRP, PCT, NLR, and APACHE II scores were associated with patient prognosis ($P < 0.05$). Multi-factor logistic regression analysis found that PCT, NLR, and APACHE II scores were independent risk factors for patient mortality within 28 days ($P < 0.05$). ROC curve analysis found that PCT and NLR both had an AUC area > 0.7 in predicting patient death within 28 days ($P < 0.05$).

Conclusion: Inflammatory factors such as NLR, CRP, and PCT have important clinical applications in the assessment of the extent of disease and prognosis of patients with bloodstream infection and sepsis.

Keywords: C-reactive protein, procalcitonin, neutrophil to lymphocyte ratio, bloodstream infection and sepsis, prognosis, condition

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Fang Wei,
Central South University, China
Wenjun Gu,
Shanghai Jiaotong University School of Medicine, China

***Correspondence:**
Feng Yu
lianghwzj198897@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *18 January 2022*
Accepted: *09 February 2022*
Published: *07 March 2022*

Citation:
Liang P and Yu F (2022) Value of CRP, PCT, and NLR in Prediction of Severity and Prognosis of Patients With Bloodstream Infections and Sepsis. Front. Surg. 9:857218. doi: 10.3389/fsurg.2022.857218

BACKGROUND

Bloodstream infection is a serious infectious disease that occurs when pathogenic microorganisms such as bacteria and fungi invade the blood circulation through a damaged skin mucosal barrier, causing systemic disseminated infection, and septicemia and bacteremia are often referred to clinically as bloodstream infection (1, 2). Clinical practice shows (3) that patients with bloodstream infections caused by bacterial infections have a very high probability of developing sepsis, and some studies (4) suggest that patients with bacterial bloodstream infections develop rapidly and can develop septic shock within a short period of time, which can lead to multi-organ failure or even death in severe cases. The incidence of sepsis is increasing every year and has a very high mortality rate (5, 6). It has been shown (7, 8) that if patients can be treated correctly within 1 h of onset, their survival rate can be 80% or more, while if patients are treated more than 6 h after onset their probability of survival is more than 30%. Thus, early risk stratification and timely identification of critical conditions are key to improving the short-term prognosis of patients with bloodstream infection sepsis.

Currently, blood cultures are the gold standard for the diagnosis of bloodstream infections, but they are time-consuming, taking 3–7 days or more, with poor timeliness and the possibility of contaminated specimens (9). In recent years, some clinical studies have found that the levels of inflammatory factors such as calcitoninogen (PCT) and C-reactive protein (CRP) have high clinical value in the early diagnosis of sepsis and determination of the disease (10, 11). PCT and CRP are two important inflammatory cytokines that are involved in apoptosis and can enable cell lysis, and their levels are significantly increased when the organism is infected with bacteria, but the relevance of changes in their levels has been less studied in patients with sepsis due to bloodstream infection (12). In addition, studies (13, 14) have shown that the neutrophil/lymphocyte ratio (NLR) can be used to predict sepsis bloodstream infections and help distinguish between different pathogenic species, but it is not widely accepted by clinicians as a definitive marker of infection and the exact threshold value is controversial. Therefore, this study was conducted to investigate the correlation between PCT, CRP, and NLR and the prognostic value of bloodstream infection in patients with sepsis, in order to provide a basis for early screening of high-risk patients and to guide clinical treatment.

INFORMATION AND METHODS

Inclusion Criteria

One hundred and forty-six patients with bloodstream infection sepsis (positive blood cultures) admitted to our intensive care unit (ICU) from October 2016 to May 2020 were selected, and only clinical data from the first admission were selected for repeat ICU admissions during the study period. Inclusion criteria: (1) referring to the International Consensus on the Definition of Sepsis and Infectious Shock, Third Edition (Sepsis-3) published in 2016 (15), the criteria for sepsis diagnosis were (i) identification of suspected infection; (ii) presence of a sequential organ failure score (SOFA) change $\geq$ 2 points; (2) the patient's age was $\geq$18 years; (3) the patient's case data and biochemical findings after admission were complete and free of defects; (4) two or more positive blood cultures, or two sites with the same positive blood culture and the same causative organism; (5) the patient's serum inflammatory factors PCT, CRP and NLR levels were measured within 24 h after admission. Exclusion criteria: (1) patients who had been hospitalized for <24 h; (2) patients with other viral or bacterial infections; (3) patients with immune deficiency, malignancy, hematologic disorders, or severe psychiatric disorders; (4) patients who had been treated with antibiotics prior to initial admission; (5) women who were breastfeeding or pregnant; (6) patients or family members who had requested that treatment be abandoned.

General Information

The clinical data of 146 patients with sepsis from bloodstream infection, 60 women and 86 men, aged 18–94 (62.45 $\pm$ 14.16) years, included in the study were retrospectively analyzed. Information on gender, age, site of infection, comorbidities [multiple organ failure syndrome (MODS), acute respiratory distress syndrome (ARDS)], underlying diseases (chronic obstructive pulmonary disease, hypertension, diabetes mellitus), blood count [leucocytes (WBC), total bilirubin (TBIL), D-Dimer (D-D), Alanine transaminase (ALT), aspartate transaminase (AST), B-type natriuretic peptide (BNP), platelet count (PLT), serum creatinine (Scr)], inflammatory factor levels (CRP, PCT, and NLR), type of infectious strain, and APACHE II score at 24 h of admission were collected from all patients by case collection.

Grouping Methods

The Acute Physiology and Chronic Health Rating Scale (APACHE II) assessment was completed within 24 h after patients were admitted to the ICU, and patients were divided into a critical group (67 patients with an APACHE II score of 20 or more) and a non-critical group (79 patients with an APACHE II score of <20) based on their scores. Patients were observed starting from the time of admission to the hospital and discharged with improvement or death within 28 days as the end point. The prognosis of all patients was counted and divided into a death group (56 patients) and a survival group (90 patients) according to their prognosis. Among them, survival means patients who improved after treatment in ICU and were transferred to other departments for further treatment or discharged from the hospital; death includes patients who died after ineffective treatment and those who were automatically discharged.

Statistical Processing

All data collected were statistically analyzed and plotted using SPSS 22.0 and Prism 8.0. The *t*-test, expressed as mean $\pm$ standard deviation ($x \pm s$), was used for

measures that conformed to normal distribution and homogeneity of variance. For the count data, the chi-square test or Fisher's exact test was performed. Pearson model was used to analyze the correlation between each index and the condition. Independent risk factors affecting prognosis were analyzed by one-way and multi-way logistic regression, and the ROC curve was used to evaluate the diagnostic sensitivity, specificity, and optimal cutoff value of each index. $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of General Data and Laboratory Indicators of Patients With Different Conditions

We compared the general data and laboratory indices of patients with sepsis from severe bloodstream infection with those of patients with sepsis from non-severe bloodstream infection. The results were no statistically significant differences between the two groups in terms of gender, age, pulmonary infection, abdominal infection, concurrent MODS, concurrent ARDS, underlying disease, strain of infection, WBC level, platelet count, ALT, D-D, BNP, and BUN levels ($P > 0.05$). The levels of NLR, CRP, PCT, TBIL, AST, and Scr were higher in patients with severe bloodstream infection and sepsis than in the non-critical group, and the differences were statistically significant ($P < 0.05$; **Table 1**).

Analysis of the Correlation Between Laboratory Indicators and the Degree of Sepsis in Bloodstream Infections

Pearson correlation analysis showed that NLR, CRP and PCT levels were positively correlated with severity of disease in patients with bloodstream infection sepsis (r-values were 0.468, 0.456, and 0.670, respectively; all $P < 0.001$), while TBIL, AST, and Scr levels were not linearly correlated with severity of disease in patients with bloodstream infection sepsis (r-values were 0.017, 0.101, and 0.117, p-values were 0.838, 0.223, and 0.159, respectively; **Figures 1A–F**).

Comparison of General Data and Laboratory Indicators of Patients With Different Prognosis

We compared the general data and laboratory indices of patients in the death group with those in the survival group. The results were no statistically significant differences between the two groups in terms of gender, age, abdominal infection, underlying disease, strain of infection, WBC level, platelet count, ALT, D-D, BNP, BUN, Scr, and TBIL levels ($P > 0.05$). The incidence of pulmonary infections, MODS and ARDS, the levels of NLR, CRP, PCT, and AST, and the APACHE II score were significantly higher in the death group than in the survival group ($P < 0.05$; **Table 2**).

TABLE 1 | Comparison of general data and laboratory indicators of patients with different conditions [(x ± s), *n* (%)].

Information		Critical group ($n = 67$)	Non-critical group ($n = 79$)	χ^2/t value	*P*-value
Gender (male)		38 (56.72)	48 (60.76)	0.245	0.621
Age (years)		63.32 ± 13.45	61.57 ± 15.16	0.903	0.369
Infection status	Pulmonary infection	47 (70.15)	62 (78.48)	2.094	0.148
	Abdominal infection	10 (14.93)	16 (20.25)	0.703	0.402
Complicated MODS		10 (14.93)	13 (16.46)	0.064	0.800
Complicated ARDS		7 (10.45)	13 (46.46)	1.107	0.293
Underlying disease	COPD	4 (5.97)	8 (10.13)	0.830	0.362
	Hypertension	22 (32.84)	36 (45.57)	2.455	0.117
	Diabetes mellitus	8 (11.94)	12 (15.19)	0.324	0.569
Types of bacteria	Gram negative bacteria	32 (47.76)	45 (56.96)	1.231	0.267
	Gram positive bacteria	28 (41.79)	41 (51.90)	1.486	0.222
NLR		27.32 ± 16.33	12.58 ± 7.14	7.250	0.000
CRP (mg/L)		143.56 ± 56.28	89.73 ± 32.51	7.204	0.000
PCT (ng/mL)		4.79 ± 1.73	1.58 ± 0.80	14.744	0.000
WBC ($\times 10^9$/L)		15.57 ± 8.24	13.26 ± 10.33	1.475	0.142
PLT ($\times 10^9$/L)		130.26 ± 62.24	113.51 ± 52.33	1.767	0.079
TBIL (μmol/L)		34.65 ± 42.13	21.83 ± 29.54	2.152	0.033
AST (U/L)		84.23 ± 33.16	56.77 ± 27.56	5.465	0.000
ALT (U/L)		37.26 ± 13.24	35.58 ± 11.48	0.821	0.413
D-D (mg/L)		4.24 ± 3.10	4.05 ± 3.25	0.360	0.720
BNP (ng/L)		3246.47 ± 3717.52	2535.24 ± 3017.28	1.276	0.204
BUN (mmol/L)		12.59 ± 5.78	11.34 ± 6.04	1.271	0.206
Scr (μmol/L)		208.13 ± 114.58	164.32 ± 132.26	2.119	0.036

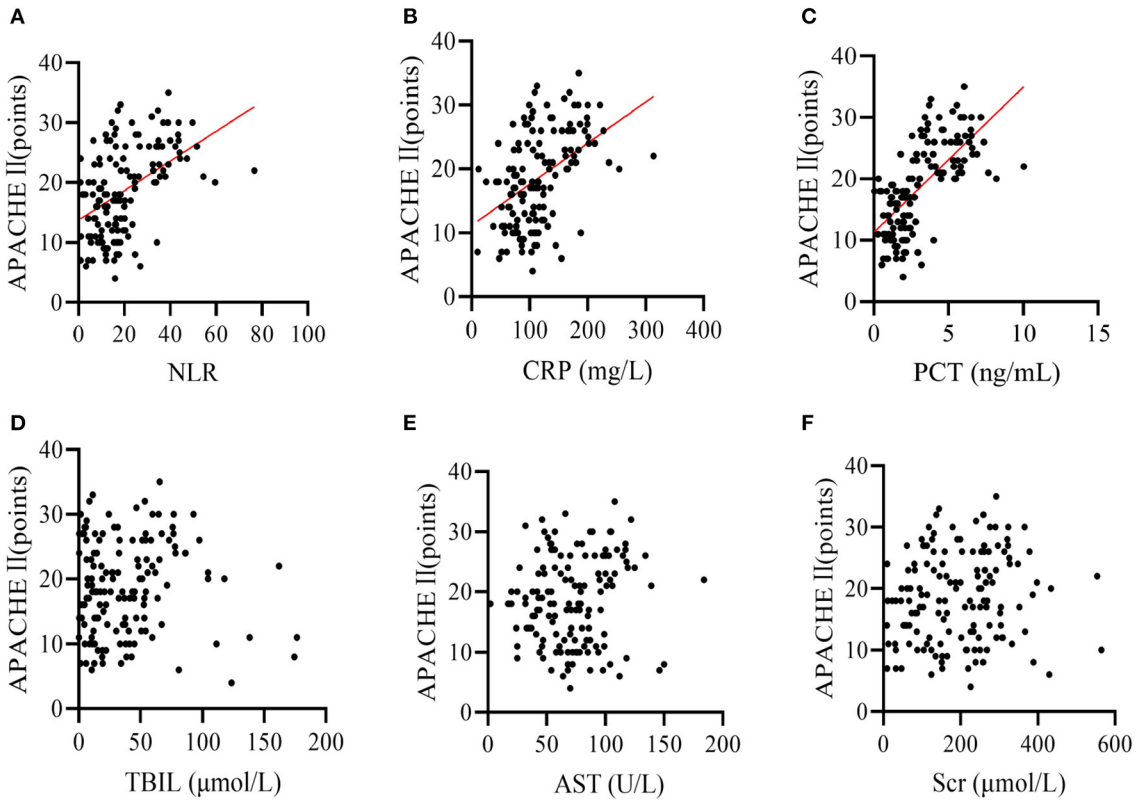


FIGURE 1 | Pearson correlation analysis showed that the levels of **(A)** NLR, **(B)** CRP, and **(C)** PCT were positively correlated with the severity of disease (APACHE II) in patients with bloodstream infection sepsis (*r* values of 0.468, 0.456, and 0.670 respectively; all *P* values <0.001); **(D)** TBIL, **(E)** AST, and **(F)** SCR levels were not linearly correlated with the severity of disease in patients with bloodstream infection sepsis (*r* values of 0.017, 0.101, and 0.117 respectively, *P* values of 0.838, 0.223, and 0.159 respectively).

Logistic Regression Analysis of Risk Factors Affecting 28 Days Mortality in Patients With Bloodstream Infection and Sepsis

Patients' prognosis at 28 days was used as the dependent variable (survival = 0, death = 1) and relevant influencing factors were used as independent variables (see **Table 3** for assignments) to enter a single multifactorial analysis. Logisti univariate analysis showed that NLR level, CRP level, PCT, and APACHE II score were associated with 28 days mortality in patients with bloodstream infection and sepsis ($P < 0.05$). Further multiple regression analysis of the indicators that differed in the univariate analysis showed that NLR level, PCT level and APACHE II score were independent risk factors for death at 28 days in patients with bloodstream infection and sepsis ($P < 0.05$; **Tables 3**, **4**).

Analysis of the Predictive Value of Relevant Indicators on the Prognosis of Patients With Bloodstream Infection and Sepsis

The area under the curve (AUC) for NLR, PCT, and APACHE II scores to predict 28 days death in patients with bloodstream infection and sepsis were 0.791 (95% CI: 0.714–0.868), 0.830 (95% CI: 0.758–0.902), and 0.718 (95% CI: 0.636–0.800), respectively, all with $P < 0.05$ (**Table 5**; **Figure 2**).

DISCUSSION

Bloodstream infection is usually defined as the same patient's blood samples obtained from different parts of the body to culture the same bacteria, and the patient shows symptoms and signs related to the pathogenic bacteria, it is a serious infectious disease that can spread throughout the body and is often life-threatening (16). Sepsis is usually triggered by dysregulation of the organism's response to infection and is an acute organ dysfunction resulting from an abnormal immune response of the host to infection (17). Some clinical studies (18) have shown that among the various types of infections that cause sepsis, bloodstream infection is the most important factor in the death of patients with sepsis. And with the gradual increase in the incidence of sepsis after bloodstream infection in China in recent years, the research on the condition, prognosis assessment and prevention and treatment of sepsis caused by bloodstream infection has become a hot spot of concern for clinical workers.

Most scholars (19, 20) currently believe that the development, progression and prognosis of sepsis in bloodstream infections are

TABLE 2 | Comparison of general data and laboratory indicators of patients with different prognosis [(x ± s), *n* (%)].

Information		Death group (*n* = 56)	Survival group (*n* = 90)	χ^2/t value	*P*-value
Gender (male)		36 (64.29)	50 (55.56)	0.016	0.900
Age (years)		60.23 ± 17.46	55.72 ± 17.65	1.507	0.134
Infection status	Pulmonary infection	48 (85.71)	61 (67.78)	5.870	0.015
	Abdominal infection	8 (14.29)	18 (20.00)	0.770	0.380
Complicated MODS		14 (25.00)	9 (10.00)	5.852	0.016
Complicated ARDS		12 (21.43)	8 (8.89)	4.592	0.032
Underlying disease	COPD	6 (10.71)	6 (6.67)	1.124	0.289
	Hypertension	19 (33.93)	39 (43.33)	1.275	0.259
	Diabetes mellitus	6 (10.71)	14 (15.56)	0.684	0.408
Types of bacteria	Gram negative bacteria	33 (58.93)	44 (48.89)	2.576	0.109
	Gram positive bacteria	23 (41.07)	46 (51.11)	1.396	0.237
NLR		29.37 ± 12.24	13.52 ± 8.22	9.360	0.000
CRP (mg/L)		150.59 ± 57.37	106.24 ± 62.25	4.312	0.000
PCT (ng/mL)		9.43 ± 4.25	2.56 ± 1.61	13.844	0.000
WBC ($\times 10^9$/L)		15.02 ± 11.34	12.57 ± 9.43	1.411	0.160
PLT ($\times 10^9$/L)		132.88 ± 58.42	118.25 ± 48.37	1.639	0.103
TBIL (μmol/L)		34.77 ± 41.82	23.98 ± 31.25	1.779	0.078
AST (U/L)		82.56 ± 31.43	58.49 ± 30.24	4.607	0.000
ALT (U/L)		36.11 ± 12.25	36.59 ± 13.12	0.220	0.826
D-D (mg/L)		4.92 ± 3.21	3.89 ± 3.41	1.815	0.072
BNP (ng/L)		3,310.25 ± 3,822.01	2,843.53 ± 3,452.24	0.762	0.447
BUN (mmol/L)		13.34 ± 6.82	12.25 ± 7.27	0.902	0.369
Scr (μmol/L)		196.34 ± 119.24	173.25 ± 124.58	1.107	0.270
APACHE II (points)		25.24 ± 5.15	20.87 ± 4.23	5.578	0.000

TABLE 3 | Assignment table.

Indicator	Assignment
Pulmonary infection	Yes = 0, No = 1
Complicated MODS	Yes = 0, No = 1
Complicated ARDS	Yes = 0, No = 1
NLR	Continuous variables
CRP	Continuous variables
PCT	Continuous variables
AST	Continuous variables
APACHEII	Continuous variables

TABLE 4 | Logistic regression analysis of risk factors affecting 28 days mortality in patients with bloodstream infection and sepsis.

Indicators	Single-factor			Multi-factor		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Pulmonary infection	1.379	0.799∼2.377	0.623	–	–	–
Complicated MODS	1.525	0.695∼3.347	0.512	–	–	–
Complicated ARDS	1.511	0.746∼3.049	0.324	–	–	–
NLR	1.923	1.575∼2.349	0.012	1.669	1.402∼1.987	0.009
CRP	1.958	1.030∼3.724	0.046	1.060	0.957∼1.173	0.206
PCT	1.684	1.347∼2.105	0.038	1.687	1.312∼2.151	0.031
AST	1.132	0.934∼1.372	0.344	–	–	–
APACHE II	2.387	1.223∼4.657	0.006	2.270	1.237∼4.169	0.007

related to the inflammatory response and the immune function status of the body. It has been reported (21) that serum levels of PCT and CRP, two important inflammatory cytokines involved in apoptosis and capable of causing cell lysis, are significantly increased when the body is infected with bacteria. PCT, a precursor of calcitonin, is a 116-amino acid glycoprotein that can be detected as a significant increase in PCT levels in the presence of bacterial infections, but is rarely seen in viral infections and is a sensitive substance for identifying bacterial and viral infections (22). CRP is an acute phase reaction protein, mainly synthesized and released by the liver, which slowly increases to hundreds or thousands of times its normal level after 8–12 h when the organism is invaded by pathogenic microorganisms or stimulated by inflammation, and gradually returns to normal level after reasonable treatment, which can reflect the severity of infection to some extent (23). As for the relationship between NLR and sepsis, some studies (24) have suggested that leukocytosis and lymphopenia are a distinctive feature of severe sepsis, and some foreign scholars (25, 26) have suggested that NLR can be used as a marker for the early detection and diagnosis of sepsis and that NLR is more effective than conventional inflammatory

TABLE 5 | Analysis of the predictive value of relevant indicators on the prognosis of patients with bloodstream infection and sepsis.

Indicators	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
NLR	0.791	0.714~0.868	0.476	64.30	83.30
PCT	0.830	0.758~0.902	0.639	83.90	80.00
APACHE II	0.718	0.636~0.800	0.326	89.30	43.30

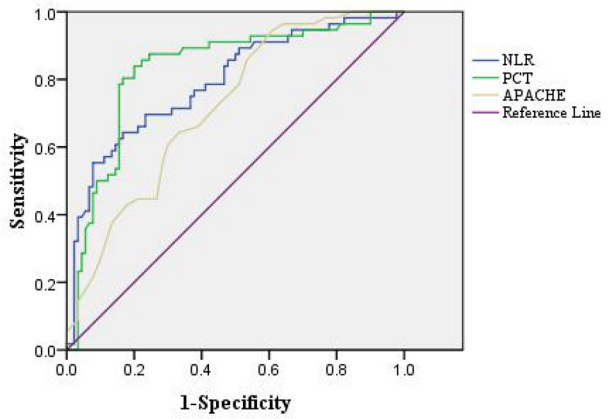


FIGURE 2 | ROC curve of the predictive value of relevant indicators for 28 days death in patients with bloodstream infection and sepsis.

biomarkers. This study focused on analyzing the differences in the levels of PCT, CRP, and NLR in patients with bloodstream infection sepsis and correlating them with the concurrently rated APACHEII to provide a reference basis for early clinical assessment of the severity of sepsis patients and their prognosis.

By evaluating the value of PCT, CRP, and NLR in assessing the condition of patients with sepsis due to bloodstream infection, it was found that the levels of NLR, CRP, and PCT were significantly higher in patients with sepsis due to severe bloodstream infection than in the non-severe group. APACHE II is currently the most commonly used disease severity scoring system in ICU, and to some extent the magnitude of its score can indicate the prognosis of the disease, with the higher the score the worse the prognosis (27). Therefore, this study further correlated the inflammatory factors PCT, CRP, and NLR with APACHE II scores and found that there was a positive correlation between serum PCT, CRP, and NLR and APACHE II scores. This suggests that the severity of the disease in patients with bloodstream infection sepsis can be effectively reflected by the inflammatory factors PCT, CRP, and NLR. Meanwhile, we compared patients with different prognosis of bloodstream infection sepsis and found that higher levels of PCT and NLR tended to suggest higher sepsis mortality, and both had comparable predictive value for 28 days death in patients with bloodstream infection and sepsis.

In conclusion, NLR, CRP, and PCT can effectively reflect the severity of patients with bloodstream infection sepsis, and higher levels of NLR, CRP, and PCT are associated with severe disease. In addition NLR, PCT, and APACHE II scores are independent risk factors for predicting death in 28 days of bloodstream infection sepsis, and early monitoring of inflammatory factors for patients with bloodstream infection sepsis can be used as a marker for assessing the extent of patients' disease as well as their prognosis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of The First Affiliated Hospital of AnHui Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FY was the supervisor of this study. All authors of this study made equal contributions, including the design of the study, the conduct of the experiments, and the writing of the paper.

REFERENCES

1. Kern WV, Rieg S. Burden of bacterial bloodstream infection-a brief update on epidemiology and significance of multidrug-resistant pathogens. *Clin Microbiol Infect.* (2020) 26:151–7. doi: 10.1016/j.cmi.2019.10.031
2. Ray-Barruel G, Xu H, Marsh N, Cooke M, Rickard CM. Effectiveness of insertion and maintenance bundles in preventing peripheral intravenous catheter-related complications and bloodstream infection in hospital patients: a systematic review. *Infect Dis Health.* (2019) 24:152–68. doi: 10.1016/j.idh.2019.03.001
3. Torres MJM, Peterson JM, Wolf SE. Detection of infection and sepsis in burns. *Surg Infect (Larchmt).* (2021) 22:20–7. doi: 10.1089/sur.2020.348
4. Kawaguchi N, Katsube T, Echols R, Wajima T. Population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of cefiderocol, a parenteral siderophore cephalosporin, in patients with pneumonia, bloodstream infection/sepsis, or complicated urinary tract infection. *Antimicrob Agents Chemother.* (2021) 65:e01437–20. doi: 10.1128/AAC.01437-20
5. Font MD, Thyagarajan B, Khanna AK. Sepsis and Septic Shock - Basics of diagnosis, pathophysiology and clinical decision making. *Med Clin North Am.* (2020) 104:573–85. doi: 10.1016/j.mcna.2020.02.011
6. Opal SM, Wittebole X. Biomarkers of Infection and Sepsis. *Crit Care Clin.* (2020) 36:11–22. doi: 10.1016/j.ccc.2019.08.002
7. Fleuren LM, Klausch TLT, Zwager CL, Schoonmade LJ, Guo T, Roggeveen LF, et al. Machine learning for the prediction of sepsis: a systematic review and meta-analysis of diagnostic test accuracy. *Intensive Care Med.* (2020) 46:383–400. doi: 10.1007/s00134-019-05872-y
8. Jones TW, Smith SE, Van Tuyl JS, Newsome AS. Sepsis with preexisting heart failure: management of confounding clinical features. *J Intensive Care Med.* (2021) 36:989–1012. doi: 10.1177/0885066620928299

9. Greninger AL, Naccache SN. Metagenomics to assist in the diagnosis of bloodstream infection. *J Appl Lab Med.* (2019) 3:643–53. doi: 10.1373/jalm.2018.026120
10. Sui YD, Xin WN, Feng LL. Comparison of the clinical application values of PCT, hs-CRP and SAA detection in the early diagnosis of sepsis. *Pak J Med Sci.* (2020) 36:1683–7. doi: 10.12669/pjms.36.7.2544
11. Shen W, Lai S. Diagnostic Value of sCD163 Combined with PCT and HS-CRP in patients with gynecological malignant tumors and fever. *J Coll Physicians Surg Pak.* (2020) 30:1053–7. doi: 10.29271/jcpsp.2020.10.1053
12. Xu YB, Ouyang Y, Zhao D. Curative effects of vancomycin and cefotaxime combined with gamma globulin respectively in neonatal septicemia and their influences on PCT, CRP and hs-CRP. *Eur Rev Med Pharmacol Sci.* (2020) 24:4486–94. doi: 10.26355/eurrev_202004_21031
13. Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: a meta-analysis. *Am J Emerg Med.* (2020) 38:641–7. doi: 10.1016/j.ajem.2019.10.023
14. Zhong X, Ma A, Zhang Z, Liu Y, Liang G. Neutrophil-to-lymphocyte ratio as a predictive marker for severe pediatric sepsis. *Transl Pediatr.* (2021) 10:657–65. doi: 10.21037/tp-21-47
15. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA.* (2016) 315:801–10. doi: 10.1001/jama.2016.0287
16. Carvalho AS, Lagana D, Catford J, Shaw D, Bak N. Bloodstream infections in neutropenic patients with haematological malignancies. *Infect Dis Health.* (2020) 25:22–9. doi: 10.1016/j.idh.2019.08.006
17. Pierrakos C, Velissaris D, Bisdorff M, Marshall JC, Vincent JL. Biomarkers of sepsis: time for a reappraisal. *Crit Care.* (2020) 24:287. doi: 10.1186/s13054-020-02993-5
18. Liljedahl Prytz K, Prag M, Fredlund H, Magnuson A, Sundqvist M, Källman J. Antibiotic treatment with one single dose of gentamicin at admittance in addition to a β-lactam antibiotic in the treatment of community-acquired bloodstream infection with sepsis. *PLoS One.* (2020) 15:e0236864. doi: 10.1371/journal.pone.0236864
19. Chou EH, Mann S, Hsu TC, Hsu WT, Liu CC, Bhakta T, et al. Incidence, trends, and outcomes of infection sites among hospitalizations of sepsis: a nationwide study. *PLoS One.* (2020) 15:e0227752. doi: 10.1371/journal.pone.0227752
20. Lenglet A, Schuurmans J, Ariti C, Borgundvaag E, Charles K, Badjo C, et al. Rectal screening displays high negative predictive value for bloodstream infection with (ESBL-producing) Gram-negative bacteria in neonates with suspected sepsis in a low-resource setting neonatal care unit. *J Glob Antimicrob Resist.* (2020) 23:102–7. doi: 10.1016/j.jgar.2020.08.017
21. Papafilippou L, Claxton A, Dark P, Kostarelos K, Hadjidemetriou M. Nanotools for sepsis diagnosis and treatment. *Adv Healthc Mater.* (2021) 10:e2001378. doi: 10.1002/adhm.202001378
22. Stocker M, van Herk W, El Helou S, Dutta S, Schuerman FABA, van den Tooren-de Groot RK, et al. C-Reactive Protein, Procalcitonin, and White Blood Count to Rule Out Neonatal Early-onset Sepsis Within 36 Hours: A Secondary Analysis of the Neonatal Procalcitonin Intervention Study. *Clin Infect Dis.* (2021) 73:e383–90. doi: 10.1093/cid/ciaa876
23. Nurmi AM, Mustonen HK, Stenman UH, Seppänen HE, Haglund CH. Combining CRP and CA19-9 in a novel prognostic score in pancreatic ductal adenocarcinoma. *Sci Rep.* (2021) 11:781. doi: 10.1038/s41598-020-80778-0
24. Root-Bernstein R. Innate receptor activation patterns involving TLR and NLR synergisms in COVID-19, ALI/ARDS and sepsis cytokine storms: a review and model making novel predictions and therapeutic suggestions. *Int J Mol Sci.* (2021) 22:2108. doi: 10.3390/ijms22042108
25. Li T, Dong G, Zhang M, Xu Z, Hu Y, Xie B, et al. Association of neutrophil-lymphocyte ratio and the presence of neonatal sepsis. *J Immunol Res.* (2020) 2020:7650713. doi: 10.1155/2020/7650713
26. Lorente L, Martín MM, Ortiz-López R, Alvarez-Castillo A, Ruiz C, Uribe L, et al. Association between neutrophil-to-lymphocyte ratio in the first seven days of sepsis and mortality. *Enferm Infecc Microbiol Clin (Engl Ed).* (2020). doi: 10.1016/j.eimc.2020.11.004. [Epub ahead of print].
27. Kuo WK, Hua CC, Yu CC, Liu YC, Huang CY. The cancer control status and APACHE II score are prognostic factors for critically ill patients with cancer and sepsis. *J Formos Med Assoc.* (2020) 119:276–81. doi: 10.1016/j.jfma.2019.05.012

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Liang and Yu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 07 March 2022
doi: 10.3389/fsurg.2022.850139

Comparison of Application Effects of Different Hemostasis Methods After Ischemic Cerebrovascular Intervention

*Yanli Zhou and Chenghua Xu**

Department of Neurology, Taizhou First People's Hospital, Taizhou, China

Objective: To explore the effects of two different hemostasis methods, namely, arterial compression devices and vascular closure devices, in the ischemic cerebrovascular intervention to provide a theoretical basis for clinical selection of hemostasis methods.

Methods: A total of 302 patients who underwent ischemic cerebrovascular intervention in our hospital from January 2016 to December 2020 were selected as the research subjects and randomly divided into the control group ($n = 151$) and the observation group ($n = 151$). The patients in both groups underwent cerebrovascular intervention. The patients in the control group were treated with an artery compressor for hemostasis after the operation, while those in the observation group were treated with vascular closure devices for hemostasis. The hemostatic indexes and vascular parameters at the puncture site before and after the operation were compared between the two groups. The comfort level of the patients was assessed at 6, 12, and 24 h after the operation with the Kolcaba Comfort Scale score, and the postoperative complications were recorded.

Results: There was no significant difference in the success rate of hemostasis between the two groups ($p > 0.05$). The hemostatic time and immobilization time of (2.69 ± 0.62) min and (4.82 ± 0.93) h in the observation group were lower than those in the control group with (16.24 ± 3.58) min and (7.94 ± 1.86) h ($p < 0.05$). The differences in the minimum inner diameter of the puncture site and its nearby vessels and the peak velocity of blood flow between the two groups before and after the operation were not statistically significant within or between groups ($p > 0.05$). The scores of the Kolcaba comfort scale in the observation group (80.16 ± 8.49) and (93.65 ± 9.26) at 6 and 12 h, respectively, after the operation, were higher than those in the control groups (72.08 ± 7.54) and (85.49 ± 8.63) ($p < 0.05$). The 24 h postoperative Kolcaba comfort scale score was (97.54 ± 9.86) in the observation group and (96.82 ± 9.64) in the control group, and the difference was not statistically significant ($p > 0.05$). In the control group, there were 7 cases of dysuria, 12 cases of low back pain,

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Yang Liu,
The First Medical Center of Chinese PLA General Hospital, China
Wenjie Song,
Fourth Military Medical University, China

***Correspondence:**
Chenghua Xu
samuel5098@126.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *07 January 2022*
Accepted: *31 January 2022*
Published: *07 March 2022*

Citation:
Zhou Y and Xu C (2022) Comparison of Application Effects of Different Hemostasis Methods After Ischemic Cerebrovascular Intervention. Front. Surg. 9:850139. doi: 10.3389/fsurg.2022.850139

14 cases of sleep disorder, 20 cases of mental stress, and 5 cases of wound bleeding, and the total incidence of complications was 38.41% (58/151). In the observation group, there were 4 cases of dysuria, 8 cases of low back pain, 10 cases of sleep disorder, 14 cases of mental stress, and 3 cases of wound bleeding, and the total incidence of complications was 25.83% (39/151). The total incidence of complications in the observation group was lower than that in the control group ($p < 0.05$).

Conclusion: For patients with ischemic cerebrovascular disease undergoing femoral artery puncture intervention, the use of vascular closure devices can stop the bleeding quickly, which can significantly shorten the bleeding time, and the postoperative braking time of patients is short, with high comfort and fewer complications.

Keywords: ischemic cerebrovascular diseases, cerebrovascular intervention, hemostatic methods, artery compressor, vascular closure devices

INTRODUCTION

Cerebrovascular disease refers to acute and chronic cerebrovascular diseases caused by various reasons. As a common and frequently occurring disease in the nervous system, cerebrovascular disease is currently one of the three major diseases leading to human death, second only to cardiovascular disease and cancer (1, 2). Ischemic cerebrovascular diseases mainly include transient ischemic attack and cerebral infarction, accounting for about 80% of all strokes, and the proportion is higher in elderly patients. At present, the clinical treatments of ischemic cerebrovascular diseases mainly include medication, surgery, and intervention (3, 4). Traditional medication has little effect on the formed plaques, especially the moderate and severe vascular stenosis. Carotid endarterectomy was once the gold standard for the treatment of carotid stenosis, but it has been limited due to its large surgical trauma and a relatively small scope of indications (5, 6). Interventional therapy belongs to minimally invasive surgery, which is usually performed under local anesthesia. Due to its advantages of not damaging brain nerve fibers, a short time of blocking the blood flow during surgery, and its applicability to high-level stenosis, it is one of the most important methods for the treatment of cerebral artery stenosis after the surgical carotid endarterectomy (7, 8). To avoid vasospasm during cerebral vascular intervention, the femoral artery, and the inguinal artery are usually used as puncture vessels in clinics. However, coagulation disorders may occur due to the treatment with anticoagulant and antiplatelet drugs during the operation, resulting in massive and continuous bleeding, which affects the prognosis of patients (9, 10). Therefore, it is extremely important to select a hemostatic method with few complications, high comfort, and easy caring. Both the arterial compression devices and the vascular staplers are new hemostatic devices. Studies have shown that, compared with traditional artificial compression hemostasis, the hemostatic effect is better (11, 12). The purpose of this study was to investigate the application effects of two different hemostasis methods, namely, the artery compressor and the arterial suture device in the ischemic cerebrovascular intervention, to provide a theoretical basis for clinical selection of hemostasis methods.

MATERIALS AND METHODS

Patients

A total of 302 patients, who underwent ischemic cerebrovascular intervention in our hospital from January 2016 to December 2020, were selected as the research subjects. There were 177 men and 125 women; the age ranged from 40 to 78 years, with an average age of (55.86 ± 9.82) years; the modified Rankin scale (mRS) was (3.15 ± 0.55) points. Inclusion criteria: preoperatively enhanced CT, MRI, and digital subtraction angiography were performed in all patients to identify the stenotic cerebral artery vessels and sites; all the patients underwent cerebrovascular intervention—those who are conscious before surgery; Preoperative examination of coagulation function, liver and kidney function, and heart function is normal. Exclusion criteria: the patients with systemic infectious diseases, the patients with urinary system diseases, the patients with back pain, the patients with severe respiratory diseases, and the patients with mental and cognitive dysfunction. All the patients were randomly divided into the control group ($n = 151$) and the observation group ($n = 151$). There was no significant difference in general data between the two groups ($p > 0.05$), as shown in **Table 1**.

Treatment Methods

All the patients in the two groups underwent cerebrovascular intervention; before the operation, all the patients had undergone routine electrocardiogram (ECG) and routine blood tests, as

TABLE 1 | Comparison of general data between the two groups.

Group	Gender		Age (years)	mRS score (points)
	Male	Female		
Control group ($n = 151$)	92	59	55.67 ± 9.68	3.12 ± 0.56
Observation group ($n = 151$)	85	66	56.05 ± 9.95	3.18 ± 0.54
t/χ^2	0.669		0.336	0.948
P	0.414		0.737	0.344

well as liver and kidney functions and bleeding and coagulation functions. Aspirin 300 mg/d and clopidogrel 75 mg/d were routinely administered orally to inhibit platelet aggregation for 3 days before surgery. Stent placement: The femoral approach was adopted, and a 6F arterial sheath was inserted into the vertebral artery, while an 8F arterial sheath was inserted into the internal carotid artery for systemic heparinization. The site and the degree of arterial stenosis and collateral circulation in the ischemic area were determined by angiography. Under the guidance of the wire and the path diagram, a 6F/8F guide catheter was inserted into the proximal end of the lesion. The microwire is inserted along that guide catheter, and the head end of the microwire is inserted through the vascular stenosis and is positioned at the distal end thereof; then, the balloon dilatation catheter was inserted along the microwire to expand the stenosis, and the stent was finally placed at the stenosis. Distal brain protection devices are used for patients with internal carotid artery stenosis. Angiography was performed to observe the dilation of the stenosis, and balloon dilatation was performed if necessary. The intra-cervical and vertebral artery angiography and intracranial angiography were repeated. The arterial dilation after stent release and the blood supply to each branch of the intracranial segment was observed. If no abnormality was found, the operation was terminated.

The control group was treated with arterial compression hemostasis (Model: YM-GU-1229, Manufacturer: Tianjin Yimei Company) after the operation. The arterial compression hemostat was mainly composed of an elliptical pressure plate, a fixed adhesive tape, a spiral handle, a base, and a dial. The operator first confirmed the position of the femoral artery puncture point, applied pressure to the puncture point, pulled out the artery sheath, covered the puncture point with gauze, and then pressed the artery puncture point with an oval pressure plate, and tightly wound the femoral part with the fixed tape. Then, the handle of the screw was rotated clockwise for 6–8 weeks to pressurize the puncture point to confirm that the puncture point could bear the pressure of the pressure plate and to avoid the puncture point bleeding due to excessive pressure. They began to relax after dressing for 2–3 h and rotated the handle counterclockwise for 1 turn. About 2–3 h later, the handle was rotated counterclockwise for 1 turn, and then, it was relaxed every 30–40 min for 1 turn. About 2 h later, the patient could slowly move the lower limb, and, about 6 h later, the patient could slowly turn over, observe exudation around the puncture point, observe the swelling of the operative limb, completely relax about 8 h later, and continue to observe for 30 min. If there is no bleeding, the hemostatic presser can be removed, and the patient moves slightly on the bed.

Hemostasis in the observation group was performed using the vascular closure devices (Model: Perclose Pro Glide, Manufacturer: Abbo TT Labora Tories); after the vascular condition was evaluated, the Perclose Pro Glide suture device was used for the local suture of the punctured vessels, and 0.035 inch wire was replaced through the catheter sheath to enter the femoral artery, followed by the guidewire into the vascular suture device, and then out of the guidewire, and push the suturing device until there is an obvious pulse blood flow in the labeled tube. Position the device at about 45°, raise the handle to expand the pin, and press the piston assembly to complete the endovascular knot when there is resistance in the pull-back. After exiting the vascular suture instrument, the suture modifier was used to push the suture knot onto the femoral artery wall, and finally, the suture knot was tightened, and the excess suture part was cut to complete the operation.

Observation Indicators

(1) Hemostatic effect indicators: The success rate of hemostasis, postoperative hemostasis time, and braking time of the patients in the two groups were recorded. Among them, the criteria for successful hemostasis were as follows: After a one-time suture or compression, there was no bleeding at the puncture point, and the bleeding did not occur again at the puncture point until discharged. Hemostasis time: the time from the removal of the arterial sheath to the completion of hemostasis. Braking time: the time from hemostasis to getting out of bed.

(2) Vascular parameters of the puncture site: The minimum inner diameter of the femoral artery within 3 cm of the puncture site and the nearby area, the peak systolic blood flow velocity, and the formation of femoral artery thrombosis were detected preoperatively, and 3 days after the operation, respectively.

(3) The comfort level during hospitalization: Kolcaba comfort scale (13) was used to score the patients at 6, 12, and 24 h after hemostasis. The scale includes physiological dimension, psycho-spiritual dimension, socio-cultural dimension, environmental dimension, and the overall comfort level. The full score is 120, and the higher the score, the higher the patient's comfort level.

(4) Complications: The occurrence of complications such as dysuria, low back pain, sleep disorder, mental stress, and wound bleeding were recorded after the operation.

Statistical Methods

All data were processed with SPSS 22.0 statistical software. The enumeration data were examined by the X^2 test and expressed by [n (%)]; the measurement data were examined by t-test and expressed by ($\mathbf{x} \pm$ s). The difference is statistically significant when $p < 0.05$.

RESULTS

Comparison of Hemostatic Efficacy Indicators Between the Two Groups

There were 147 cases of successful hemostasis in the control group, and the success rate of hemostasis was 97.35% (147/151), 149 cases of successful hemostasis in the observation group, and the success rate of hemostasis was 98.68% (149/151). There was no significant difference in the success rate of hemostasis between the two groups ($p > 0.05$). The hemostatic time and immobilization time (2.69 ± 0.62) min and (4.82 0.93) h in the observation group were lower than those in the control group (16.24 ± 3.58) min and (7.94 1.86) h ($p < 0.05$) as shown in **Figure 1**.

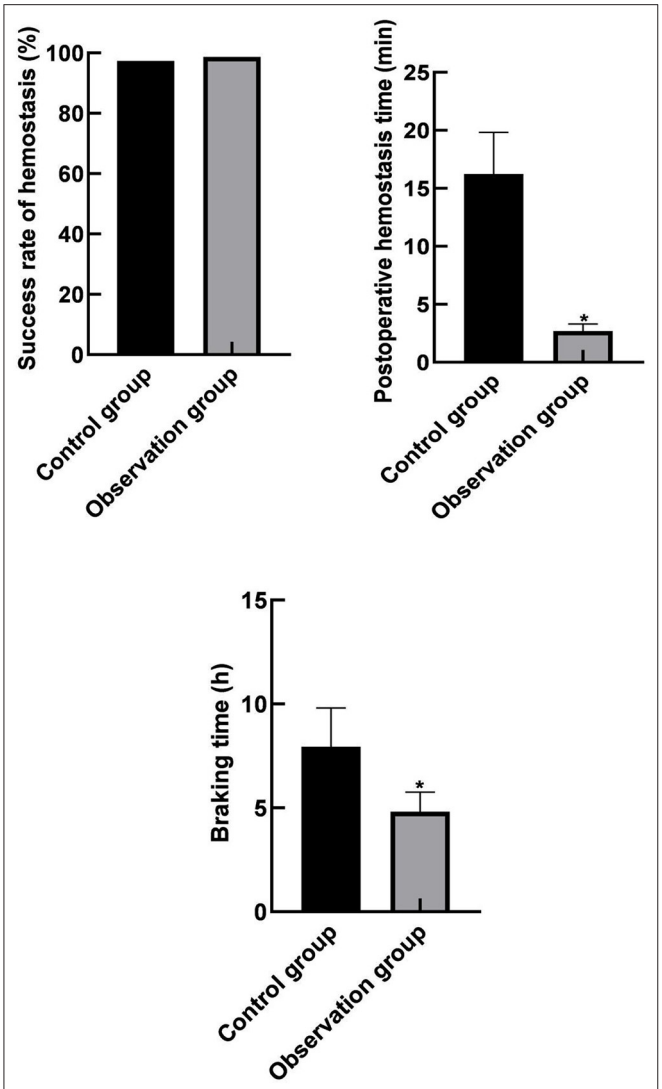


FIGURE 1 | Comparison of hemostatic efficacy indicators between the two groups. Compared with the control group, $^*p < 0.05$.

Comparison of Vascular Parameters at the Puncture Site Between the Two Groups

The differences in the minimum inner diameter of the puncture site and its nearby vessels and the peak velocity of blood flow between the two groups before and after the operation were not statistically significant within or between groups ($p > 0.05$) as shown in **Figure 2**.

Comparison of the Comfort Level During Hospitalization Between the Two Groups

The scores of the Kolcaba comfort scale in the observation group (80.16 ± 8.49), (93.65 ± 9.26) at 6 and 12 h after operation were higher than those in the control groups (72.08 ± 7.54), (85.49 ± 8.63) ($p < 0.05$). The 24-h postoperative Kolcaba comfort scale score was (97.54 ± 9.86) in the observation group and (96.82 ± 9.64) in the control group, and the difference was not statistically significant ($p > 0.05$), as shown in **Figure 3**.

Comparison of Complications Between the Two Groups

In the control group, there were 7 cases of dysuria, 12 cases of low back pain, 14 cases of sleep disorder, 20 cases of mental stress, and 5 cases of wound bleeding, and the total incidence of complications was 38.41% (58/151). In the observation group, there were 4 cases of dysuria, 8 cases of low back pain, 10 cases of sleep disorder, 14 cases of mental stress, and 3 cases of wound bleeding, and the total incidence of complications was 25.83% (39/151). The total incidence of complications in the observation group was lower than that in the control group ($p < 0.05$), as shown in **Figure 4**.

DISCUSSION

Cerebrovascular disease is one of the three leading causes of human death nowadays, with a high incidence, high disability, high mortality, and a high recurrence rate. Cerebrovascular interventional surgery is a commonly used method of cerebral vascular examination and treatment, it is mainly through the femoral artery or groin artery puncture into the cerebral vascular, and an interventional surgery or after check can clearly display a collateral compensatory situation of brain vascular blood flow condition and vascular anomalies, and helps the brain aneurysm, arteriovenous malformation in the diagnosis, and treatment of diseases (14–16). A small amount of antiplatelet drugs and anticoagulants is needed to maintain smooth blood vessels during the interventional surgery, but they often cause hemorrhage and hematoma at the puncture site after surgery, which can further lead to low back pain, mental stress, and dysuria. Most of the patients with cerebrovascular disease are elderly patients with poor physical function, varying degrees of impairment of limb sensation and motor ability, and abnormal coagulation function. Special attention should be paid to interventional surgery, and the postoperative puncture site is also prone to bleeding (17, 18). Therefore, how to quickly and effectively stop the bleeding is extremely important.

Traditional manual compression hemostasis, vascular stapler, and arterial compression hemostasis are currently the three commonly used hemostasis methods at the puncture site after interventional surgery. Traditional artificial compression hemostasis is simple and feasible, but compression dressing is required after hemostasis, and patients are required to stay in bed for 24 h, which can lead to many adverse reactions, such as dysuria and soreness of the waist and back caused by staying in bed for a long time (19, 20). The artery compression hemostat uses a bionic pressing plate to replace a finger, and the adhesive tape is matched with the base so that the problem with gauze that is difficult to fix in artificial compression hemostasis is solved; meanwhile, nursing staff can directly observe the hemostasis of patients and timely handle sudden unexpected situations at

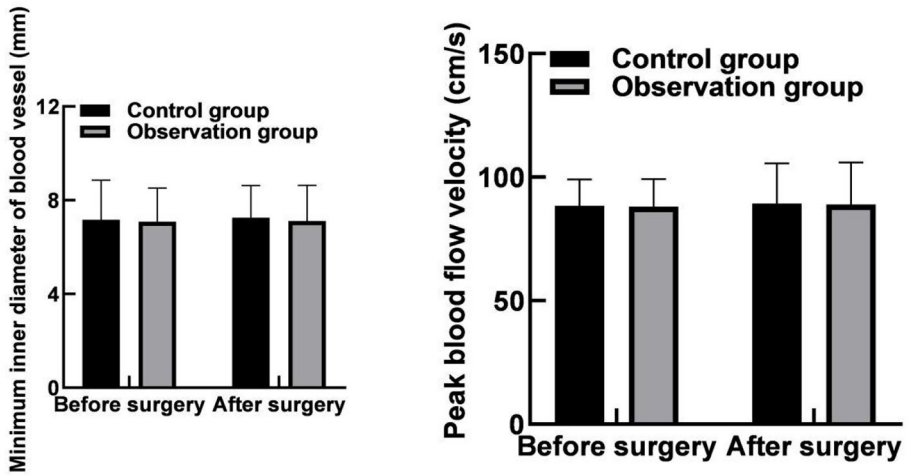


FIGURE 2 | Comparison of vascular parameters at the puncture site between the two groups.

puncture sites. Although the arterial compression device has a good hemostatic effect, its postoperative patients need to be braked for 8 h to move freely, which easily causes complications, such as subcutaneous thrombosis and hematoma and is not conducive to the recovery of patients and affects their comfort levels (21, 22).

The results of this study showed that the hemostatic time and the braking time after operation in the observation group were lower than those in the control group. These results indicated that hemostasis with a vascular stapler could shorten the hemostasis time, and the postoperative braking time for patients was short. The reason for this was analyzed as the vascular stapler was a new type of hemostatic device that could directly suture and puncture blood vessels for rapid hemostasis; besides, the amount of blood leakage from blood vessels after suture was less, the local hematoma was less, and the hemostatic effect was better. Moreover, the results of this study showed that the minimum inner diameter and the peak velocity of blood flow at the puncture site and its nearby vessels in the two groups were not statistically different before and after the operation within and between groups. These results indicated that the use of vascular staplers for hemostasis did not increase the risk of lower extremity ischemia as compared with the arterial compression hemostats for hemostasis.

The results of this study showed that the Kolcaba comfort scale scores of the observation group at 6 and 12 h after the surgery were higher than those of the control group. It indicated that the patients using vascular stapler for hemostasis after the neural intervention had a higher comfort level. The reason was analyzed as follows: The hemostatic principle of arterial hemostat was mainly to compress the vascular puncture point with the pressure plate and fix it with adhesive tape for hemostasis, which required long-time compression of the artery, with high requirements on the strength and time of compression. Generally, the bandage could not be removed until 8 h, which might induce a variety of complications, such as lower extremity

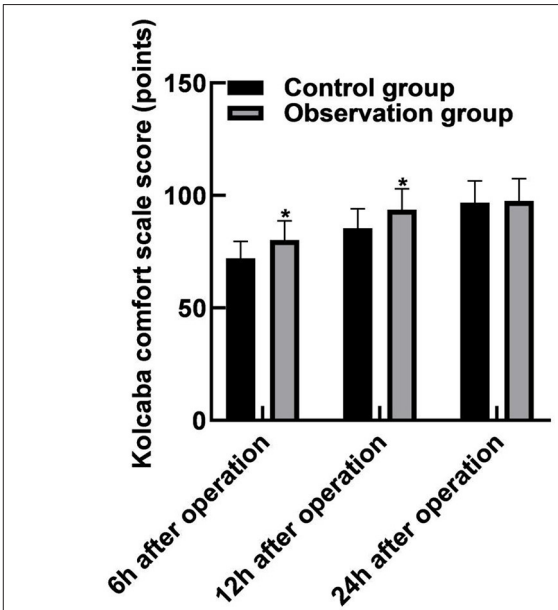


FIGURE 3 | Comparison of the comfort level during hospitalization between the two groups. Compared with the control group, $^{*}p < 0.05$.

arterial ischemia, vasovagal reflex, and others, seriously affecting the patient's motor ability, and the patient's comfort level was poor. The vascular suture device directly sutures the punctured blood vessels through suture lines, which are simple to operate and rapid to stop bleeding and can significantly reduce the compression on the artery. Moreover, the patient's limb braking time is short, and the patient's motor ability is not affected, so, the patient's comfort level is high (23, 24). However, 24 h after the surgery, there was no significant difference in the scores between the two groups based on Kolcaba Comfort Scale. It indicated that the comfort levels of the patients between the two

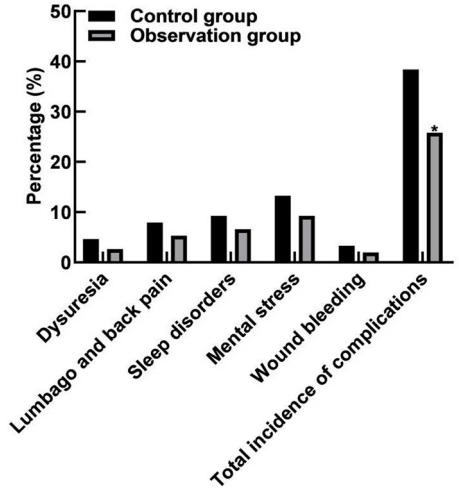


FIGURE 4 | Comparison of complications between the two groups. Compared with the control group, $^*p < 0.05$.

groups were not significantly different 24 h after the operation. The reasons were analyzed as follows: The patients using the arterial compression hemostat for hemostasis could move slightly on the bed 8 h after the operation so that the patients could relax and do not feel nervous all the time. This could improve sleep quality and significantly increase the comfort level. Moreover, the results of this study showed that the total incidence of complications in the observation group (25.83%) was lower than that in the control group (38.41%). These results indicated that hemostasis with a vascular stapler could significantly reduce the postoperative complications of patients. Compared with the arterial compression hemostat for hemostasis, although the vascular stapler has a better hemostatic effect, the applicability of the arterial compression hemostat for hemostasis is more extensive. The vascular suture device needs to suture the blood vessels directly. Therefore, the vascular suture device is not suitable for patients with a puncture point at the bifurcation of the blood vessels, a vessel diameter of < 4 mm, atherosclerosis in the blood vessel wall, repeated fitting of the blood vessel wall, and severe tortuous iliac artery.

CONCLUSION

For patients with ischemic cerebrovascular disease undergoing femoral artery puncture intervention, the use of vascular closure devices can stop bleeding quickly, which can significantly shorten the bleeding time, and the postoperative braking time of patients is short, with high comfort and fewer complications.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Taizhou First People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CX is responsible for the design and guidance of the study. YZ is responsible for the inclusion of cases, the detection of results, and the writing of the paper. Both authors of this study have made equal contributions.

FUNDING

This study was supported by the Zhejiang Medical and Health Science and Technology Plan Project (No. 2020KY1041), Zhejiang Public Welfare Technology Application, and the Social Development Project (No. LGF19H090001).

REFERENCES

1. Yu YP, Tan L. The vulnerability of vessels involved in the role of embolism and hypoperfusion in the mechanisms of ischemic cerebrovascular diseases. *Biomed Res Int.* (2016) 2016:8531958. doi: 10.1155/2016/8531958
2. Zhao DD, Li YR, Yu XY, Zhu YZ, Ma BX. Associations between miR-146a rs2910164 polymorphisms and risk of ischemic cardio-cerebrovascular diseases. *Medicine.* (2019) 98:e17106. doi: 10.1097/MD.0000000000017106
3. Konstantinova EV, Chipigina NS, Shurdumova MH, Kovalenko EI, Sapozhnikov AM. Heat shock protein 70 kDa as a target for diagnostics and therapy of cardiovascular and cerebrovascular diseases. *Curr Pharm Des.* (2019) 25:710–14. doi: 10.2174/1381612825666190329123924
4. Nurmohamed MT, van der Horst-Bruinsma I, Maksymowych WP. Cardiovascular and cerebrovascular diseases in ankylosing spondylitis: current insights. *Curr Rheumatol Rep.* (2012) 14:415–21. doi: 10.1007/s11926-012-0270-6
5. Lu J, Liu W, Zhao H. Headache in cerebrovascular diseases. *Stroke Vasc Neurol.* (2020) 5:205–10. doi: 10.1136/svn-2020-000333
6. Tuttolomondo A, Pinto A. Epigenomics in acute cerebrovascular diseases. *Epigenomics.* (2020) 12:471–4. doi: 10.2217/epi-2019-0388
7. Pasarikovski C R, Tanner B K, Marques A, Da CL, Howard P, Dyer EE, et al. Neurointerventional procedural complications in a growing Canadian Regional Stroke Center: single hospital experience analysis in the context of recommended case volumes. *World Neurosurg.* (2019) 127:e94–100. doi: 10.1016/j.wneu.2019.02.137
8. Davis MC, Deveikis JP, Harrigan MR. Clinical presentation, imaging, and management of complications due to neurointerventional procedures. *Semin Intervent Radiol.* (2015) 32:98–107. doi: 10.1055/s-0035-1549374
9. Zalocar L, Doroszuk G, Goland J. Transradial approach and its variations for neurointerventional procedures: literature review. *Surg Neurol Int.* (2020) 11:248. doi: 10.25259/SNI_366_2020
10. Nguyen TH, Hirsch JA, Chen MM, Golding L, Leslie-Mazwi TM, Nicola GN, et al. The impending conversion factor crisis and neurointerventional practice. *J Neurointerv Surg.* (2021) 13:301–3. doi: 10.1136/neurintsurg-2020-017005

11. Barrette LX, Vance AZ, Shamimi-Noori S, Nadolski GP, Reddy S, Kratz KM, et al. Nonfemoral arterial hemostasis following percutaneous intervention using a focused compression device. *Cardiovasc Intervent Radiol.* (2020) 43:714–20. doi: 10.1007/s00270-020-02431-7
12. Krishnasamy VP, Hagar MJ, Scher DJ, Sanogo ML, Gabriel GE, Sarin SN. Vascular closure devices: technical tips, complications, and management. *Tech Vasc Interv Radiol.* (2015) 18:100–12. doi: 10.1053/j.tvir.2015.04.008
13. Krinsky R, Murillo I, Johnson J. A practical application of Katharine Kolcaba's comfort theory to cardiac patients. *Appl Nurs Res.* (2014) 27:147–50. doi: 10.1016/j.apnr.2014.02.004
14. Rafii MS, Hillis AE. Compendium of cerebrovascular diseases. *Int Rev Psychiatry.* (2006) 18:395–407. doi: 10.1080/09540260600935405
15. Chen PP, Lou PA, Zhang P, Qiao C, Li T, Dong ZM. Trend analysis on the death rate of ischemic heart disease and cerebrovascular disease among Xuzhou residents from 2011 to 2015. *Chin J Cardiol.* (2017) 45:597–607. doi: 10.3760/cma.j.issn.0253-3758.2017.07.009
16. Liesz A, Ruger H, Purrucker J, Zorn M, Dalpke A, Mohlenbruch M, et al. Stress mediators and immune dysfunction in patients with acute cerebrovascular diseases. *PLoS ONE.* (2013) 8:e74839. doi: 10.1371/journal.pone.0074839
17. Cox M, Atsina KB, Sedora-Roman NI, Pukenas BA, Parker L, Levin DC, et al. Neurointerventional radiology for the aspiring radiology resident: current state of the field and future directions. *AJR Am J Roentgenol.* (2019) 212:899–904. doi: 10.2214/AJR.18.20336
18. Dowlati E, Zhou T, Stewart J, Felbaum DR, Liu AH, Mai JC, et al. Head repositioning during neurointerventional procedures to optimize biplanar imaging. *J Neuroimaging.* (2020) 30:603–8. doi: 10.1111/jon.12750
19. Sanghvi KA, Montgomery M, Varghese V. Effect of hemostatic device on radial artery occlusion: a randomized comparison of compression devices in the radial hemostasis study. *Cardiovasc Revasc Med.* (2018) 19:934–8. doi: 10.1016/j.carrev.2018.08.013
20. Robertson L, Andras A, Colgan F, Jackson R. Vascular closure devices for femoral arterial puncture site haemostasis. *Cochrane Database Syst Rev.* (2016) 3:D9541. doi: 10.1002/14651858.CD009541.pub2
21. Kawamura Y, Yoshimachi F, Nakamura N, Yamamoto Y, Kudo T, Ikari Y. Impact of dedicated hemostasis device for distal radial arterial access with an adequate hemostasis protocol on radial arterial observation by ultrasound. *Cardiovasc Interv Ther.* (2021) 36:104–10. doi: 10.1007/s12928-020-00656-4
22. Sato M, Matsumaru Y, Sakai N, Imamura H, Hirohata M, Takeuchi Y, et al. Usefulness of an access-site hemostasis device in neuroendovascular treatment. *Acta Neurochir.* (2017) 159:2331–5. doi: 10.1007/s00701-017-3299-5
23. Hurie J. Vascular closure devices are an option for antegrade access but carry a higher rate of complications highlighting the need for careful patient and device selection. *J Vasc Surg.* (2021) 73:731. doi: 10.1016/j.jvs.2020.09.008
24. Freitas B, Steiner S, Bausback Y, Staab H, Branzan D, Banning-Eichenseer U, et al. Single-center experience with vascular closure devices in real-world endovascular peripheral interventions. *J Cardiovasc Surg.* (2018) 59:797–803. doi: 10.23736/S0021-9509.16.09207-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhou and Xu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 07 March 2022
doi: 10.3389/fsurg.2022.847068

Observation of the Intervention Effect of Biofeedback Therapy Combined With Cluster Nursing on Perioperative Constipation in Patients With Thoracolumbar Fracture

Jin Luo[1], *Nan Xie*[2] *and Liping Yang*[3]*

[1] Department of Spine Surgery, Suining Central Hospital, Suining, China, [2] Nursing Department, Suining Central Hospital, Suining, China, [3] Department of Arthrosurgery, Zhuji People's Hospital of Zhejiang Province, Zhuji, China

Purpose: To discuss the intervention effect of biofeedback therapy combined with cluster nursing on perioperative constipation in patients with thoracolumbar fracture.

Methods: From June 2019 to June 2020, a total of 482 patients with thoracolumbar fracture who were treated by surgery in our department were selected. The random number table method was used to divide into experimental group ($n = 241$) and control group ($n = 241$). The control group was given routine constipation care, the experimental group was given biofeedback therapy combined with cluster nursing based on the control group. The constipation score, Bristol stool scale score, the short health questionnaire (SF-36) scale score, and the satisfaction of two groups were observed.

Results: The constipation scores of the experimental group were lower than those of the control group, while the Bristol stool scale score, SF-36 score, and satisfaction degree of the experimental group were higher than those of the control group ($p < 0.05$).

Conclusion: Biofeedback therapy combined with cluster nursing has a good intervention effect in perioperative constipation of patients with thoracolumbar fracture, which can reduce the degree of constipation, improve stool traits, improve the quality of life, and improve the satisfaction of patients.

Keywords: thoracolumbar fracture, constipation, perioperative, biofeedback therapy, cluster nursing

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Li Zhu,
Central South University, China
Liang Hui,
Hainan General Hospital, China

***Correspondence:**
Liping Yang
yangliping19831008@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *01 January 2022*
Accepted: *25 January 2022*
Published: *07 March 2022*

Citation:
Luo J, Xie N and Yang L (2022) Observation of the Intervention Effect of Biofeedback Therapy Combined With Cluster Nursing on Perioperative Constipation in Patients With Thoracolumbar Fracture. Front. Surg. 9:847068. doi: 10.3389/fsurg.2022.847068

INTRODUCTION

Thoracolumbar fracture is a kind of spinal injury disease in the transition region from thoracic segment to lumbar segment, this area is prone to stress concentration, which can lead to fracture (1). Thoracolumbar fracture accounts for >60% of spinal injuries. When the body suffers from acute injuries, such as car accidents, falling from a height, or when the elderly have risk factors, such as osteoporosis, it can lead to thoracolumbar fracture (2, 3). Surgical intervention is the most important treatment for the thoracolumbar fracture. However, due to the influence of long-term bed rest and psychological factors, thoracolumbar fracture patients are prone to gastrointestinal

dysfunction during the perioperative period, among which constipation is more common (4). The main clinical manifestations of constipation are strenuous defecation, reduced defecation times, incomplete defecation or dry, and hard stool (5). The incidence of constipation can occur in 50–90% of patients with thoracolumbar fractures, which usually occur within 24 h after fracture and sometimes lasts for more than 7 d (6). Constipation will weaken the gastrointestinal barrier ability of patients, increase the incidence of anorectal diseases, increase hypertension, increase oxygen consumption, and even induce cardiovascular and cerebrovascular diseases in forced defecation. Constipation can also lead to the poor nutritional status of patients, causing patients to have problems, such as irritability and anxiety. In severe cases, it may even affect fracture healing, prolong hospitalization time, and reduce patients' quality of life (7–9). Therefore, perioperative constipation in patients with thoracolumbar fracture requires attention and appropriate treatment.

Biofeedback therapy, with the help of modern physiological scientific instruments, records much imperceptible information of people's psychological and physiological processes, such as electromyography, skin electricity, electroencephalography, then amplifies and converts them into information that people can understand, which can be displayed in the form of vision and hearing with easy recognition (10). When individuals are aware of these physiological or pathological changes, medical personnel train people to consciously control the changes in signal activities and regulate abnormal physiological responses, so as to improve physical functions, which have the effect of disease prevention and disease treatment (11).

Cluster nursing based on evidence-based medicine, according to the principle of "people-oriented" and combined with the actual situation of the hospital and patients, to provide patients with a variety of high-quality nursing services, which can improve the overall quality of nursing, is conducive to improving the prognosis of patients (12). The cluster nursing intervention program is not only the implementation process of nursing methods but also the management process of nursing quality. At the same time, it also reminds medical staff to pay attention to the relationship between a certain measure and prognosis, thus improving the clinical treatment effect (13). A clustering strategy is a set of intervention measures related to a certain disease process, and compared with a single implementation, the intervention effect is better.

In this study, the intervention effect of biofeedback therapy combined with cluster nursing on perioperative constipation in patients with thoracolumbar fracture was observed, in order to improve the living standard of patients.

MATERIALS AND METHODS

Research Object

From June 2019 to June 2020, a total of 482 patients with thoracolumbar fracture treated by surgery in our department were selected. The random number table method was used to divide into experimental group ($n = 241$) and control group ($n = 241$). Inclusion criteria are as follows: (1) patients with a thoracolumbar fracture who have undergone open surgery; (2) the operation was performed by the same doctor; and (3) age $\geq$18 years old. Exclusion criteria are as follows: (1) complicated with serious physical diseases; (2) those who have mental disorders and cannot cooperate with the investigation; (3) patients with original gastrointestinal organic diseases; and (4) there was a history of constipation before surgery.

Research Methods

(1) The control group was given routine constipation care, specifically as follows: (1) Dietary guidance: patients were instructed to eat more coarse grains, vegetables, fruits and other cellulose-rich food, avoid eating spicy and stimulating food, easy to produce intestinal gas, give up smoking and alcohol, drinking water 2–3 L/d; (2) patients who had not defecated for 3 d were given oral laxatives, such as kaiserol and fruit guide tablets, as prescribed by the doctor; (3) manual assistance with defecation was used if all these treatments failed; and (4) patients should actively engage in functional exercises to prevent muscle atrophy and joint stiffness.

(2) The experimental group was given biofeedback therapy combined with cluster nursing based on the control group.

Biofeedback therapy: GAP-08A biofeedback therapy training system (Mida Medical Instrument Co., Ltd.) was used. Before training, explained the relevant precautions to the patients and helped them to know the defecation action and the way to coordinate muscles when defecating correctly. On the day of training, patients were instructed to empty urine and feces, all patients were placed in the lateral position, the proper amount of paraffin oil was used to smear the skin around the anus and biofeedback catheter with balloon, single-channel pressure measuring catheter and anal electrode were inserted into the anus and rectum of patients with a depth of about 9–10 cm, and the catheter was adjusted to the appropriate position according to the pressure curve. The anorectal pressure signal recorded and amplified by the computer can be displayed by the display, so that patients can identify whether their anorectal muscles were moving normally or not. At the same time, with the help of intuitive images and audio images of the biofeedback therapy system, the patients were instructed to understand the movement key points of abdominal exertion and anal relaxation during correct defecation. Constant training and feedback were conducted under real-time monitoring pressure, 40 min/time, 2–3 times a week, 10 treatments were given.

Cluster nursing: The orthopedic medical staff and relevant professionals of the rehabilitation department were convened to discuss together, and the clinically proven effective and recommended elements were incorporated into the clustered nursing plan. Standardized training was conducted for researchers, the concept of cluster nursing was introduced, and the evidence-based medicine basis and implementation approach of each element were understood. The researchers should analyze the current problems and shortcomings and make timely adjustments to the plan according to the specific situation of patients. The specific operations were as follows: (1) Health education: Constipation-related knowledge presentations were carried out to enable patients to understand its hazards and

preventive measures. (2) The regular bowel habit was established, and patients were instructed to drink a glass of honey water or light salt water in the morning on the basis of a regular diet, and to instruct patients to chew and swallow slowly when eating. (3) Defecation-related muscle exercises: Patients were instructed to perform anus contraction exercises, abdominal muscle contraction exercises, abdominal deep breathing exercises, a total of 10–15 min. Patients with more than 6 thoracic fractures may have hypertension, coronary heart disease, and cerebrovascular accidents caused by excessive phytonerve reflexes during abdominal deep breathing exercises. Special attention needs to be paid to these patients clinically. (4) Rectal stimulation induces defecation: Before the operation, the nursing staff instructed the patient to empty the bladder and clean the hands in a six-step wash procedure. The patient took the supine position, and the nursing staff paid attention to the patient's umbilicus, gently and slowly massaged in a clockwise direction for 5–10 min. Then, nurses inserted the fingers into the patient's anus and rotated clockwise in the intestinal wall for 15–20 s, which could be repeated 3–5 times to induce reflex defecation in the rectum. If the above operations were ineffective or the bowel movement was incomplete, the nursing staff could use their fingers to assist the bowel movement. (5) Psychological support: Nurses gave full affirmation to patients, dealt with patients' negative emotions in time, encouraged patients to express their worries and distress, and provided psychological counseling to patients.

Observation Index

All subjects were assessed 1 month after the intervention.

The basic data of patients were collected, such as gender, age, education level, marital status, and thoracolumbar injury severity score (TLISS).

The constipation score method was used to assess the severity of constipation, such as difficulty defecation, the defecation was incomplete, defecation time, and defecation times. The score of each item was grade 4 standard, with 0–3 points according to different degrees. Difficulty defecation: 0 point (none), 1 point (occasionally), 2 points (often), and 3 points (every time); the defecation was incomplete: 0 point (none), 1 point (occasionally), 2 points (obvious), and 3 points (very obvious); defecation time: 0 point (<5 min), 1 point (5–10 min), 2 points (11–16 min), and 3 points (>16 min); and defecation times: 0 point (1–2 days), 1 point (3 days), 2 points (4–5 days), and 3 points (>5 days). The higher the score, the more serious constipation was.

According to the Bristol stool scale, stool traits were divided into 7 types. Type 1: stool showed nut-shaped hard balls; Type 2: stool was lumpy but sausage-like; Type 3: stool was sausage-like with cracks on the surface; Type 4: stool surface was smooth and soft, but it looks like sausage; Type 5: soft lump stool; Type 6: pasty stool; and Type 7: watery stool. Type 1 corresponded to 1 point, type 2 corresponded to 2 points, and so on. The higher the score, the looser the stool was.

The short health questionnaire (SF-36) was used to evaluate patients' quality of life. The questionnaire consisted of 36 items, i.e., 8 dimensions: physical function, physical function, physical pain, general health, energy, social function, emotional function, psychological function, and additional health changes. The total score of each dimension was 100 points, and the final score was the average score of each dimension. The higher the score, the better the quality of life. The Cronbach's α coefficient of SF-36 was 0.871.

The satisfaction questionnaire made by our hospital was used to evaluate patients' satisfaction with nursing work, i.e., treatment effect, working ability, working attitude, and daily guidance. The total score was 100 points, and the survey results were divided into unsatisfied: <60 points, satisfied: 60–80 points, very satisfied: >80 points, total satisfaction = (very satisfied + satisfied)/total cases × 100%. The content validity index of the self-made satisfaction questionnaire was 0.90.

Statistical Methods

SPSS22.0 software was used, and the measurement data were expressed as $\bar{x} \pm s$, and t-test was used for comparison. The counting data were expressed by %, and the χ^2-test was used for comparison. $p < 0.05$, the difference was statistically significant.

RESULTS

Baseline Data of Two Groups

The baseline data of the two groups were balanced and comparable ($p > 0.05$; **Table 1**).

TABLE 1 | Baseline data of two groups (n, %, $\bar{x} \pm s$).

Group		Control group ($n = 241$)	Experimental group ($n = 241$)	χ^2/t-value	P-value
Gender	Male	136 (56.43%)	129 (53.53%)	0.411	0.522
	Female	105 (43.57%)	112 (46.47%)		
Age (years)		49.31 ± 8.62	48.64 ± 8.17	0.875	0.381
Education level	Junior high school and below	87 (36.10%)	84 (34.85%)	0.520	0.771
	Senior high school	93 (38.59%)	89 (36.93%)		
	College degree or above	61 (25.31%)	68 (28.22%)		
Marital status	Married	169 (70.12%)	166 (68.88%)	0.585	0.746
	Be unmarried	42 (17.43%)	48 (19.92%)		
	Divorced or widowed	30 (12.45%)	27 (11.20%)		
TLISS score (point)		6.46 ± 1.31	6.37 ± 1.24	0.774	0.439

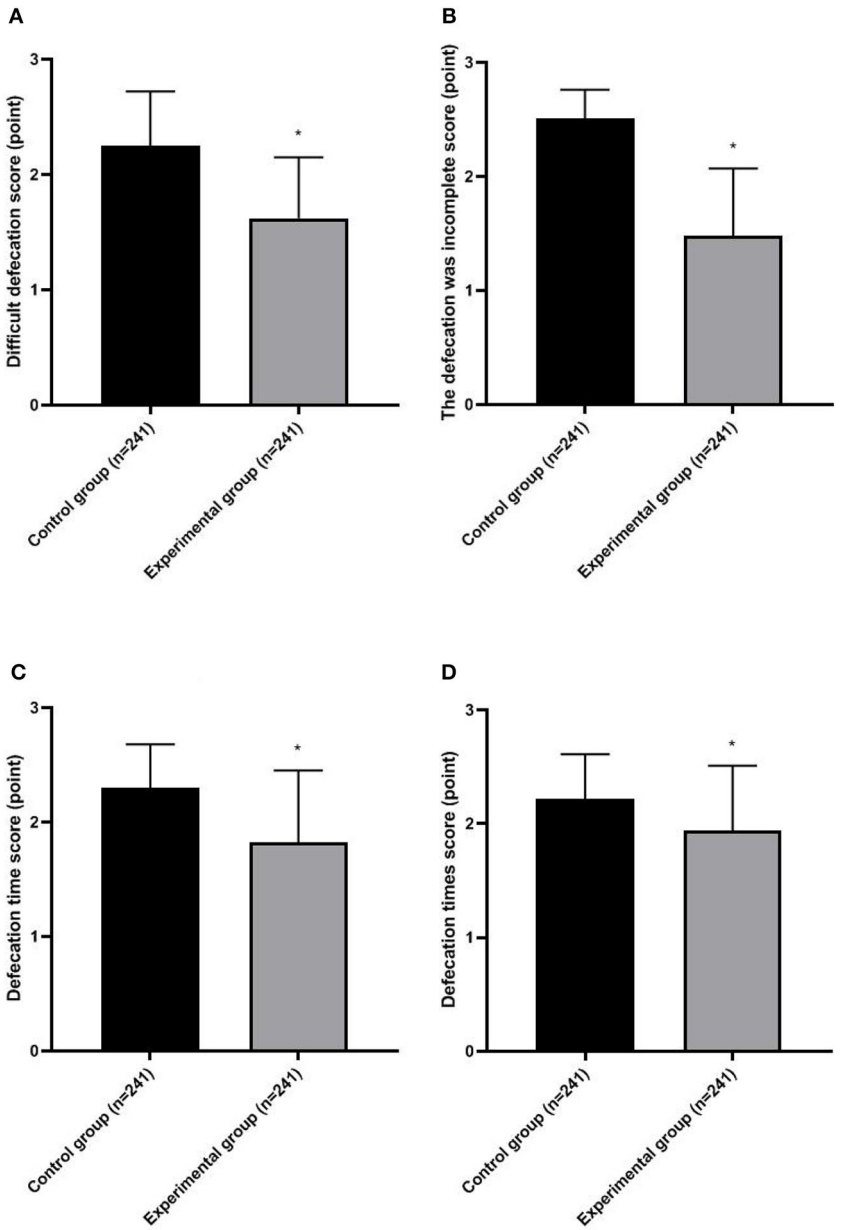


FIGURE 1 | Severity of constipation in two groups. **(A)** Difficulty defecation score; **(B)** The defecation was incomplete score; **(C)** Defecation time score; **(D)** Defecation times score. Compared with the control group, $^{*}p < 0.05$.

The Severity of Constipation in Two Groups

The constipation scores of the experimental group were lower than those of the control group ($p < 0.05$; **Figure 1**).

Stool Traits of Two Groups

The Bristol stool scale of the experimental group was higher than that of the control group ($p < 0.05$; **Figure 2**).

Quality of Life of Two Groups

The SF-36 score of the experimental group was higher than that of the control group ($p < 0.05$; **Figure 3**).

Satisfaction of Two Groups

The satisfaction of the experimental group (90.46%) was higher than that of the control group (83.40%; $p < 0.05$; **Table 2**).

DISCUSSION

Common causes of constipation in patients with a thoracolumbar fracture are as follows: abundant sympathetic nerves are distributed inside and outside the spinal canal, and injuries of thoracolumbar vertebrae can stimulate sympathetic nerves, leading to intestinal peristalsis dysfunction. After the fracture

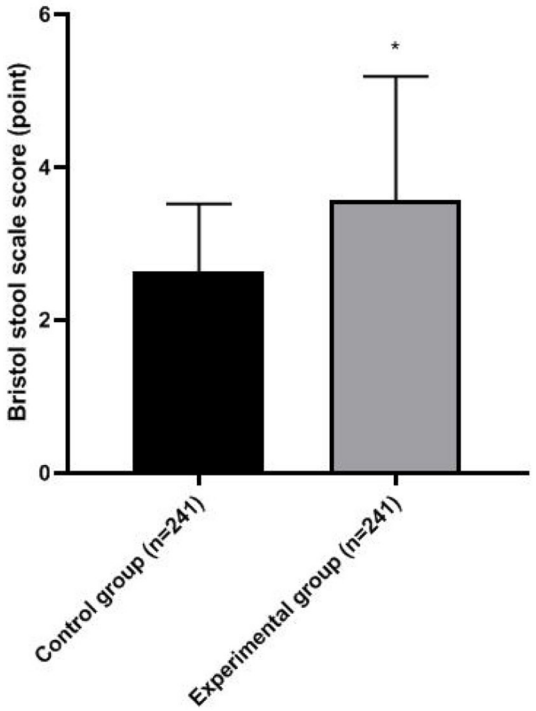


FIGURE 2 | Stool traits of two groups. Compared with the control group, *$p < 0.05$.

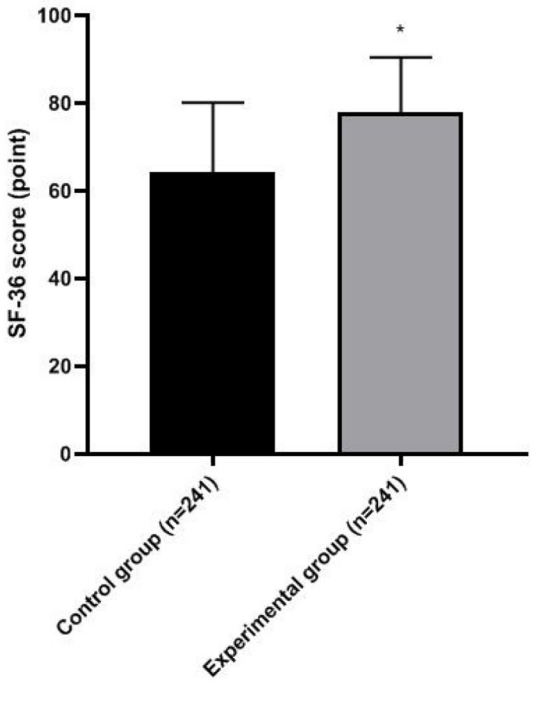


FIGURE 3 | Quality of life of two groups. Compared with the control group, *$p < 0.05$.

surgery, patients need to stay in bed for a long time, spend less time to get out of bed, and eat fewer fruits and vegetables, which leads to the decrease of systemic metabolism, weakened gastrointestinal activity, reduced colonic peristalsis, and excessive retention of colonic contents, which are closely related to constipation. Patients with the fracture are often accompanied by negative emotions, such as anxiety and irritability. Psychological stress may affect gastrointestinal function through the autonomic efferent nerve pathway (14–16). When constipation occurs in patients with thoracolumbar fractures, feces stay in the intestinal cavity for a long time, and wastes and poisons cannot be excreted in time, which will lead to abdominal distension, nausea, and loss of appetite and increase the pain of patients (17). Therefore, it is necessary to take effective clinical nursing measures to solve this problem.

Biofeedback therapy uses receptors to transform physiological activity information that the human body cannot be perceived into intuitive information that can be perceived, so that patients can accurately perceive their own physiological activities, and at the same time, guide patients to exercise, form a normal physiological feedback channel, so as to achieve the purpose of regulating their own physical functions (18). Skardoon's et al. team research has shown (19) that biofeedback therapy has a better therapeutic effect than drug therapy alone, and patients are well-tolerated by this therapy. About 88% of constipation patients can get an improvement of symptoms, and the benefit time of constipation patients can be as long as 44 months. Verma's et al. team reported (20) that biofeedback therapy can effectively improve constipation patients' defecation, reduce anal relaxation pressure during simulated defecation, increase the maximum rectal pressure during simulated defecation, and improve the coordination between intra-abdominal pressure and pelvic floor muscles during defecation, 62% of patients were satisfied with the intervention effect. At present, the routine clinical intervention methods have played a certain role in the constipation nursing of patients with thoracolumbar fracture, but the intervention content is relatively simple, lacking pertinence and comprehensiveness. Cluster nursing is a method to implement various nursing elements on the basis of evidence. According to the actual situation of hospitals and patients, making a series of personalized nursing measures, following the people-oriented principle, and the implementation of optimized nursing intervention can improve the comprehensive nursing effect to the greatest extent (21). This nursing model is patient-centered, with all-around intervention, all contents are in line with evidence-based medicine, and it has the advantages of practicality and integrity (22).

In this study, biofeedback therapy and cluster nursing were integrated and applied to patients with thoracolumbar fracture. The results showed that the constipation scores of the experimental group were lower than those of the control group, while the Bristol stool scale score, SF-36 score, and satisfaction degree of the experimental group were higher than those of the control group. This revealed that biofeedback therapy combined with cluster nursing has a good intervention effect

TABLE 2 | Satisfaction of two groups (*n*, %).

Group	Very satisfied	Satisfied	Dissatisfied	Total satisfaction
Control group ($n = 241$)	117 (48.55%)	84 (39.25%)	40 (16.60%)	201 (83.40%)
Experimental group ($n = 241$)	145 (60.17%)	73 (30.29%)	23 (9.54%)	218 (90.46%)
χ^2-value				5.277
P-value				0.022

in perioperative constipation of patients with thoracolumbar fracture, which can reduce the degree of constipation, improve stool traits, improve the quality of life, and improve the satisfaction of patients. Biofeedback therapy, with the help of intuitive vision and hearing provided by anorectal pressure measuring equipment, enables patients to visually perceive the muscle activity of the anus during defecation. After repeated training, they can understand the changes of figures or sounds corresponding to different defecation movements, learn the methods of relaxing pelvic floor muscles during defecation, adjust the coordination between abdominal and anorectal muscles, correct abnormal physiological activities, and help to improve the score of constipation symptoms of patients (23). We use the biofeedback system mediated by perfusion pressure sensor with a balloon catheter, the operation steps are simple, the pressure changes are sensitive, and the patient has well-tolerance. In cluster nursing, health education can effectively improve the bad living habits of patients and reduce constipation by adjusting diet and exercising properly. Drinking honey water and light salt water in the morning can lubricate the intestinal tract, replenish the body's water, and stimulate intestinal peristalsis, which help to improve defecation function. When eating, eating slowly can prevent patients from swallowing more air, thus reducing abdominal distension and achieving the purpose of defecation. The exercise of defecation-related muscles can strengthen the strength of patients' abdominal and pelvic muscles, while the anal contraction training and abdominal muscle training contraction can increase abdominal pressure, strengthen the contraction of abdominal and anal muscles, thus promoting rectal movement and increasing defecation feeling. Abdominal deep breathing training can massage and pull the internal organs, strengthen gastrointestinal peristalsis, and reduce constipation in patients. Abdominal massage is a kind of mechanical stimulation to the gastrointestinal tract, and signals are transmitted to the brain through the tactile sensation and pressure receptors of skin, and the sympathetic nervous system is reflexively excited, which promotes the downward movement of the contents of descending colon, thereby enhancing the body's metabolism and keeping the digestive system in a good balance. When the finger is inserted into the rectum and rotated clockwise in the intestinal wall, the signal of finger stimulation is equivalent to that of stool to the rectal wall, which is beneficial to stimulate the intestinal tract to empty the stool (24). In addition, the brain-intestine axis is a biochemical signal that constantly adjusts the internal and external environment of the body, and mental factors are closely related to intestinal function (25). Therefore, clustered nursing is a positive effect on reducing the incidence of constipation by giving full recognition to patients with thoracolumbar fracture, building self-confidence, and reducing unhealthy psychology. The combined application of biofeedback therapy and cluster nursing can Gather the strengths and complement the weaknesses, which has a better intervention effect on constipation of patients with thoracolumbar fracture.

CONCLUSION

Through this study, it can be known that biofeedback therapy combined with cluster nursing has a good intervention effect in perioperative constipation of patients with thoracolumbar fracture, which can reduce the degree of constipation, improve stool traits, improve the quality of life, and improve the satisfaction of patients. However, this study is a single-center study with a short observation time, and the results of this study may be interfered by many factors. Further multi-center studies and extended study time are needed to clarify the conclusion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Suining Central Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JL conducts research design and writes papers. NX evaluates test results and conducts data statistics. LY guides the entire research. All authors contributed to this research, contributed to the article, and approved the submitted version.

REFERENCES

1. Prajapati HP, Kumar R. Thoracolumbar fracture classification: evolution, merits, demerits, updates, and concept of stability. *Br J Neurosurg.* (2021) 35:92–7. doi: 10.1080/02688697.2020.1777256
2. Rahimizadeh A, Asgari N, Rahimizadeh A. Complete thoracolumbar fracture-dislocation with intact neurologic function: explanation of a novel cord saving mechanism. *J Spinal Cord Med.* (2018) 41:367–76. doi: 10.1080/10790268.2017.1336300
3. Wei Y, Tian W, Zhang GL, Lv YW, Cui GY. Thoracolumbar kyphosis is associated with compressive vertebral fracture in postmenopausal women. *Osteoporos Int.* (2017) 28:1925–9. doi: 10.1007/s00198-017-3971-x
4. Jing D, Jia L. Assessment of patients' psychological state and self-efficacy associated with postoperative constipation after thoracolumbar fracture surgery. *J Int Med Res.* (2019) 47:4215–24. doi: 10.1177/0300060519859732
5. Liu X, Wang Y, Ye Q, Sun Y, Yang J, Dai Y, et al. External treatment of traditional Chinese medicine for constipation after thoracolumbar compression fractures: a protocol for systematic review and meta-analysis. *Medicine.* (2021) 100:e27110. doi: 10.1097/MD.0000000000027110
6. Trads M, Håkonson SJ, Pedersen PU. Validation of the Danish version of the constipation risk assessment scale (CRAS). *Int J Orthop Trauma Nurs.* (2017) 27:7–15. doi: 10.1016/j.ijotn.2016.11.004
7. Yamada M, Sekine M, Tatsuse T, Fujimura Y. Lifestyle, psychological stress, and incidence of adolescent constipation: results from the Toyama birth cohort study. *BMC Public Health.* (2021) 21:47. doi: 10.1186/s12889-020-10044-5
8. Ranasinghe N, Devanarayana NM, Benninga MA, van Dijk M, Rajindrajith S. Psychological maladjustment and quality of life in adolescents with constipation. *Arch Dis Child.* (2017) 102:268–73. doi: 10.1136/archdischild-2016-310694
9. Mearin F, Ciriza C, Mínguez M, Rey E, Mascort JJ, Peña E, et al. [Irritable bowel syndrome with constipation and functional constipation in adults: treatment (Part 2 of 2)]. *Aten Primaria.* (2017) 49:177–94. doi: 10.1016/j.aprim.2017.01.003
10. Yao G, Kang L, Li C, Chen S, Wang Q, Yang J, et al. A self-powered implantable and bioresorbable electrostimulation device for biofeedback bone fracture healing. *Proc Natl Acad Sci USA.* (2021) 118:e2100772118. doi: 10.1073/pnas.2100772118
11. Goessl VC, Curtiss JE, Hofmann SG. The effect of heart rate variability biofeedback training on stress and anxiety: a meta-analysis. *Psychol Med.* (2017) 47:2578–86. doi: 10.1017/S0033291717001003
12. Liu Y, Fu M, Zhou Q, Tian M, Zhang X, Wang Z. The application of patient-centered care bundle significantly reduces incidence of perioperative respiratory complications in hip fracture patients aged 80 and over. *Geriatr Nurs.* (2021) 43:213–8. doi: 10.1016/j.gerinurse.2021.11.014
13. Curtis K, Moules P, McKenzie J, Weidl L, Selak T, Binks S, et al. Development of an early activation hip fracture care bundle and implementation strategy to improve adherence to the national hip fracture clinical care standard. *J Multidiscip Healthc.* (2021) 14:2891–903. doi: 10.2147/JMDH.S323678
14. Yin H, Wang G, Wang J, Ma Y, Wu M, Qiu S, et al. Prevalence and risk factor analysis of constipation after thoracolumbar vertebral compression fractures. *Int J Gen Med.* (2021) 14:4117–23. doi: 10.2147/IJGM.S320953
15. Dzierzanowski T, Ciałkowska-Rysz A. The occurrence and risk factors of constipation in inpatient palliative care unit patients vs. nursing home residents. *Prz Gastroenterol.* (2018) 13:299–304. doi: 10.5114/pg.2018.79809
16. Tan S, Hou Y, Cui C, Chen X, Li W. Real-time monitoring of biofoulants in a membrane bioreactor during saline wastewater treatment for anti-fouling strategies. *Bioresour Technol.* (2017) 224:183–7. doi: 10.1016/j.biortech.2016.11.021
17. Trads M, Pedersen PU. Constipation and defecation pattern the first 30 days after hip fracture. *Int J Nurs Pract.* (2015) 21:598–604. doi: 10.1111/ijn.12312
18. Narayanan SP, Bharucha AE. A practical guide to biofeedback therapy for pelvic floor disorders. *Curr Gastroenterol Rep.* (2019) 21:21. doi: 10.1007/s11894-019-0688-3
19. Skardoon GR, Khera AJ, Emmanuel AV, Burgell RE. Review article: dyssynergic defaecation and biofeedback therapy in the pathophysiology and management of functional constipation. *Aliment Pharmacol Ther.* (2017) 46:410–23. doi: 10.1111/apt.14174
20. Verma A, Misra A, Ghoshal UC. Effect of biofeedback therapy on anorectal physiological parameters among patients with fecal evacuation disorder. *Indian J Gastroenterol.* (2017) 36:99–104. doi: 10.1007/s12664-017-0731-y
21. Chuan A, Zhao L, Tillekeratne N, Alani S, Middleton PM, Harris IA, et al. The effect of a multidisciplinary care bundle on the incidence of delirium after hip fracture surgery: a quality improvement study. *Anaesthesia.* (2020) 75:63–71. doi: 10.1111/anae.14840
22. Trads M, Deutch SR, Pedersen PU. Supporting patients in reducing postoperative constipation: fundamental nursing care - a quasi-experimental study. *Scand J Caring Sci.* (2018) 32:824–32. doi: 10.1111/scs.12513
23. Rao SSC, Valestin JA, Xiang X, Hamdy S, Bradley CS, Zimmerman MB. Home-based versus office-based biofeedback therapy for constipation with dyssynergic defecation: a randomised controlled trial. *Lancet Gastroenterol Hepatol.* (2018) 3:768–77. doi: 10.1016/S2468-1253(18)30266-8
24. Zhao X, Meng J, Dai J, Yin ZT. Effect of biofeedback combined with high-quality nursing in treatment of functional constipation. *World J Clin Cases.* (2021) 9:784–91. doi: 10.12998/wjcc.v9.i4.784
25. Black CJ, Thakur ER, Houghton LA, Quigley EMM, Moayyedi P, Ford AC. Efficacy of psychological therapies for irritable bowel syndrome: systematic review and network meta-analysis. *Gut.* (2020) 69:1441–51. doi: 10.1136/gutjnl-2020-321191a

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Luo, Xie and Yang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 09 March 2022
doi: 10.3389/fsurg.2022.846470

Correlation of Serum CysC, IMA, and LP-PLA2 Levels With Type 2 Diabetes Mellitus Patients With Lower Extremity Atherosclerotic Occlusive Disease

Fen Feng[1], *Yong Chen*[2], *Gang Wang*[3], *Ping Huang*[3], *Qiaolin Zhu*[3] *and Bin Zhou*[3]*

[1] School of Pharmacy, Shaoyang University, Shaoyang, China, [2] Department of Oncology and Hematology, The Central Hospital of Shaoyang, Shaoyang, China, [3] Department of Endocrinology, The Central Hospital of Shaoyang, Shaoyang, China

Objective: To investigate the serum level of cystatin C (CysC), ischemia-modified albumin (IMA), and lipoprotein-associated phospholipase A2 (LP-PLA2) in patients with type 2 diabetes mellitus (T2DM) and with lower extremity atherosclerotic occlusive disease (LEASOD) and their correlation.

Methods: From March 2017 to December 2019, 110 patients with T2DM with LEASOD, who were treated in our hospital, were selected as the observation group. One hundred ten healthy persons who received medical examination in our hospital during the same period were selected as the control group. Serum CysC, IMA, LP-PLA2, and ankle-brachial index (ABI) were detected in each group. According to the ABI index, the observation group was divided into three subgroups, namely, the mild group ($n = 45$), the moderate group ($n = 42$), and the severe group ($n = 23$). Pearson correlation analysis was used to analyze the relationship between serum CysC, IMA, and LP-PLA2 levels in patients with T2DM with LEASOD and their condition. The receiver operator characteristic (ROC) curve was used to analyze the diagnostic value of serum CysC, IMA, and LP-PLA2 levels in patients with T2DM with LEASOD.

Results: The serum levels of CysC, IMA, and LP-PLA2 in the observation group were higher than those in the control group ($p < 0.05$). The serum levels of CysC, IMA, and LP-PLA2 in the severe and the moderate group were higher than those in the mild group, and the serum levels of CysC, IMA, and LP-PLA2 in the severe group were higher than those in the moderate group ($p < 0.05$). Pearson correlation analysis showed that CysC, IMA, and LP-PLA2 levels were all negatively correlated with ABI ($r = -0.802$, $r = -0.757$, $r = -0.764$, $p < 0.001$). The ROC curve results showed that the area under the curve (AUC) of serum CysC in the diagnosis of T2DM with LEASOD was 0.806, and the best cut-off value was 1.74 mg/L. The AUC of serum IMA for diagnosis of T2DM with LEASOD was 0.772, and the best cut-off value was 92.58 g/L. The AUC of serum LP-PLA2 in the diagnosis of T2DM with LEASOD was 0.781, and the best cut-off value was 544.86 ng/L. The AUC of the three combined diagnoses of T2DM with LEASOD was 0.863.

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Yang Liu,
The First Medical Center of Chinese PLA General Hospital, China
Wenjie Song,
Fourth Military Medical University, China

***Correspondence:**
Bin Zhou
zhoubin790921@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *31 December 2021*
Accepted: *21 January 2022*
Published: *09 March 2022*

Citation:
Feng F, Chen Y, Wang G, Huang P, Zhu Q and Zhou B (2022) Correlation of Serum CysC, IMA, and LP-PLA2 Levels With Type 2 Diabetes Mellitus Patients With Lower Extremity Atherosclerotic Occlusive Disease. Front. Surg. 9:846470. doi: 10.3389/fsurg.2022.846470

Conclusion: Serum levels of CysC, IMA, and LP-PLA2 were increased in patients with T2DM with LEASOD. Serum CysC, IMA, and LP-PLA2 are closely related to the severity of the disease. The higher the serum levels of CysC, IMA, and LP-PLA2, the more serious the degree of lower extremity arteriosclerosis occlusion, which can be used as an important serum marker to monitor the severity of T2DM with LEASOD. The combined detection of serum CysC, IMA, and LP-PLA2 has good diagnostic value for patients with T2DM with LEASOD.

Keywords: type 2 diabetes mellitus, lower extremity atherosclerotic occlusive disease, cystatin C, ischemia modified albumin, lipoprotein phospholipase A2, correlation

INTRODUCTION

Diabetes is a group of metabolic diseases caused by decreased insulin secretion, insensitivity to insulin action of the body, or both, with a chronic increase of blood glucose level and multiple chronic complications as the main clinical features (1, 2). Type 2 diabetes mellitus (T2DM) mainly occurs in middle-aged and older people. In recent years, the incidence of T2DM shows a rising trend. The T2DM can cause microvascular and peripheral vascular lesions, leading to lower extremity atherosclerotic occlusive disease (LEASOD), limb ischemia and intermittent claudication, and even lower extremity ulcer, gangrene, or amputation in the severe cases. LEASOD is one of the most common peripheral arteriosclerosis occlusive diseases in the current society, and it is an important part of systemic arteriosclerosis disease. Its pathological changes are a group of chronic ischemic diseases that cause arterial stenosis or occlusion, such as thickening of the arterial intima, calcification, and secondary thrombosis (3, 4). The incidence of LEASOD is increasing year by year, and 70–80% of patients have no clinical symptoms. Some early manifestations, such as fatigue after exercise and soreness of the lower limbs, are often mistaken by people as a presentation of old age and/or fatigue. Some patients are insensitive to pain due to neuropathy caused by diabetes, and most patients have intermittent claudication, resting pain, ischemic gangrene, and other symptoms when it is difficult to treat, thus, seriously affecting the physical and mental health and quality of life of patients (5, 6).

Cystatin C (CysC) is a cysteine protease inhibitor that is only cleared by a glomerular filtration and almost entirely reabsorbed by the renal tubules. The CysC can regulate the development of inflammation mediated by inflammatory factors and plays an important role in the occurrence and development of atherosclerosis (7, 8). Ischemia modified albumin (IMA) is closely related to coronary artery disease and can be used as an ideal marker of ischemic heart disease (9, 10). Lipoprotein-associated phospholipase A2 (LP-PLA2), a phospholipase, can enter the atherosclerotic plaque under the intima of blood vessels by binding to a low-density lipoprotein, serving as a vascular-specific inflammatory marker (11, 12). The CysC, IMA, and LP-PLA2 are all closely related to vascular lesions and arteriosclerosis. At present, although the technology for diagnosis and treatment of T2DM with LEASOD has become increasingly mature, as a chronic disease requiring continuous medication, it is still very important to seek simple and fast serological indicators to dynamically track the progression of the disease. In this study, the serum levels of CysC, IMA, and LP-PLA2 in patients with T2DM with LEASOD were measured, and the correlation with the severity of the disease was analyzed to make an effective assessment of the degree of lesions in these patients with this index and to provide the basis for clinical diagnosis and treatment.

MATERIALS AND METHODS

Patients

A total of 110 patients with T2DM with LEASOD, who were treated in our hospital from March 2017 to December 2019, were selected as the observation group. The inclusion criteria were as follows: all patients met the diagnostic guidelines for T2DM and lower extremity arteriosclerosis obliterans (13, 14); all patients had a medical history of T2DM with symptoms such as limb pain, intermittent claudication or ischemic ulcer, and gangrene in the lower limbs, and LEASOD was confirmed through color Doppler ultrasound, CT angiography, and other imageological tests to detect the corresponding artery stenosis or occlusion; and all patients should have complete clinical data. The exclusion criteria were as follows: patients who had acute complications of T2DM; patients with hemorrhagic diseases or disorders of the coagulation system; patients with cerebrovascular diseases; patients with severe cardiopulmonary liver and kidney failure; patients with infectious or autoimmune diseases; patients with malignant tumor/s; and patients with alcohol or drug addiction. In the same period, 110 healthy patients, who received physical examination in our hospital, were selected as the control group. There was no significant difference in general data of gender and age between the two groups ($p > 0.05$), indicating that they were comparable as shown in **Table 1**.

Research Methods

Ten milliliters of fasting blood was collected from the patients in the morning. The blood was allowed to stand at room temperature for 30 min before being centrifuged at 3,500 r/min for 15 min. Afterwards, supernatant was taken and stored in a 2-ml dry and clean serum cold storage tube and stored in −70°C refrigerator for testing. Serum CysC and LP-PLA2 levels were determined by ELISA, and the serum IMA level was determined by the free cobalt colorimetric method.

TABLE 1 | Comparison of general data between the two groups.

Group	Gender		Age (years)	BMI (kg/m^2)
	Male	Female		
Control group ($n = 110$)	61	49	58.69 ± 3.57	23.38 ± 4.65
Observation group ($n = 110$)	59	51	58.23 ± 3.52	24.19 ± 3.58
t/χ^2	0.073		0.962	1.448
P	0.787		0.337	0.149

Relevant test kits were purchased from Today's Chemical Technology (Shanghai) Co., Ltd, which included Ankle brachial index (ABI) measuring instrument and a Doppler blood flow detector EMS-9PB (Shanghai Sanwei Medical Equipment Co., Ltd.).

After a quiet rest for 5 min, the patient was placed in the supine position. The Doppler probe was placed at the brachial artery on the right elbow to obtain the earliest signal. The left upper arm was then measured with the same measuring instrument, and the side with a high value of both arms was taken as the brachial artery systolic blood pressure. The Doppler probe obtained the earliest signal from the right dorsal artery of the foot (or posterior tibial artery) and was then used as the same meter to measure the left foot. The side, with the high value of the left and right feet, was taken as the ankle systolic blood pressure. With the ABI index as the index of the severity of arteriosclerosis obliterans in the lower extremities (ABI = ankle systolic pressure/brachial systolic pressure), lower extremity ischemia could be diagnosed if ABI $\leq$ 0.90. A lower ABI index indicated that the severity of LEASOD was more serious (15).

According to ABI index, the observation groups were divided into the following three subgroups: mild group ($n = 45$): $0.80 \leq$ ABI ≤ 0.90, moderate group ($n = 42$): $0.60 \leq$ ABI < 0.80, and severe group ($n = 23$): ABI < 0.60.

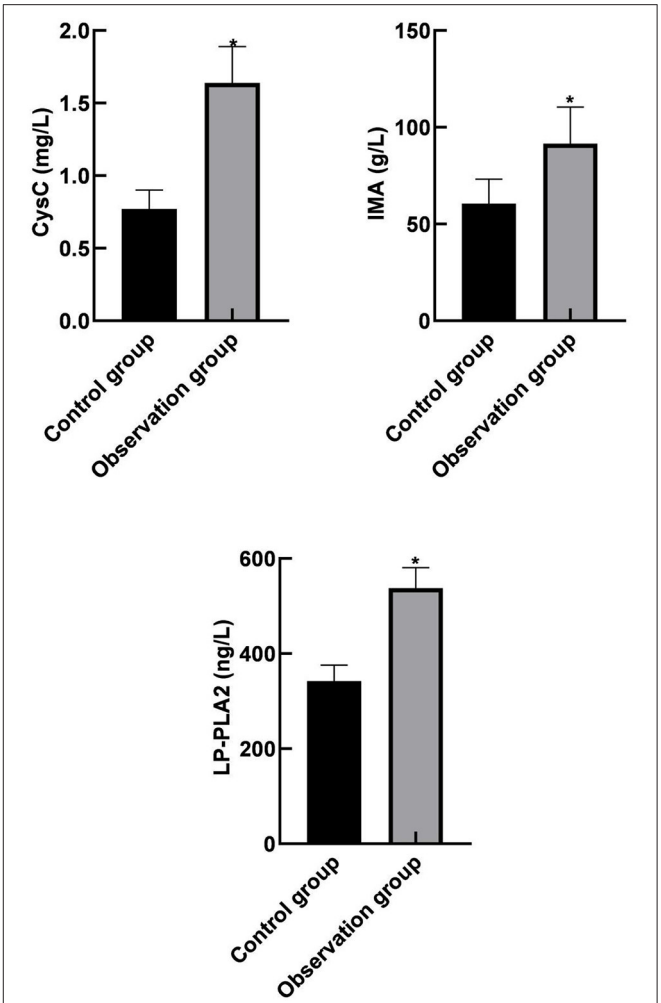


FIGURE 1 | Comparison of serum cystatin C (CysC), ischemia modified albumin (IMA), and lipoprotein phospholipase A2 (LP-PLA2) levels between the two groups. Compared with the control group, $^*p < 0.05$.

Statistical Methods

All data were processed with SPSS 22.0 statistical software, and GraphPad prism 8 was used to make statistical graphs. The *t*-test was used for pairwise comparison of measurement data between groups. Pearson correlation analysis was used for correlation analysis. The ROC curve was used to analyze the diagnostic value of serum CysC, IMA, and LP-PLA2 levels in patients with T2DM with LEASOD. The difference was considered to be statistically significant if $p < 0.05$.

RESULTS

Comparison of Serum CysC, IMA, and LP-PLA2 Levels Between the Two Groups

Serum CysC, IMA, and LP-PLA2 levels in the observation group were higher than those in the control group ($p < 0.05$) as shown in **Figure 1**.

Comparison of Serum CysC, IMA, and LP-PLA2 Levels Among Different Subgroups in the Observation Group

Serum CysC, IMA, and LP-PLA2 levels in the severe and the moderate group were higher than those in the mild group. In addition, serum CysC, IMA, and LP-PLA2 levels in the severe group were higher than those in the moderate group ($p < 0.05$) as shown in **Figure 2**.

Correlation Between Serum CysC, IMA, and LP-PLA2 Levels and the Severity of the Disease in the Observation Group

Pearson correlation analysis showed that serum CysC, IMA, and LP-PLA2 levels were negatively correlated with the ABI index ($r = -0.802$, $r = -0.757$, $r = -0.764$, $p < 0.001$). Therefore, they were all positively correlated with the severity of the disease as shown in **Figure 3**.

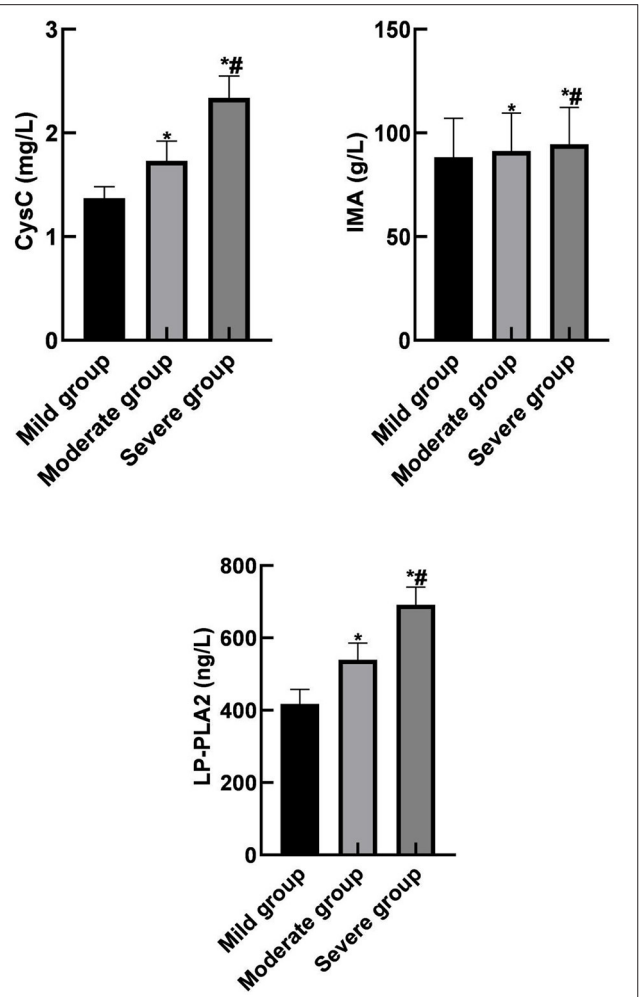


FIGURE 2 | Comparison of serum CysC, IMA, and LP-PLA2 levels among different subgroups in the observation group. Compared with the mild group, $^{*}p < 0.05$; compared with the moderate group, $^{\#}p < 0.05$.

Analysis of the Diagnostic Value of Serum CysC, IMA, and LP-PLA2 Levels in Patients

Receiver operator characteristic (ROC) curve analysis showed that the area under the curve (AUC) of serum CysC in the diagnosis of T2DM with LEASOD was 0.806 (95% CI: 0.720–0.891). When the best cut-off value was 1.74 mg/L and the Youden index was 0.446, the sensitivity was 87.9% and the specificity was 66.7%. The AUC of serum IMA in the diagnosis of patients with T2DM with LEASOD was 0.772 (95% CI: 0.678–0.866). When the best cut-off value was 92.58 g/L and the Youden index was 0.503, the sensitivity was 69.7% and the specificity was 80.6%. The AUC of serum LP-PLA2 for the diagnosis of T2DM with LEASOD was 0.781 (95% CI: 0.689–0.872). When the best cut-off value was 544.86 ng/L and the Youden index was 0.473, the sensitivity was 72.7% and the specificity was 74.6%. The AUC of the three combined diagnoses of patients with T2DM with LEASOD was 0.863 (95%CI: 0.791–0.935). When the Youden index was 0.580, the sensitivity was 87.9% and the specificity was 70.1% (**Table 2**; **Figure 4**).

DISCUSSION

In recent years, the prevalence of diabetes has risen sharply and has become one of the important chronic diseases affecting human health with patients with T2DM in the majority (16–18). LEASOD is one of the serious complications of diabetes. It is caused by the influence of a long-term hyperglycemia on the arterial wall, leading to atherosclerosis embolism in the middle layer of the artery, obstruction of lower limb microcirculation, blockage of peripheral nerves, and the formation of diabetic lower limb vascular lesions. It leads to chronic ischemia of and organic lesions of the lower limb. If not treated in time, irreversible damage may eventually be life threatening and may result in amputation in severe cases (19, 20). Therefore, early diagnosis and timely understanding of the condition of the patient is extremely important. The ABI index is characteristically non-invasive, simple, and highly specific. The systolic blood pressure of the ankle in normal people is basically equal to or slightly greater than the systolic blood pressure of the brachial artery. In patients with LEASOD, due to the stenosis or occlusion of the artery of the lower limb, the blood perfusion of the distal artery is reduced, and the arterial pressure of the ankle is decreased, which is roughly proportional to the severity of the disease. Clinically, ABI is commonly used to detect the peripheral artery disease of lower limbs (21, 22). In this study, the severity of LEASOD disease was assessed by ABI index.

Serum crystatin C (CysC), a secretory protein with a small molecular weight, is a cysteine protease inhibitor which is mainly distributed in the extracellular fluid. The highest concentration of CysC can be found in the cerebrospinal fluid and the lowest is in urine (23, 24). Serum CysC can freely pass through the glomerular filtration membrane and degrade after being mostly reabsorbed by the proximal renal tubules. It is not secreted by the renal tubules; hence, the serum concentration is basically determined by glomerular filtration, which is a very ideal endogenous marker reflecting the glomerular filtration rate. In recent years, it was found that CysC is closely connected with cerebrovascular disease, may be involved in many pathophysiological processes of the cardiovascular system, can be involved in inflammation and the extracellular matrix reconstruction process, and is closely related to the development of the occurrence of arterial sclerosis. Some scholars believe that the loss of CysC and the imbalance of proteolytic enzymes and their inhibitors in the vascular wall may be one of the pathogenesis of atherosclerosis (25, 26).

The results of this study showed that serum CysC level in the observation group was significantly higher than that in the control group and that there was a significant negative correlation between CysC level and ABI index. These results suggested that CysC might be involved in the occurrence of T2DM with LEASOD. In addition, the higher the level of CysC, the more serious the LEASOD condition would be, which was positively correlated with the severity of the disease. This is

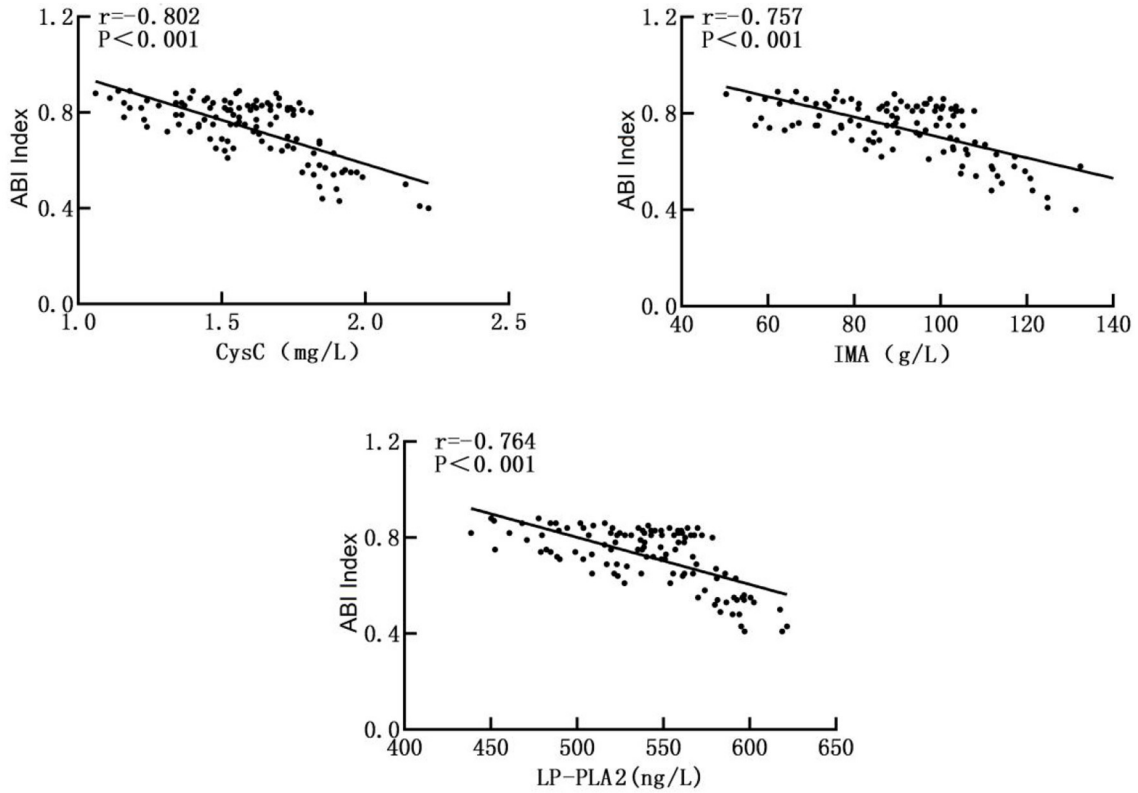


FIGURE 3 | Correlation between serum CysC, IMA, and LP-PLA2 levels and the severity of the disease in the observation group.

TABLE 2 | Analysis of the diagnostic value of serum cystatin C (CysC), ischemia modified albumin (IMA), and lipoprotein phospholipase A2 (LP-PLA2) levels in patients.

Predictive indexes	AUC	95%CI	Youden index	Sensitivity (%)	Specificity (%)	Cut-off value
CysC	0.806	0.720–0.891	0.446	87.9	66.7	1.74 mg/L
IMA	0.772	0.678–0.866	0.503	69.7	80.6	92.58 g/L
LP-PLA2	0.781	0.689–0.872	0.473	72.7	74.6	544.86 ng/L
Combined predictive	0.863	0.791–0.935	0.580	87.9	70.1	–

due to how CysC is a low-molecular-weight basic non-glycated protein, the level of which is determined by glomerular filtration rate, which can mediate the inflammatory response and lead to arteriosclerosis through the regulation of inflammatory factors and cytokines. In addition, CysC can inhibit the oxidative low-density lipoprotein-induced apoptosis of the vascular smooth muscle cells to stabilize plaques, thereby causing arteriosclerosis obliteration of the lower limbs. Therefore, CysC can be used as a serum marker for monitoring the severity of LEASOD.

At present, IMA is an ideal marker of ischemia, which has been widely studied mainly in acute coronary syndrome, pulmonary embolism, and cerebrovascular ischemic lesions (27, 28). IMA is an isomer converted into the n-terminus of plasma albumin by exposure to ischemia and oxidative stress, which is caused by changes in the amino terminus sequence of plasma albumin that reduce the ability of metal-binding to the n-terminus of human albumin. In some clinical and experimental studies to date, the elevation of IMA is mainly dependent on oxidative stress after acute ischemia. IMA is elevated during organ ischemic necrosis and generally returns to normal within a few hours after the reperfusion has resumed (29, 30). Therefore, serum IMA levels can be used as important reference indicators when predicting ischemia of atherosclerotic lesions, which is partially consistent with the results of this study. It indicated that IMA was involved in the occurrence of T2DM combined with LEASOD, which was in a significant negative correlation with the ABI index. The higher the level of IMA was, the more serious the condition of LEASOD was, which was in a positive correlation with the severity of the disease. Therefore, IMA can be used as a serum marker for monitoring the severity of LEASOD.

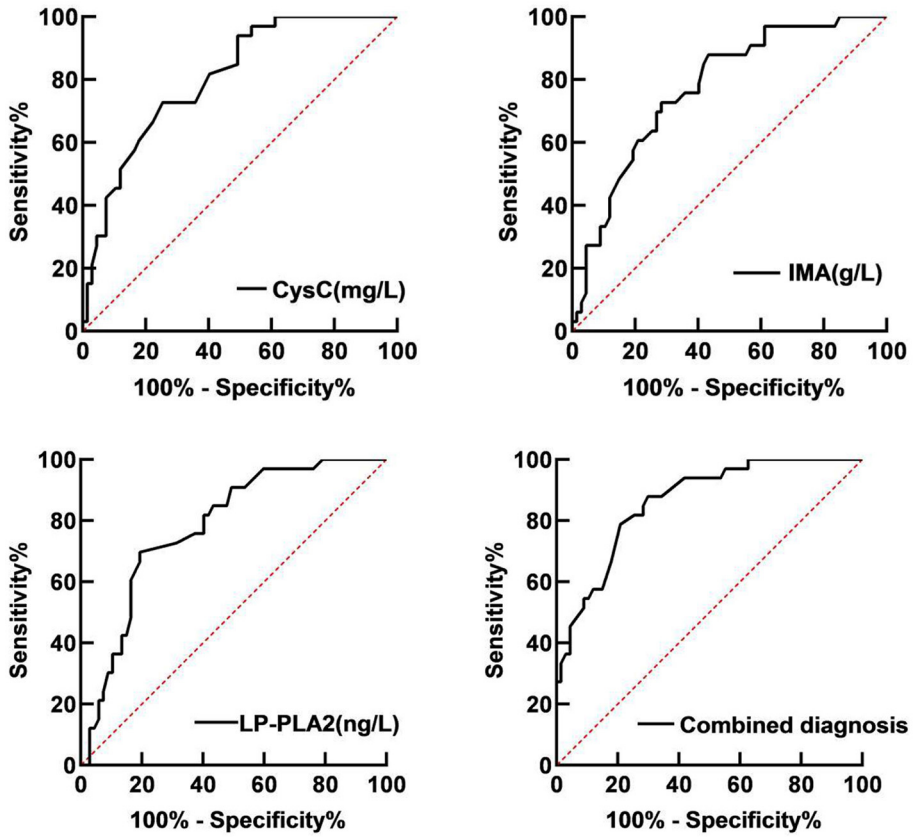


FIGURE 4 | Receiver operator characteristic (ROC) curve of serum CysC, IMA, and LP-PLA2 for the diagnosis of patients with T2DM with LEASOD.

Lipoprotein phospholipase A2 (LP-PLA2) is a new vascular-specific inflammatory marker, also known as plasma platelet activator acetylhydrolase, which is mainly secreted by macrophages and lymphocytes in atherosclerotic plaques and regulated by inflammatory mediators (31, 32). The LP-PLA2 in plasma mainly existed in the form of lipoprotein particle binding, of which about 70–80% is bound to a low-density lipoprotein cholesterol to promote the occurrence of inflammatory reaction, while the remaining 20–30% of LP-PLA2 is bound to a high-density lipoprotein cholesterol or a very low-density lipoprotein cholesterol to play an important role in the anti-oxidation and anti-atherosclerosis effects (33, 34). A prospective study from Sweden found a 4.4% incidence of peripheral artery disease in 5,500 middle-aged men, without a diagnosis of peripheral artery disease and with a mean follow-up of 23.4 years. In addition, it was found that plasma LP-PLA2 activity and quality are risk markers for peripheral vascular disease (35). The results of this study showed that LP-PLA2 was highly expressed in patients with T2DM with LEASOD, and it was significantly and negatively correlated with the ABI index, suggesting that the higher the level of LP-PLA2 was, the more serious the condition of LEASOD was, and it was positively correlated with the severity of the disease. This was due to the fact that LP-PLA2 is a serine esterase that promotes the secretion of inflammatory factors and produces lipid proinflammatory substances, which act on the inner epidermis to dysfunction of the vascular wall, leading to atherosclerosis. Therefore, LP-PLA2 can be used as a serum marker for monitoring the severity of LEASOD.

The ROC curve analysis of this study showed that the AUC of serum CysC, IMA, and LP-PLA2 in patients with T2DM with LEASOD were 0.806, 0.772, and 0.781, respectively, and the AUC of patients with a combined diagnosis of the three was 0.863. It shows that the diagnostic value of the combined diagnosis of serum CysC, IMA, and LP-PLA2 is significantly higher than that of a single diagnosis and has a better diagnostic value.

CONCLUSION

The serum levels of CysC, IMA, and LP-PLA2 were increased in patients with T2DM with LEASOD. Serum CysC, IMA, and LP-PLA2 are closely related to the severity of the disease. The higher the serum levels of CysC, IMA, and LP-PLA2, the more serious the degree of lower extremity arteriosclerosis occlusion, which can be used as an important serum marker to monitor the severity of T2DM with LEASOD. The combined detection of serum CysC, IMA, and LP-PLA2 has good diagnostic value for patients with T2DM with LEASOD.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Shaoyang Central Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FF is responsible for the writing of the article. YC is responsible for the design of the study. GW is responsible for the inclusion of cases. PH is responsible for the evaluation of the results. QZ is responsible for data recording and statistics. BZ is the instructor of the entire study. All authors contributed to the article and approved the submitted version.

FUNDING

This study was funded by the Hunan Provincial Health Commission Project Fund (202203063365).

REFERENCES

1. Sen S, Chakraborty R. Treatment and diagnosis of diabetes mellitus and its complication: advanced approaches. *Mini Rev Med Chem.* (2015) 15:1132–3. doi: 10.2174/1389557515141510061546l6
2. Dos S M M, Castellsague M, Perrenoud L, Coppin G, Gastaldi G. Diabetes mellitus: impact of affects on self-management skills. *Rev Med Suisse.* (2020) 16:1206–9.
3. Shen C, Li W. Interpretation and consideration of the Society for Vascular Surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities management of asymptomatic disease and claudication. *Chin J Surg.* (2016) 54:81–3. doi: 10.3760/cma.j.issn.0529-5815.2016.02.001
4. Cai H, Fu F, Wang Y, Li J, Cao J, Huang M, et al. Correlation between the stenosis degree of aorto-iliac artery and superior mesenteric artery in patients with lower extremity atherosclerotic occlusive disease by CT angiography. *Chin Crit Care Med.* (2018) 30:635–9. doi: 10.3760/cma.j.issn.2095-4352.2018.07.004
5. Dionyssiou-Asteriou A, Papastamatiou M, Vatalas I, Bastounis E. Serum Lp(a) lipoprotein levels in patients with atherosclerotic occlusive disease of the lower extremities. *Eur J Vasc Endovasc Surg.* (2000) 20:57–60. doi: 10.1053/ejvs.2000.1100
6. Wu WW, Jiang XY, Liu CW Li YJ, Zeng R. Lower extremity arterial occlusive disease as a rare complication of Crohn's disease. *Chin Med Sci J.* (2009) 24:167–71. doi: 10.1016/s1001-9294(09)60083-3
7. Chung YK, Lee YJ, Kim KW, Cho RK, Chung SM, Moon JS, et al. Serum cystatin C is associated with subclinical atherosclerosis in patients with type 2 diabetes: a retrospective study. *Diab Vasc Dis Res.* (2018) 15:24–30. doi: 10.1177/1479164117738156
8. Ferraro S, Marano G, Biganzoli EM, Boracchi P, Bongo AS. Prognostic value of cystatin C in acute coronary syndromes: enhancer of atherosclerosis and promising therapeutic target. *Clin Chem Lab Med.* (2011) 49:1397–404. doi: 10.1515/CCLM.2011.607
9. Ma S G, Wei C L, Hong B, Yu WN. Ischemia-modified albumin in type 2 diabetic patients with and without peripheral arterial disease. *Clinics.* (2011) 66:1677–80. doi: 10.1590/s1807-59322011001000003
10. Zhong Y, Wang N, Xu H, Hou X, Xu P, Zhou Z. Ischemia-modified albumin in stable coronary atherosclerotic heart disease: clinical diagnosis and risk stratification. *Coron Artery Dis.* (2012) 23:538–41. doi: 10.1097/MCA.0b013e328358a5e9
11. Wang C, Fang X, Hua Y, Liu Y, Zhang Z, Gu X, et al. Lipoprotein-associated phospholipase A2 and risk of carotid atherosclerosis and cardiovascular events in community-based older adults in China. *Angiology.* (2018) 69:49–58. doi: 10.1177/0003319717704554
12. Yamamoto K, Isogai Y, Sato H, Taketomi Y, Murakami M. Secreted phospholipase A2, lipoprotein hydrolysis, and atherosclerosis: integration with lipidomics. *Anal Bioanal Chem.* (2011) 400:1829–42. doi: 10.1007/s00216-011-4864-z
13. Kerner W, Bruckel J. Definition, classification and diagnosis of diabetes mellitus. *Exp Clin Endocrinol Diabetes.* (2014) 122:384–6. doi: 10.1055/s-0034-1366278
14. Conte MS, Pomposelli FB. Society for vascular surgery practice guidelines for atherosclerotic occlusive disease of the lower extremities management of asymptomatic disease and claudication. *Introduction J Vasc Surg.* (2015) 61:1S. doi: 10.1016/j.jvs.2014.12.006
15. Ko SH, Bandyk DF. Interpretation and significance of ankle-brachial systolic pressure index. *Semin Vasc Surg.* (2013) 26:86–94. doi: 10.1053/j.semvascsurg.2014.01.002
16. Li Z, Wang S, He Y, Li Q, Gao G, Tong G. Regulation of apelin-13 on Bcl-2 and caspase-3 and its effects on adipocyte apoptosis. *Evid Based Complement Alternat Med.* (2021) 2021:1687919. doi: 10.1155/2021/1687919
17. Herold Z, Doleschall M, Kovesdi A, Patocs A, Somogyi A. Chromogranin A and its role in the pathogenesis of diabetes mellitus. *Endokrynol Pol.* (2018) 69:598–610. doi: 10.5603/EP.a2018.0052
18. Tan S, Jiang T, Ebrahimi A, Langrish T. Effect of spray-drying temperature on the formation of flower-like lactose for griseofulvin loading. *Eur J Pharm Sci.* (2018) 111:534–9. doi: 10.1016/j.ejps.2017.10.040
19. Zhang T, Liu HY, Zhang XM, Zhang CF, Liu J, Jia SH, et al. Relationship between serum β2-microglobulin and lower extremity atherosclerotic occlusive disease. *Natl Med J China.* (2013) 93:2450–3.
20. Blessing E, Lugenbiel I, Holden A. The evidence to support the use of focal force balloon technology to improve outcomes in the treatment of lower extremity arterial occlusive disease. *J Cardiovasc Surg.* (2019) 60:14–20. doi: 10.23736/S0021-9509.18.10766-X
21. Sadeghi M, Heidari R, Mostanfar B, Tavassoli A, Roghani F, Yazdekhasti S. The relation between ankle-brachial index (ABI) and coronary artery disease severity and risk factors: an angiographic study. *ARYA Atheroscler.* (2011) 7:68–73.
22. Flanigan DP, Ballard JL, Robinson D, Galliano M, Blecker G, Harward TR. Duplex ultrasound of the superficial femoral artery is a better screening tool than ankle-brachial index to identify at risk patients with lower extremity atherosclerosis. *J Vasc Surg.* (2008) 47:789–92. doi: 10.1016/j.jvs.2007.11.023
23. Mcclean M, Buzkova P, Budoff M, Estrella M, Freiberg M, Hodis HN, et al. Brief report: cystatin C-based estimation of glomerular filtration rate and association with atherosclerosis imaging markers in people living with HIV. *J Acquir Immune Defic Syndr.* (2020) 85:466–9. doi: 10.1097/QAI.0000000000002467
24. Kaneko R, Sawada S, Tokita A, Honkura R, Tamura N, Kodama S, et al. Serum cystatin C level is associated with carotid arterial wall elasticity in subjects with type 2 diabetes mellitus: a potential marker of early-stage atherosclerosis. *Diabetes Res Clin Pract.* (2018) 139:43–51. doi: 10.1016/j.diabres.2018.02.003
25. Ren J, Dong X, Nao J. Serum cystatin C is associated with carotid atherosclerosis in patients with acute ischemic stroke. *Neurol Sci.* (2020) 41:2793–800. doi: 10.1007/s10072-020-04383-9
26. Fu J, Deng HY, Hu ML, Liao LY Li YK. Relationships between serum cystatin C, chemerin levels and subclinical atherosclerosis in

type 2 diabetes mellitus patients. *Natl Med J China.* (2019) 99:307–11. doi: 10.3760/cma.j.issn.0376-2491.2019.04.014
27. Kazanis K, Dalamaga M, Nounopoulos C, Manolis AS, Sakellaris N, Jullien G, et al. Ischemia modified albumin, high-sensitivity c-reactive protein and natriuretic peptide in patients with coronary atherosclerosis. *Clin Chim Acta.* (2009) 408:65–9. doi: 10.1016/j.cca.2009.07.007
28. El-Eshmawy M M, Gad D F, El-Baiomy A A. Elevated serum levels of ischemia modified albumin and malondialdehyde are related to atherogenic index of plasma in a cohort of prediabetes. *Endocr Metab Immune Disord Drug Targets.* (2020) 20:1347–54. doi: 10.2174/1871530320666200503052226
29. Uslu A U, Kucuk A, Balta S, Ozturk C, Arslan S, Levent T, et al. The relation between ischemia modified albumin levels and carotid intima media thickness in patients with rheumatoid arthritis. *Int J Rheum Dis.* (2019) 22:32–7. doi: 10.1111/1756-185X.12851
30. Etli M. Investigation of serum ischemia-modified albumin levels in coronary artery disease patients. *Indian J Thorac Cardiovasc Surg.* (2021) 37:147–52. doi: 10.1007/s12055-020-01061-5
31. Sofogianni A, Alkagiet S, Tziomalos K. Lipoprotein-associated phospholipase A2 and coronary heart disease. *Curr Pharm Des.* (2018) 24:291–6. doi: 10.2174/1381612824666180111110550
32. Pan G, Kou L, Wu Y, Hu Y, Lin X, Guo J, et al. Regulation of lipoprotein-associated phospholipase A2 silencing on myocardial fibrosis in mice with coronary atherosclerosis. *Biochem Biophys Res Commun.* (2019) 514:450–5. doi: 10.1016/j.bbrc.2019.04.129
33. Zhang J, Xu DL, Liu XB Bi SJ, Zhao T, Sui SJ, et al. Darapladib, a lipoprotein-associated phospholipase A2 inhibitor, reduces rho kinase activity in atherosclerosis. *Yonsei Med J.* (2016) 57:321–7. doi: 10.3349/ymj.2016.57.2.321
34. Huang F, Wang K, Shen J. Lipoprotein-associated phospholipase A2: the story continues. *Med Res Rev.* (2020) 40:79–134. doi: 10.1002/med.21597
35. Fatemi S, Gottsater A, Zarrouk M, Engstrom G, Melander O, Persson M, et al. Lp-PLA(2) activity and mass and CRP are associated with incident symptomatic peripheral arterial disease. *Sci Rep.* (2019) 9:5609. doi: 10.1038/s41598-019-42154-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Feng, Chen, Wang, Huang, Zhu and Zhou. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 14 March 2022
doi: 10.3389/fsurg.2022.859180

Clinical Classification, Pregnancy Outcomes and Risk Factors Analysis of Severe Preeclampsia Complicated With HELLP Syndrome

Hui Huang†, *Bo Liu*†, *Xia Gao** and *Yunju Wang**

Department of Obstetrics, Renmin Hospital, Hubei University of Medicine, Shiyan, China

Purpose: To investigate the clinical classification, pregnancy outcomes and risk factors of pregnant women with severe preeclampsia (SPE) complicated with HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome.

Methods: The clinical data of 50 pregnant women diagnosed with SPE complicated with HELLP syndrome in our hospital from January 2014 to January 2021 were retrospectively analyzed, and they were selected as the observation group. An additional 50 maternities diagnosed with preeclampsia (PE) during the same period were selected as the control group. The clinical classification and pregnancy outcomes of pregnant women in the observation group were recorded. The age and gestational age of onset of pregnancy were recorded and compared between the two groups. Univariate analysis and multivariate logistic regression model were used to analyze the risk factors for its occurrence.

Results: Among the 50 maternities in the observation group, there were 10 cases of type I, accounting for 20.00%; 35 cases of type II, accounting for 70.00%; 5 cases of type III, accounting for 10.00%. Partial 33 cases, the composition ratio of 66.00%; complete 17 cases, the composition ratio of 34.00%. Among the fetuses of 50 maternities in the observation group, 35 were premature, accounting for 70.00%; 13 had fetal growth restriction, accounting for 26.00%; and 2 died during perinatal period, accounting for 4.00%. Among the 50 maternities in the observation group, 48 cases were cesarean section, the composition ratio was 96.00%; 2 cases were induced labor, the composition ratio was 4.00%; there was no natural birth, the composition ratio was 0.00%. Univariate analysis showed that age, gestational age at onset, gestational age at termination of pregnancy, HGB, LDH, ALT, AST, TBIL, PLT, PT, and FIB were all associated with the occurrence of SPE complicated with HELLP syndrome ($P < 0.05$). Multivariate logistic analysis showed that gestational age at onset, gestational age at termination of pregnancy, HGB, LDH, ALT, AST, TBIL, PLT, and FIB were independent risk factors for SPE complicated with HELLP syndrome ($P < 0.05$).

Conclusion: SPE complicated with HELLP syndrome has significantly increased adverse pregnancy outcomes. Understanding its clinical classification is of great significance for the preventive application of platelet transfusion therapy and the selection

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Lihong Chen,
The First Affiliated Hospital of Fujian Medical University, China
Li Genlin,
University of South China, China

***Correspondence:**
Xia Gao
gaoxia1299@163.com
Yunju Wang
1347658439@qq.com

†*These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *21 January 2022*
Accepted: *10 February 2022*
Published: *14 March 2022*

Citation:
Huang H, Liu B, Gao X and Wang Y (2022) Clinical Classification, Pregnancy Outcomes and Risk Factors Analysis of Severe Preeclampsia Complicated With HELLP Syndrome. Front. Surg. 9:859180. doi: 10.3389/fsurg.2022.859180

of transfusion timing. Gestational age at onset and gestational age at termination of pregnancy are independent risk factors for its occurrence. Fully understanding the high-risk factors of HELLP syndrome, taking preventive measures in time, and carrying out targeted nursing can effectively improve the prognosis of pregnant women and reduce the risk of HELLP syndrome.

Keywords: HELLP syndrome, severe preeclampsia, clinical classification, pregnancy outcome, risk factors

INTRODUCTION

HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome is a severe form of preeclampsia, which refers to a group of clinical syndromes typically characterized by hemolysis, elevated liver enzymes and low platelets in pregnant women on the basis of gestational hypertension or severe preeclampsia (SPE) and other diseases (1). Affected patients are often accompanied by epigastric/right upper quadrant pain (40–100% incidence) (2), hypertension and proteinuria (80–85% incidence) (3), fatigue, nausea and vomiting, sudden weight gain and headache etc. HELLP syndrome occurs mostly in the second and third trimesters of pregnancy (usually between 27 and 7 weeks antenatally), and 15–30% of women present in the puerperium (usually within 7 days after delivery) (4). The pathological mechanism of the disease is not yet very clear, which may be related to placental origin (5), autoimmunity (6), mutations in coagulation factor V gene (7), fatty acid oxidation disorder symptoms (8) and so on. The incidence of HELLP syndrome is relatively low, accounting for only 0.5–0.9% of the pregnant population (the incidence in China can be about 2.5%), but the clinical manifestations are diverse, the disease develops rapidly, and poses a greater risk to maternal and child health, and the lives of mothers and children are often endangered by delayed treatment, with a high rate of maternal and child complications and death (9). Among them, the mortality rate of pregnant women is 3.4–24.2%, and the mortality rate of children in the perinatal period is as high as 7.7–60.0% (10). The vast majority of patients with HELLP syndrome should terminate their pregnancy by cesarean section after active treatment of hypertensive disorder of pregnancy (HDP). However, patients still have a 4–27% chance of recurrence when they become pregnant again. Therefore, early detection and provision of timely and effective interventions are particularly important. In this study, the clinical characteristics, pregnancy outcomes and risk factors of pregnant women with SPE complicated with HELLP syndrome were discussed and analyzed, in order to provide relevant reference materials for preventing and reducing the occurrence of HELLP syndrome.

TABLE 1 | Clinical classification of 50 maternities in observation group (*n*, %).

	Cases	Composition ratio
HELLP syndrome subtypes		
Type I	10	20.00% (10/50)
Type II	35	70.00% (35/50)
Type III	5	10.00% (5/50)
Partial/complete HELLP syndrome		
Partial	33	66.00% (33/50)
Complete	17	34.00% (17/50)

MATERIALS AND METHODS

Research Object

The clinical data of 50 pregnant women diagnosed with SPE complicated with HELLP syndrome in our hospital from January 2014 to January 2021 were retrospectively analyzed, and they were selected as the observation group. Inclusion criteria: patients with SPE combined with HELLP syndrome

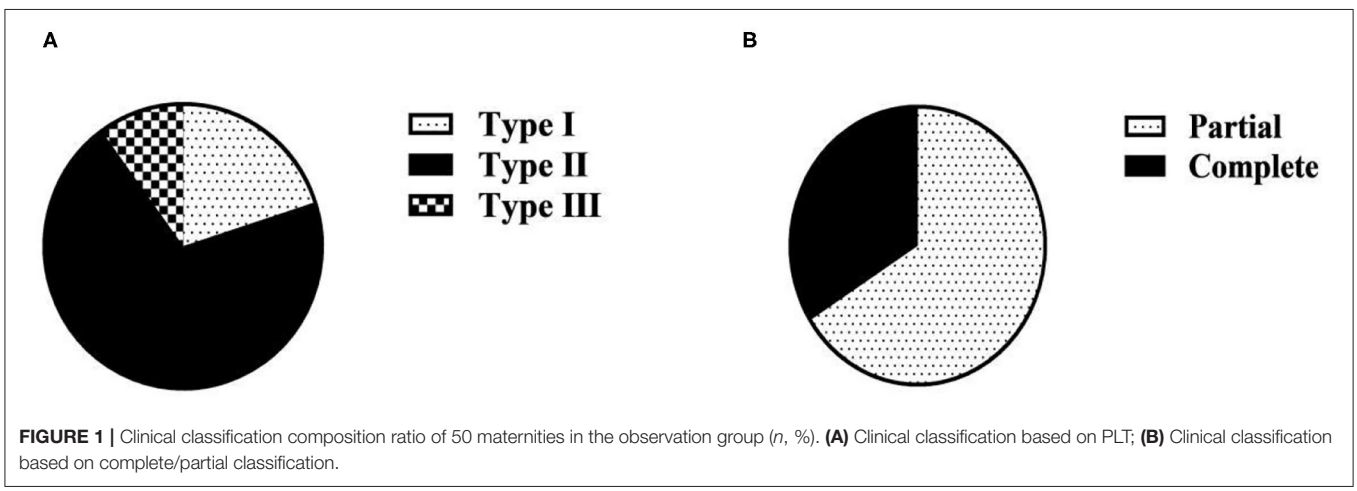


FIGURE 1 | Clinical classification composition ratio of 50 maternities in the observation group (*n*, %). **(A)** Clinical classification based on PLT; **(B)** Clinical classification based on complete/partial classification.

with a clear diagnosis; aged 18–50 years old; patients with complete medical records; patients or their family members who had signed the informed consent. Exclusion criteria: primary hypertension combined with pregnancy; HELLP syndrome caused by diseases other than SPE; combined with other acute and chronic life-threatening diseases not caused by SPE; combined with gestational diabetes mellitus, acute fatty liver during pregnancy, autoimmune diseases; previous hematological diseases or cardiopulmonary, hepatic and renal insufficiency; patients transferred to hospital for treatment during treatment. In addition, 50 pregnant and lying-in women diagnosed with preeclampsia (PE) during the same period were selected as the control group. An additional 50 maternal cases diagnosed with preeclampsia (PE) during the same period were selected as the control group. Inclusion criteria: those with a clear diagnosis of PE; those aged 18 to 50 years; those with complete medical records; those whose patients or their families had signed an informed consent. Exclusion criteria: primary hypertension combined with pregnancy; combined with gestational diabetes mellitus, acute fatty liver during pregnancy, autoimmune diseases; previous hematological diseases or cardiopulmonary, hepatic and renal insufficiency; patients transferred to hospital for treatment during treatment.

Diagnostic Criteria

In accordance with the diagnostic criteria of American College of Obstetricians and Gynecologists (ACOG) for SPE (11). Hypertension: systolic blood pressure $\geq$160 mmHg or diastolic blood pressure $\geq$110 mmHg twice within 6 h of bed rest; Proteinuria: $\geq$5 g/24 h, or twice urinary protein (+ + +) at an interval of 4 h; Oliguria: 24-h urine output $<$500 ml; Decreased platelets (PLT): $<100 \times 10^9$/L; abnormal liver enzymes; persistent headache, visual disturbances, or other symptoms; Heart failure, pulmonary edema, or cyanosis; Persistent epigastric or right upper quadrant pain; Intravascular hemolysis: anemia, jaundice, elevated lactate dehydrogenase (LDH); Fetal growth restriction or oligohydramnios, etc. It met the diagnostic criteria of the University of Tennessee for HELLP syndrome (12). HELLP syndrome was considered when any one of the following was present. Hemolysis: bilirubin (BIL) $\geq$ 1.2 mg/dl, hemoglobin (HGB) slightly decreased, lactate dehydrogenase (LDH) $>$ 600 U/L, broken red blood cells (RBC) on blood smear; Elevated liver enzymes: alanine aminotransferase (ALT) $\geq$40 U/L or aspartate aminotransferase (AST) $\geq$70 U/L; Decreased platelets (PLT): PLT$<50 \times 10^9$/L was type I, 50×10^9/L$\leq$PLT$\leq100 \times 10^9$/L was type II, 100×10^9/L$<$PLT$<150 \times 10^9$/L was type III. Partial abnormality of the above three indicators was defined as partial HELLP syndrome, and all abnormality was defined as complete HELLP syndrome.

TABLE 2 | Pregnancy outcomes and mode of delivery of 50 maternities in observation group (*n*, %).

	Cases	Composition ratio
Pregnancy outcome		
Premature delivery	35	70.00% (35/50)
Fetal growth restriction	13	26.00% (13/50)
Perinatal death of the fetus	2	4.00% (2/50)
Mode of delivery		
Cesarean section	48	96.00% (48/50)
Induced labor	2	4.00% (2/50)
Natural birth	0	0.00% (0/50)

Research Methods

The clinical classification and pregnancy outcomes of maternities in the observation group were recorded. The maternal age, gestational age of onset and laboratory parameters were recorded and compared between the two groups. Univariate analysis was used to analyze the related factors of HELLP syndrome, and multivariate logistic regression model was used to analyze the statistically significant indexes.

Observation Index

General information such as age, gestational age of onset, gestational age of termination of pregnancy, clinical characteristics, maternal and fetal outcomes were recorded for all mothers. Maternal RBC, HGB, LDH, ALT, AST, TBIL, blood urea nitrogen (BUN), blood calcium ion (Ca^{2+}), PLT, prothrombin time (PT), prothrombin time (TT), activated partial thromboplastin time (APTT), fibrinogen (FIB) and other laboratory indicators were recorded.

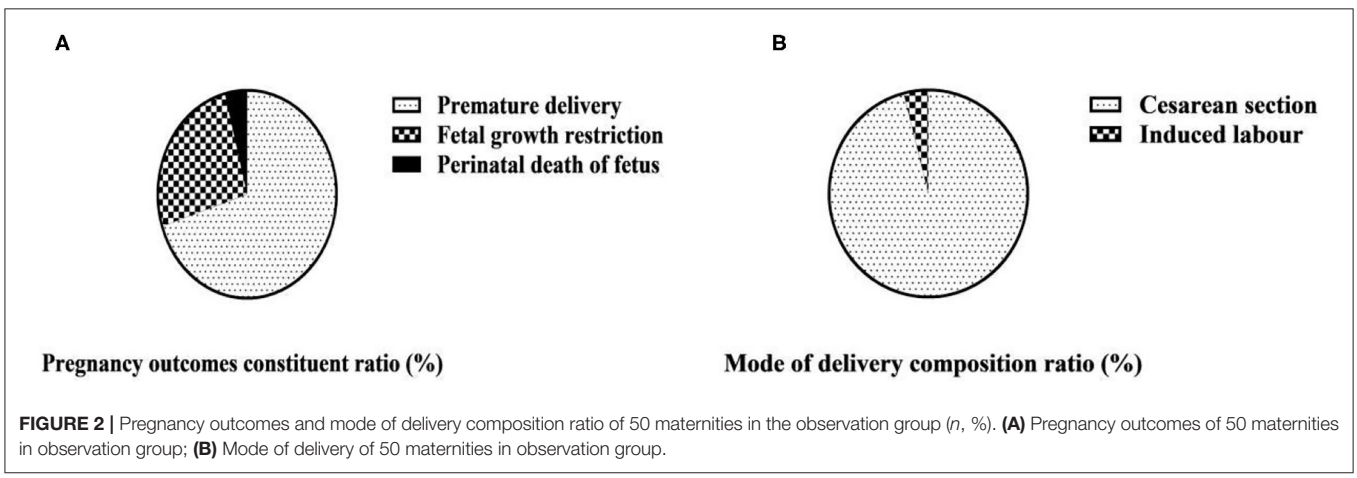


FIGURE 2 | Pregnancy outcomes and mode of delivery composition ratio of 50 maternities in the observation group (*n*, %). **(A)** Pregnancy outcomes of 50 maternities in observation group; **(B)** Mode of delivery of 50 maternities in observation group.

Statistical Methods

SPSS 22.0 software was used for processing, and measurement data of experimental data were expressed as mean ± standard deviation (M ± SD). One-way analysis of variance was used for comparison, and SNK-q method was used for pairwise comparison. Enumeration data are expressed as (%). Multivariate analysis was performed using a multivariate logistic regression model. The test level was $\alpha = 0.05$, and $P < 0.05$ was considered statistically significant.

TABLE 3 | Results of univariate analysis of SPE complicated by HELLP syndrome (*n*, M ± SD).

Factors	Control group (*n* = 50)	Observation group (*n* = 50)	*t-value*	*P-value*
Age (years old)	30.54 ± 5.57	34.11 ± 6.15	3.042	0.003
Gestational age at onset (week)	33.10 ± 3.97	30.54 ± 3.02	3.629	<0.001
Gestational age at termination of pregnancy (week)	34.55 ± 3.24	31.97 ± 3.93	3.582	0.001
RBC ($\times 10^{12}$)	4.30 ± 2.07	3.64 ± 1.45	1.847	0.068
HGB (g/L)	114.13 ± 16.12	96.36 ± 26.30	4.073	<0.001
LDH (U/L)	482.29 ± 100.23	811.84 ± 150.21	12.904	<0.001
ALT (U/L)	37.98 ± 9.36	170.21 ± 51.30	17.930	≤0.001
AST (U/L)	37.78 ± 11.65	120.20 ± 59.40	9.628	≤0.001
TBIL (μmol/L)	18.65 ± 2.11	56.29 ± 13.16	19.969	≤0.001
BUN (mmol/L)	7.73 ± 3.60	8.96 ± 3.69	1.687	0.095
Blood Ca^{2+} (mmol/L)	1.98 ± 0.13	1.97 ± 0.15	0.356	0.722
PLT ($\times 10^9$/L)	132.45 ± 38.77	72.86 ± 11.64	10.409	≤0.001
PT (s)	11.57 ± 3.21	20.34 ± 4.45	11.302	≤0.001
TT (s)	17.22 ± 1.36	17.70 ± 1.26	1.831	0.070
APTT (s)	25.33 ± 8.26	28.32 ± 7.96	1.843	0.068
FIB (mg/dl)	3.61 ± 1.65	2.98 ± 1.44	2.034	0.045

TABLE 4 | Assignment for multivariate analysis of factors.

Factors	Variables	Assignment
Age	X1	Continuous variable
Gestational age at onset	X2	Continuous variable
Gestational age at termination of pregnancy	X3	Continuous variable
HGB	X4	Continuous variable
LDH	X5	Continuous variable
ALT	X6	Continuous variable
AST	X7	Continuous variable
TBIL	X8	Continuous variable
PLT	X9	Continuous variable
PT	X10	Continuous variable
FIB	X11	Continuous variable

RESULTS

Clinical Classification of 50 Maternities in Observation Group

Among the 50 maternities in the observation group, there were 10 cases of type I, accounting for 20.00%; 35 cases of type II, accounting for 70.00%; 5 cases of type III, accounting for 10.00%. Partial 33 cases, the composition ratio of 66.00%; complete 17 cases, the composition ratio of 34.00% (**Table 1** and **Figure 1**).

Pregnancy Outcomes and Mode of Delivery of 50 Maternities in Observation Group

Among the fetuses of 50 maternities in the observation group, 35 were premature, accounting for 70.00%; 13 had fetal growth restriction, accounting for 26.00%; and 2 died during perinatal period, accounting for 4.00%. Among the 50 maternities in the observation group, 48 cases were cesarean section, the composition ratio was 96.00%; 2 cases were induced labor, the composition ratio was 4.00%; there was no natural birth, the composition ratio was 0.00% (**Table 2** and **Figure 2**).

Results of Univariate Analysis of SPE Complicated by HELLP Syndrome

Univariate analysis showed that age, gestational age at onset, gestational age at termination of pregnancy, HGB, LDH, ALT, AST, TBIL, PLT, PT, and FIB were all associated with the occurrence of HELLP syndrome ($P < 0.05$) (**Table 3**).

Results of a Multifactorial Analysis of SPE Complicated by HELLP Syndrome

Multivariate Logistic analysis showed that gestational age at onset, gestational age at termination of pregnancy, HGB, LDH, ALT, AST, TBIL, PLT, and FIB were all independent risk factors for HELLP syndrome ($P < 0.05$) (**Tables 4**, **5**).

DISCUSSION

The incidence of HELLP syndrome is low, but it often leads to maternal placental abruption, fetal distress, and perinatal death, and has a high maternal and child mortality rate (13). The disease is typically characterized by hemolysis, elevated liver enzymes, and thrombocytopenia in pregnant women during pregnancy. The clinical manifestations are diverse, and pregnant women are often accompanied by symptoms such as fatigue and upper abdominal pain. Early detection and early treatment is the most effective and safe way to block the progression of SPE complicated with HELLP syndrome and reduce adverse outcomes. It is reported that the physiological and pathological changes of the disease are similar to those of HDP, but the initiation mechanism of its development into HELLP syndrome is still unclear. Maternal unexplained systemic small blood vessel spasm, red blood cells are squeezed and ruptured when passing through the spastic blood vessels, resulting in hemolysis (14); tissue ischemia and hypoxia lead to damage to important organs

TABLE 5 | Results of a multifactorial analysis of SPE complicated by HELLP syndrome.

Factors	*B*	*SE*	*Walds*	*P*	*OR*	*95% CI*
Age	0.220	0.231	2.449	0.117	1.246	0.792–1.960
Gestational age at onset	0.452	0.201	3.998	0.046	1.571	1.060–2.330
Gestational age at termination of pregnancy	0.310	0.124	4.577	0.032	1.363	1.069–1.739
HGB	0.534	0.211	5.997	0.013	1.706	1.128–2.579
LDH	0.320	0.124	6.698	0.008	1.377	1.080–1.756
ALT	0.298	0.117	3.989	0.047	1.347	1.071–1.694
AST	0.247	0.110	4.537	0.033	1.280	1.032–1.588
TBIL	0.312	0.102	4.604	0.032	1.366	1.119–1.668
PLT	0.453	0.118	5.254	0.021	1.573	1.248–1.982
PT	0.301	0.287	3.389	0.066	1.351	0.770–2.371
FIB	0.330	0.125	3.934	0.047	1.391	1.089–1.777

of the human body, after liver damage, liver enzymes are released, resulting in elevated liver enzymes (15); exposure of collagenous tissue after endothelial cell damage leads to platelet activation, aggregation, and excessive consumption resulting in decreased PLT (16) as its main pathological changes. Thus, the PLT count has become the most important basis for the diagnosis and staging of SPE complicated by HELLP syndrome.

The severity of the condition of maternitie complicated with HELLP syndrome is closely related to the level of serum PLT. In this study, PLT count was used as the clinical classification standard of HELLP syndrome. Among the 50 maternitie in the observation group, there were 10 cases of type I, 35 cases of type II, and 5 cases of type III. The proportion of patients with type II HELLP syndrome was 70.00%, which was much higher than the other two types. Decreased PLT is an important early warning indicator of HDP complicated with HELLP syndrome and an important manifestation of vascular endothelial injury. The main manifestation is that the lower the PLT, the more severe the vascular endothelial injury and the more severe the disease (17). In this study, the diagnosis of HELLP syndrome was used as its clinical classification criteria. Among the 50 maternities in the observation group, there were 33 cases of partial HELLP syndrome, accounting for 66.00%, and 17 cases of complete HELLP syndrome, accounting for 34.00%. This is consistent with the classification based on PLT in this study. It also suggests that in clinical, partial HELLP syndrome is more common than complete HELLP syndrome. According to the progress of diagnosis and treatment of HELLP syndrome, platelet transfusion as indicated in combination with the specific condition of the patient is an effective treatment measure. The study of the clinical classification of HELLP syndrome in this study can provide reference for the preventive platelet transfusion therapy and transfusion timing for pregnant and lying-in women with HELLP syndrome.

The occurrence of HELLP syndrome can be accompanied by irreversible damage to organs, often complicated by adverse symptoms such as placental abruption, resulting in adverse pregnancy outcomes (18). This study analyzed the pregnancy outcomes of women with SPE complicated by HELLP syndrome. Among the fetuses of 50 maternities in the observation group, 35 were premature, accounting for 70.00%; 13 had fetal growth restriction, accounting for 26.00%; and 2 died during perinatal period, accounting for 4.00%. Among the 50 maternities in the observation group, 48 cases of cesarean section, the composition ratio of 96.00%; 2 cases of induced labor, the composition ratio of 4.00%; no natural delivery. Early onset and rapid progression of HELLP syndrome can often lead to preterm delivery, and in more severe cases, it can lead to placental decline, inadequate placental blood and oxygen supply, fetal growth restriction and neonatal asphyxia, which can seriously affect fetal growth and development and increase fetal perinatal mortality (19). The mode of delivery is related to the severity of the disease and the gestational age of onset. If the condition of maternities is serious, cesarean section is often chosen to terminate the pregnancy; if the condition is mild and the intrauterine condition of the fetus is good, labor can also be induced appropriately, but the changes in the condition should be closely monitored during the process of labor induction (20).

In the risk factor analysis of this study, gestational age at onset, gestational age at termination of pregnancy, HGB, LDH, ALT, AST, TBIL, PLT, and FIB were all independent risk factors for HELLP syndrome. Analysis of the reasons, HELLP syndrome onset early in gestation, often lead to premature birth and perinatal death. The gestational age of pregnancy termination can affect the growth of the fetus in the uterus, and premature or untimely termination of pregnancy can affect HELLP syndrome. For maternities whose gestational age is >34 weeks, cesarean section is preferred, and pregnancy is terminated in time; for those whose gestational age is <34 weeks, active antispasmodic, antihypertensive and other treatments are required, or the pregnancy should be terminated within 4 days of expectant management (21). HGB is a specialized protein that transports oxygen in erythrocytes, and reduction can lead to tissue hypoxia, which is a risk factor for the development of HELLP syndrome (22). The more severely damaged the liver and the higher the serum LDH, ALT, AST and TBIL levels, the more likely HELLP syndrome will develop (23). When hemolysis occurs, LDH release is increased and serum LDH levels are elevated, affecting HELLP syndrome (24). Platelets have the effect of promoting hemostasis and can protect the endothelium of small

blood vessels in the body from damage. When PLT is lowered, the protective effect of microvessels is weakened, resulting in HELLP syndrome. FIB is a glycoprotein that plays an important role in human coagulation and hemostasis, and can sensitively reflect the disorder of the coagulation system. When FIB is low, there is a risk of massive bleeding and HELLP syndrome is prone to occur (25).

Domestic studies have also pointed out that with the increase of age, maternal body function declines, and the resistance to the outside world is weakened. Therefore, advanced pregnancy is an independent risk factor for the incidence of HELLP syndrome. In the risk factor analysis of this study, age was associated with the occurrence of severe preeclampsia complicated by HELLP syndrome, but was not an independent risk factor for it. Considering that it is related to the small sample inclusion in this study, future studies with expanded samples are needed to further clarify the above risk factors.

To sum up, SPE complicated with HELLP syndrome has significantly increased adverse pregnancy outcomes. Understanding its clinical classification is of great significance for the preventive application of platelet transfusion therapy and the selection of transfusion timing. Gestational age at onset and gestational age at termination of pregnancy are independent risk factors for its occurrence. Fully understanding the high-risk factors of HELLP syndrome, taking preventive measures in time, and carrying out targeted nursing can effectively improve the prognosis of pregnant women and reduce the risk of HELLP syndrome.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Renmin Hospital, Hubei University of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

REFERENCES

1. Kang S, Zhou L, Wang X, Li Y, Wang Y. Effectiveness of high-dose glucocorticoids on hemolysis, elevating liver enzymes, and reducing platelets syndrome. *J Int Med Res*. (2019) 47:738–47. doi: 10.1177/0300060518809783
2. Nam IC, Won JH, Kim S, Bae K, Jeon KN, Moon JI, et al. Transcatheter arterial embolization for spontaneous hepatic rupture associated with HELLP syndrome: a case report. *Medicina*. (2021) 57:1055. doi: 10.3390/medicina57101055
3. Amraoui F, Hassani Lahsinoui H, Spijkers LJA, Vogt L, Peters SLM, Wijesinghe DS, et al. Plasma ceramide is increased and associated with proteinuria in women with pre-eclampsia and HELLP syndrome. *Pregnancy Hypertens*. (2020) 19:100–5. doi: 10.1016/j.preghy.2019.12.006
4. Rath W, Faridi A, Dudenhausen JW. HELLP syndrome. *J Perinat Med*. (2000) 28:249–60. doi: 10.1515/JPM.2000.033
5. Haram K, Mortensen JH, Nagy B. Genetic aspects of preeclampsia and the HELLP syndrome. *J Pregnancy*. (2014) 2014:910751. doi: 10.1155/2014/910751
6. Stojanovska V, Zenclussen AC. Innate and adaptive immune responses in HELLP syndrome. *Front Immunol*. (2020) 11:667. doi: 10.3389/fimmu.2020.00667
7. Muetze S, Leeners B, Ortlepp JR, Kuse S, Tag CG, Weiskirchen R, et al. Maternal factor V Leiden mutation is associated with HELLP syndrome in Caucasian women. *Acta Obstet Gynecol Scand*. (2008) 87:635–42. doi: 10.1080/00016340802112740
8. Yu H, Yang Z, Ding X, Wang Y, Han Y. Effects of serum from patients with early-onset pre-eclampsia, HELLP syndrome, and antiphospholipid syndrome on fatty acid oxidation in trophoblast cells. *Arch Gynecol Obstet*. (2015) 292:559–67. doi: 10.1007/s00404-015-3669-2
9. Han X, Fan Y, Yu Y. Two cases of severe preeclampsia were diagnosed with HELLP postpartum after caesarian section. *Case Rep Obstet Gynecol*. (2014) 2014:747510. doi: 10.1155/2014/747510
10. Liu Q, Ling GJ, Zhang SQ, Zhai WQ, Chen YJ. Effect of HELLP syndrome on acute kidney injury in pregnancy and pregnancy outcomes: a systematic review and meta-analysis. *BMC Pregnancy Childbirth*. (2020) 20:657. doi: 10.1186/s12884-020-03346-4
11. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*. (2013) 122:1122–31. doi: 10.1097/01.AOG.0000437382.03963.88
12. Westbrook RH, Dusheiko G, Williamson C. Pregnancy and liver disease. *J Hepatol*. (2016) 64:933–45. doi: 10.1016/j.jhep.2015.11.030
13. Sánchez-Bueno F, García Pérez R, Torres Salmerón G, Fernández-Carrión J, Ramírez Romero P, Parrilla Paricio P. Síndrome de HELLP con disfunción hepática severa: presentación de cuatro casos [HELLP syndrome with severe liver dysfunction: a presentation of three cases]. *Cir Esp*. (2012) 90:33–7. doi: 10.1016/j.ciresp.2011.07.008
14. McCormick PA, Higgins M, McCormick CA, Nolan N, Docherty JR. Hepatic infarction, hematoma, and rupture in HELLP syndrome: support for a vasospastic hypothesis. *J Matern Fetal Neonatal Med*. (2021) 15:1–6. doi: 10.1080/14767058.2021.1939299
15. Bodnar LM, Simhan HN, Catov JM, Roberts JM, Platt RW, Diesel JC, et al. Maternal vitamin D status and the risk of mild and severe preeclampsia. *Epidemiology*. (2014) 25:207–14. doi: 10.1097/EDE.0000000000000039
16. Zeng M, Luo Y, Xu C, Li R, Chen N, Deng X, et al. Platelet-endothelial cell interactions modulate smooth muscle cell phenotype in an *in vitro* model of type 2 diabetes mellitus. *Am J Physiol Cell Physiol*. (2019) 316:186–97. doi: 10.1152/ajpcell.00428.2018
17. Haram K, Mortensen JH, Mastrolia SA, Erez O. Disseminated intravascular coagulation in the HELLP syndrome: how much do we really know? *J Matern Fetal Neonatal Med*. (2017) 30:779–88. doi: 10.1080/14767058.2016.1189897
18. Gomez-Tolub R, Rabinovich A, Kachko E, Benshalom-Tirosh N, Tirosh D, Thachil J, et al. Placental abruption as a trigger of DIC in women with HELLP syndrome: a population-based study. *J Matern Fetal Neonatal Med*. (2020) 15:1–11. doi: 10.1080/14767058.2020.1818200
19. Zhong L, Deng W, Zheng W, Yu S, Huang X, Wen Y, et al. The relationship between circadian blood pressure variability and maternal/perinatal outcomes in women with preeclampsia with severe features. *Hypertens Pregnancy*. (2020) 39:405–10. doi: 10.1080/10641955.2020.1797777
20. Wallace K, Harris S, Addison A, Bean C. HELLP syndrome: pathophysiology and current therapies. *Curr Pharm Biotechnol*. (2018) 19:816–26. doi: 10.2174/1389201019666180712115215

21. Wallace K, Martin JN Jr, Tam Tam K, Wallukat G, Dechend R, Lamarca B, et al. Seeking the mechanism(s) of action for corticosteroids in HELLP syndrome: SMASH study. *Am J Obstet Gynecol*. (2013) 208:380.1-8. doi: 10.1016/j.ajog.2013.01.049
22. Kang SY, Wang Y, Zhou LP, Zhang H. New indicators in evaluation of hemolysis, elevated liver enzymes, and low platelet syndrome: a case-control study. *World J Clin Cases*. (2021) 9:1259–70. doi: 10.12998/wjcc.v9.i6.1259
23. Nelson DB, Khan A, Bailey A, Yokoo T, Pedrosa I, McIntire DD, et al. Liver injury in hemolysis, elevated liver enzymes, and low platelets syndrome measured by diffusion-weighted magnetic resonance imaging. *Am J Perinatol*. (2018) 35:741–7. doi: 10.1055/s-0037-1613684
24. Gordon JS, Wood CT, Luc JGY, Watson RA, Maynes EJ, Choi JH, et al. Clinical implications of LDH isoenzymes in hemolysis and continuous-flow left ventricular assist device-induced thrombosis. *Artif Organs*. (2020) 44:231–8. doi: 10.1111/aor.13565
25. Cui C, Ma S, Qiao R. Prenatal plasma fibrinogen level predicts postpartum hemorrhage of patients with HELLP syndrome. *Clin Appl Thromb Hemost*. (2020) 26:1076029619894057. doi: 10.1177/1076029619894057

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Huang, Liu, Gao and Wang. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 15 March 2022
doi: 10.3389/fsurg.2022.856312

Influence of Fine Management Combined With PDCA Cycle Method on Disinfection Qualified Rate and Performance Grade of Ophthalmic Precision Instruments

Fanli Zeng[1†], *Xiuling Wang*[2†], *Yan Gao*[3] *and Ling Hu*[4*]

[1] *Department of Anesthesiology, Chongqing General Hospital, Chongqing, China,* [2] *Department of Ophthalmology, Chongqing Banan District People's Hospital, Chongqing, China,* [3] *Central Sterile Supply Department, Chongqing General Hospital, Chongqing, China,* [4] *Central Sterile Supply Department, Chongqing Hospital of Traditional Chinese Medicine, Chongqing, China*

Objective: The aim of this study is to explore the influence of fine management combined with the plan-do-check-action (PDCA) cycle method on the management of ophthalmic precision instruments.

Methods: The ophthalmic precision instruments centralized in the disinfection supply room of our hospital were selected as the research objects and divided into groups A and B. Traditional instrument management method was adopted in group A, and fine management combined with the PDCA cycle method based on the group A was adopted in group B. The instrument management risk scores, the qualified rate of disinfection, instrument performance grade, and incidence of toxic anterior segment syndrome (TASS) of the two groups were compared.

Results: The risk scores of instrument management and incidence of TASS in group B were lower than those in group A ($p < 0.05$). The qualified rate of disinfection and instrument performance grades in group B were higher than those in group A ($p < 0.05$).

Conclusion: Fine management combined with the PDCA cycle method can improve the qualified rate of disinfection of ophthalmic precision instruments, optimize the performance of instruments, reduce the risk of instrument management, and reduce the incidence of TASS.

Keywords: ophthalmic precision instruments, fine management, PDCA cycle method, disinfection qualified rate, performance grade, failure mode and effect analysis

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Fang Wei,
Central South University, China
Feng Qin,
Shanghai Jiao Tong University School of Medicine, China

***Correspondence:**
Ling Hu
hl751128@163.com

[†]*These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *17 January 2022*
Accepted: *08 February 2022*
Published: *15 March 2022*

Citation:
Zeng F, Wang X, Gao Y and Hu L (2022) Influence of Fine Management Combined With PDCA Cycle Method on Disinfection Qualified Rate and Performance Grade of Ophthalmic Precision Instruments. Front. Surg. 9:856312. doi: 10.3389/fsurg.2022.856312

INTRODUCTION

Disinfection supply room is a special department of hospital, and its work quality can directly affect nursing work and medical safety, which is closely related to nosocomial infection rate, and makes the clinical nursing management of disinfection supply room have higher requirements. With the continuous development of medical technology, the skill of ophthalmic surgery is gradually improved, and fine ophthalmic instruments are the prerequisite for the successful completion of ophthalmic surgery. However, ophthalmic precision instruments have a complicated structure, fast

turnover, high price, high precision, and high maintenance requirements which are difficult to clean and require high disinfection and maintenance (1, 2). If the ophthalmic precision instruments are not handled in time and maintained properly in the cleaning and disinfection process, it is easy to cause the corrosion and damage of the instruments and destroy the performance, which will not only affect the operator's operation process, but also possibly lead to the phenomenon of intraocular infection, which will adversely affect the surgical effect (3, 4). The research shows that infections caused by incomplete sterilization of surgical instruments account for about 20% of patients with infections after ophthalmic surgery (5). Therefore, attention should be paid to the treatment of ophthalmic precision instruments in clinic. Strengthening the cleaning and disinfection of ophthalmic instruments plays an important role in improving the safety of surgery.

At present, people's requirements for medical services are gradually increasing, and nursing work is gradually becoming more refined. Fine management is an intervention means of fine care for every detail, which can carry out quality management from many angles, such as sorting, rectification, treatment, and supervision, focusing on finding problems in detail, actively looking for reasons, formulating a series of management procedures, and comprehensively supervising the operation of every link, so as to achieve the purpose of solving problems (6). Fine management through process control and continuous improvement is helpful to improve the management efficiency of hospitals, further coordinate and unify the management mechanism, and provide better service intervention for patients, thus effectively avoiding nursing defects and improving the clinical work quality (7). Plan-do-check-action (PDCA) cycle method is a working procedure of all-round quality management, which divides quality management into four stages: planning, implementation, inspection, and treatment (8). In the PDCA cycle, each stage promotes each other, interlocks with each other, and spirals upward. The purpose of implementation is to reduce the shortage of management schemes and improve the overall work quality through a continuous cyclic operation (9).

At present, how to use effective methods to avoid the risk factors of eye infection and improve the qualified rate of disinfection of instruments has become a hot issue for the staff of disinfection supply room and medical staff. Therefore, to explore whether the fine management combined with the PDCA cycle method is practical in the management of ophthalmic precision instruments, we have carried out the following research.

MATERIALS AND METHODS

Object

In this study, 80 sets of ophthalmic instrument packages centralized from the disinfection supply rooms of two hospitals were selected as the research objects. A number of 40 sets of ophthalmic instrument packages (785 ophthalmic precision instruments) randomly selected from July 2020 to December 2020 were taken as group A, and 40 sets of ophthalmic instrument packages (791 ophthalmic precision instruments) randomly selected from January 2021 to June 2021 were taken as group B. Inclusion criteria were as follows class I ophthalmic precision instruments; the use time of surgical instruments was <2 years; the information of surgical instruments was complete. Exclusion criteria were experienced derusting treatment, the fact that before the study, it was defective or the performance was greatly reduced, and surgical instruments did not meet the management requirements of the disinfection supply room.

Methods

Group A

A traditional instrument management method was adopted. Cleaning and disinfection of instruments adopted traditional manual cleaning, assigned personnel to recycle the used instruments after the operation, and classify the instruments before cleaning. According to the characteristics of ophthalmic precision instruments, prewashing, soaking, rinsing, drying, lubrication, disinfection, and sterilization were carried out in turn. The processed instruments were inspected regularly, the existing problems were found in time, and corresponding measures to intervene were formulated.

Group B

On the basis of group A, fine management combined with PDCA cycle method was adopted.

(1) ① Determining the goals that need to be achieved. It was agreed that the qualified rate of instruments cleaning quality should reach above 90%; hence, the two hospitals adopted the same model and established a fine management joint PDCA cycle method team, which included ophthalmology specialist nurses, and disinfection supply center nurses. The cleaning station was moved to the ophthalmology department, and cleaning and sterilization were performed at the disinfection supply center. After the group was established, specialized knowledge training and technical operation assessment were actively carried out, so as to inspect the group members' mastery of professional skills. The problems existing in the management of ophthalmic precision instruments were identified, such as the lack of continuous and effective monitoring of the cleaning quality of instruments, the lack of refinement in the process of different types of instruments, and the failure to strictly follow the cleaning process, when the workload was heavy. The members of the group were informed of relevant knowledge and matter needing attention in disinfection management of ophthalmic precision instruments, and the rules and regulations of hospital disinfection supply room were further improved. The nurses in the disinfection and supply room completed the classification of instruments, clarified them into books, and placed them in the recycling and packaging area. ② The reasons for unqualified cleaning and disinfection quality of instruments in the past were clarified, and the main causes were analyzed and summarized. ③ A fine management system of ophthalmic precision instruments was established.

(2) ① A group meeting was held, division of labor was formulated, responsibilities were clarified, and the awareness

of infection prevention and control of among medical staff was improved. ② Then, through the combination of the actual instrument and the picture of the instrument, the department staff was trained on the related operation links of instrument cleaning and disinfection, the atlas of ophthalmic precision instruments was made, name and performance of the instruments were indicated, and the nursing staff was asked to master the cleaning points, such as matters needing attention in packaging and maintenance, disinfection and sterilization methods of ophthalmic precision instruments, etc. ③ When checking the instruments, nurses should be paid attention to whether the instruments were in good condition, whether there was any defect, whether the alignment was tight, and whether the functions were good. The instrument was handled with care to prevent its precision from being damaged. A special treatment table for ophthalmic instruments was set up and they were treated separately from ordinary instruments. ④ According to the characteristics of the instruments, the cleaning process was established. The scissors, pliers, tweezers, and cavity instruments were cleaned manually, when washing the instruments manually, the action should be gentle, and cleaning tools, such as regular brushes and sponge brushes, should be used correctly. The instruments with difficult cleaning and complicated structure were cleaned ultrasonically, during which they were first pre-cleaned by hand after which the instrument was disassembled. The shaft joint was then opened and then put it into an ultrasonic cleaning machine. After cavitation and vibration for 2–3 min, the joints were cleaned by the hand-cleaning method, and the cavity was rinsed with a high-pressure water gun. When cleaning cavity instruments, appropriate cleaning agents should be chosen according to the instructions of device manufacturers to remove residual substances on the wall of the tube and then washed with pure water. Instruments that were not resistant to moist heat disinfection should be soaked in 75% ethanol for disinfection and dried by an air gun. ⑤ The cleaning methods of ophthalmic precision instruments with high unqualified rates were analyzed. The eyelid opener should focus on brushing the eyelid opening to remove mucus and glue. Small scissors should focus on cleaning the blade and the adhesive should be wiped off with alcohol gauze. Scleral presser should focus on brushing the top pressure and removing mucus. During microshear cleaning, the joints should be completely opened. The ultrasonic emulsification tube and IA head should be cleaned with a water gun and an air gun. When cleaning the effusion box, the cavity should be filled with water, water should be poured while shaking, rinsing, and disinfecting. ⑥ When cleaning, the operator should move gently without violence, and used soft tools to clean the occlusal parts or parts with sharp tips. A special fine basket with a built-in silicone pad to hold ophthalmic precision instruments should be used, and the tip of the instrument should face upward to prevent the tip from being damaged. When packaging instruments, fine-grained baskets, precision instrument boxes, and protective sleeves that match the instruments should be used to avoid instruments' damage caused by the instrument bag being squeezed or inverted. ⑦ After cleaning and disinfection of ophthalmic precision instruments, the cleaner shall sign and improve the handover register. When packing, silica gel head and plastic protective sleeve should be used, and when transporting, a special container to prevent the instrument from being damaged should be used.

(3) Check the designed daily monitoring record of cleaning and disinfection quality of ophthalmic precision instruments, appoint team members to check the cleaning and disinfection quality of the instruments every day, and check whether the cleaning effect of the surfaces, shaft joints, tooth slots, and other parts of the instruments was up to standard, if the surface of the surgical instrument was smooth and there was no residual bloodstain or rust stain, it was qualified, and the registration was unqualified. The sterilized instruments should be checked one by one for sharpness, good function, defects, or serious corrosion. If the instruments were defective or improperly maintained, the nursing staff should report for repair or update the instruments in time.

(4) A group meeting should be held once a month, the problems existing in the inspection should be summarized, analyzed and the reasons for unqualified disinfection quality of instruments should be found. Specific and effective measures to solve the problems should be put forward and the corresponding work contents should be adjusted. A refined work plan should be formulated for all employees to prevent the same work defects from recurring, or the unresolved problems will roll into the next PDCA cycle.

Observation Index

(1) The basic information of ophthalmic precision instruments, such as service time of instruments and instrument type of the two groups, were recorded.

(2) The management risks of ophthalmic precision instruments according to the failure mode and effect analysis (FMEA) evaluation standard, including unqualified cleaning quality, instrument defect, improper handover of the instrument, and difficulty in instrument turnover, were evaluated. The evaluation method was divided into severity (S), occurrence (O), and detection ability (D). On calculating the risk priority number (RPN) = S × O × D, with a total score of 1–1,000 points, we defined RPN ≥ 150 points as high risk. The higher the score, the higher the risk of management of ophthalmic precision instruments. The specific scoring content is shown in **Table 1**.

(3) Different methods were used to evaluate the qualified rate of disinfection of ophthalmic precision instruments. ① Magnifying glass detection: The smoothness of the surface of the instrument was observed under a 5x magnification lens, and whether there was any contamination residue. The external surface was clean and free of pollution residue, which was qualified; ② Microbial culture detection: sterile cotton swabs were sampled on the instruments for bacterial culture, and the number of bacterial flora was calculated. The number of bacteria in a single instrument

TABLE 1 | FMEA evaluation standard.

S evaluation	
1 point	Without any effect on the instrument.
2–3 points	Affect the instruments, not affect the normal use.
4–6 points	The instrument is inconvenient to use, and the doctor is slightly dissatisfied.
7–8 points	Doctors are seriously dissatisfied with the status quo of instruments.
9–10 points	Doctors are seriously dissatisfied, and the status quo of instruments may cause medical accidents.
O evaluation	
1 point	Almost impossible to happen.
2 points	It may happen slightly.
3 points	Could happen.
4–6 points	Occasional, but unlikely.
7–8 points	Be of frequent occurrence.
9–10 points	Almost inevitable.
D evaluation	
1–2 points	Almost certainly.
3–5 points	Good detection means exist.
6–8 points	May be detected.
9 points	It is very likely that it will not be detected.
10 points	Can't be detected with high probability.

was <20 cfu, which was qualified; ③ Adenosine triphosphate (ATP) bioluminescence detection: the irrigating apparatus was purified five times, irrigating fluid was collected, the irrigating fluid with 3M ATP fluorescence detection swab was dipped, and the ATP fluorescence value was measured. Relative light unit ≤150 was qualified; ④ Jerry test paper method detection: dip the washing solution with Jerry test paper and observe the color change of the test paper. After 1 min, the yellow test paper was qualified.

(4) The performance questionnaire of ophthalmic precision instruments made by our hospital was used for evaluation. The score range was 4–12 points, 4 points: four levels, 5–6 points: three levels, 7–9 points: two levels, and 10–12 points: one level. The higher the score, the better the instrument performance. Specific scoring content is shown in **Table 2**.

(5) A total number of 200 patients with ophthalmic surgery were selected from each of the two groups, and the incidence of toxic anterior segment syndrome (TASS) during the management of the two groups was recorded. TASS diagnostic criteria were as follows: ① 22–24 h after cataract surgery; ② decreased vision, but no obvious pain, or mild pain; ③ the patient had diffused corneal edema accompanied by ciliary hyperemia, and the endothelial cell loss rate was >70%; ④ a large amount of cellulose protrudes into the anterior atrial abscess, and the pupil was irregularly dilated; ⑤ there was an inflammatory reaction in the anterior segment, but no obvious inflammatory reaction in the posterior segment. ⑥ Gram staining and bacterial culture were performed on aqueous humor and vitreous, and both the results were negative.

Statistical Methods

The SPSS 22.0 software was used, the measured data were expressed by $\bar{x} \pm s$, and the t-test was used for comparison. The counting data were expressed as %, and the χ^2 test was used for comparison; $p < 0.05$, the difference was significant.

TABLE 2 | Ophthalmic precision instrument performance questionnaire.

Scissors type	
1 point	Cut thin cotton sheets, fail to cut them neatly and/or are sticky.
2 points	Cut neatly without sticking, dull.
3 points	Cut it neatly without sticking.
Clamp type	
1 point	The palm of your hand is slapped or thrown from the air, and it automatically pops open and/or cannot be completely closed.
2 points	It doesn't bounce off automatically, it can clamp the No. 1 thread end, and there is a sense of pause when used.
3 points	It does not bounce off automatically. When it is completely closed, it clamps the No. 1 thread end and does not fall off.
Tweezers type	
1 point	Touched by hand when closed, rough, staggered and/or defective.
2 points	Smooth, staggered or defective.
3 points	Smooth, without misalignment and defects.
Cavity type	
1 point	Visually, there is dirt, blood, and rust. Under the condition that the cavity is not dried, the water in the cavity is blown to a clean white gauze with an air gun, and the color of the gauze changes obviously.
2 points	Visually, there is no dirt, blood, and rust, but the color of gauze changed slightly.
3 points	Visually, there is no dirt, blood, and rust, and the gauze is clean as before, with the same color.

RESULTS

Basic Information of Ophthalmic Precision Instruments

There was no significant difference in the basic information of ophthalmic precision instruments between the two groups ($p > 0.05$), as shown in **Table 3**.

Comparison of Instrument Management Risk Scores Between Two Groups

The risk scores of instrument management in group B were lower than those in group A ($p < 0.05$), as shown in **Figure 1**.

Comparison of Qualified Rate of Disinfection Between Two Groups

The qualified rate of disinfection in group B was higher than that in group A ($P < 0.05$), as shown in **Table 4**.

TABLE 3 | Basic information of ophthalmic precision instruments (n, $\bar{x} \pm s$, %).

Group	Service time of instruments (months)	Instrument type				
		Scissors type	Clamp type	Tweezers type	Cavity type	Other type
Group A ($n = 785$)	13.18 ± 2.05	121 (15.41%)	164 (20.89%)	175 (22.29%)	149 (18.98%)	176 (22.42%)
Group B ($n = 791$)	13.26 ± 1.97	130 (16.43%)	152 (19.22%)	177 (22.38%)	153 (19.34%)	179 (22.63%)
χ^2 / t value	0.789			0.845		
P-value	0.429			0.932		

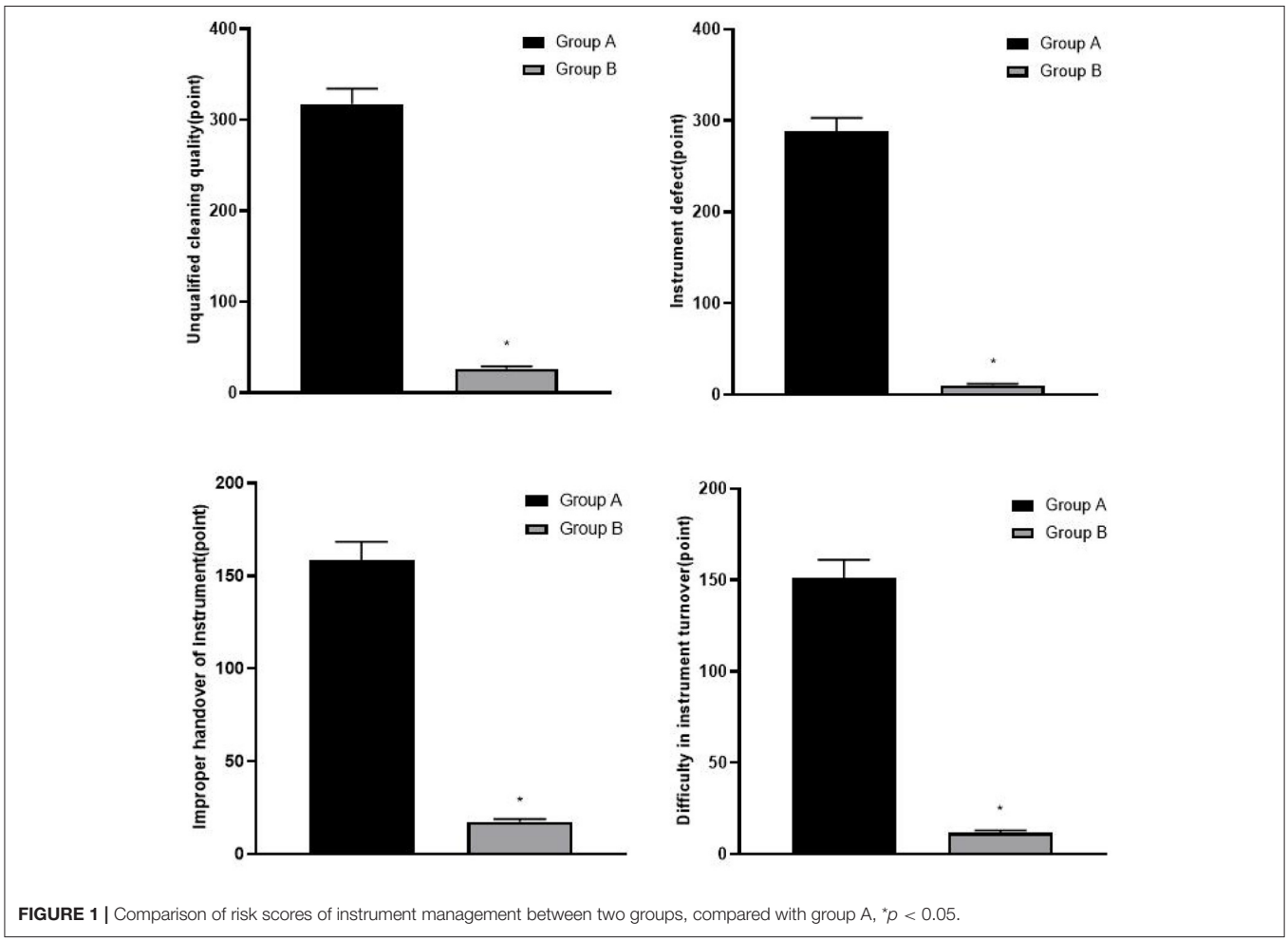


FIGURE 1 | Comparison of risk scores of instrument management between two groups, compared with group A, $^*p < 0.05$.

TABLE 4 | Comparison of qualified rate of disinfection between two groups (n, %).

Group	Magnifying glass detection	Microbial culture detection	ATP bioluminescence detection	Jerry test paper method detection
Group A ($n = 785$)	776 (98.85%)	773 (98.47%)	743 (94.65%)	712 (90.70%)
Group B ($n = 791$)	791 (100.00%)	790 (99.87%)	768 (97.09%)	742 (93.81%)
χ^2 value	9.121	9.470	5.945	5.318
P-value	0.003	0.002	0.015	0.021

Comparison of Instrument Performance Grade Between Two Groups

The instrument performance grade in group B was better than that in group A (rank sum test $z = 4.012$, $p < 0.05$), as shown in **Figure 2**.

Comparison of the Incidence of TASS Between Two Groups

The incidence of TASS in group B (0.50%) was lower than that in group A (3.50%) ($p < 0.05$), as shown in **Table 5**.

DISCUSSION

People's eye structure is complex and there are many kinds of diseases. To meet the needs of various ophthalmic operations, ophthalmic surgical instruments are developing toward complexity and refinement. This not only brings convenience to ophthalmic surgery, but also increases the management difficulty of ophthalmic precision instruments. Ophthalmic precision instruments are easily damaged, and have high maintenance requirements. If the bacteria of the instruments are not completely eliminated or the cleaning quality is not up to standard, it will adversely affect the operation effect (10, 11). Therefore, it is of great significance to find a scientific instrument management method to promote the smooth development of ophthalmic surgery.

Although the traditional instrument management method adopted in the disinfection supply room can achieve a good management effect, there are relatively many problems and high instrument loss. Improper management can damage ophthalmic precision instruments, cause waste of medical resources, may also damage patients, affect the safety of clinical use, and cause medical accidents and medical disputes (12). Fine management is a management means to formulate a series of detailed operations according to the actual situation, which can identify, observe, extend the details, and improve the overall medical quality (13). This model starts with details, with the idea of improving management level, and continuously optimizes the intervention scheme, which can meet the requirements of managers to the greatest extent, and is professional and comprehensive (14). The PDCA cycle method includes small cycle and large cycle, which is a process of dynamic cycle rising step by step, and is managed repeatedly (15). Before the implementation of PDCA cycle method, it is necessary to set up an activity group to find and analyze the causes of past management errors, and then determine the expected goals, formulate improvement plans, and then carry out implementation and inspection. Finally, evaluate the effectiveness of improvement measures, think about unresolved problems, and enter the next round of PDCA cycle (16). Fine management and PDCA cycle method have received extensive attention in clinic. Therefore, we applied the two methods to the management of ophthalmic precision instruments and achieved good results.

Toxic anterior segment syndrome is an acute noninfectious postoperative inflammatory reaction, and it has become one of the common complications after eye surgery. The main clinical manifestations are diffused corneal edema and irregular pupil enlargement caused by anterior chamber cellulose exudation. At present, it is generally believed that the occurrence of TASS is closely related to the imperfect cleaning technology and incomplete disinfection of surgical instruments. In this study, compared with group A, group B has a lower risk score of instrument management, lower incidence of TASS, and better-qualified rate of disinfection and instrument performance. This suggests that fine management combined with PDCA cycle method can improve the qualified rate of disinfection of ophthalmic precision instruments, optimize the performance of instruments, reduce the risk of instrument management, and reduce the incidence of TASS. Fine management can optimize the operation process of each link, establish and improve the instrument maintenance measures, control the occurrence of risk factors, effectively improve the instrument performance, reduce the instrument loss, significantly improve the cleaning quality and functional quality of instruments, and ensure smooth operation. The quality of medical staff is an important prerequisite for fine management. Fine management can actively carry out specialized knowledge training and inform team members of relevant knowledge and precautions in disinfection management of ophthalmic precision instruments, so as to improve the awareness of prevention and control

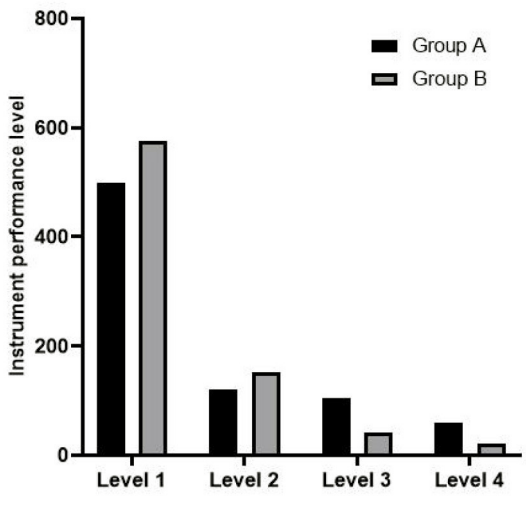


FIGURE 2 | Comparison of instrument performance grade between two groups.

TABLE 5 | Comparison of the incidence of TASS between two groups (*n*, %).

Group	Number of TASS cases	Incidence of TASS
Group A ($n = 200$)	7	3.50%
Group B ($n = 200$)	1	0.50%
χ^2 value		4.592
P-value		0.032

of infection among medical staff and ensure the cleaning quality and performance of ophthalmic surgical instruments in good condition, which is very important to ensure the safety of surgery, prolong the service life of instruments, and reduce medical costs. In the fine management, by optimizing the process of recycling, cleaning, packaging, sterilization and transportation of instruments, and strengthening the disinfection management of the storage environment of instruments, we can not only avoid the errors of instruments, but also avoid the pollution and damage of instruments. Cleaning instruments by combining both manual and utrasonic methods is time- and labor-saving, quick and convenient, and can thoroughly clean small stains. The administrator needs to carefully check whether each instrument is in good condition and without defects, strengthen the daily maintenance of precision instruments, and ensure that the instruments are in the best use state (17–19). The PDCA cycle method adopts different cleaning methods for different instrument fineness. Solid instruments are cleaned by hand, instruments with complicated structures are disassembled and cleaned ultrasonically, and cavities are repeatedly washed by a high-pressure water gun. When cleaning, appropriate cleaning agents are injected into the cavity. Additionally, nurses focus on cleaning and disinfection of instruments with high unqualified rate, thus effectively avoiding potential safety hazards in the management process and providing effective guarantee for improving the quality of instruments. In the process of implementing the PDCA cycle method, after each cycle, the group will integrate the problems existing in the instrument management, analyze and find out the reasons, formulate targeted improvement plans, adjust the work specifications, supervise and inspect, evaluate the improvement measures after inspection, and summarize the management experience. In addition, the manager will modify the measures with inaccurate management effect and incorporate new problems into the next PDCA cycle, so as to improve the instrument management quality in the continuous cycle and achieve the purpose of functional quality control (20–22). According to the uniqueness of ophthalmic precision instruments, fine management, and the PDCA cycle method are carried out on the basis of routine management, and the quality of ophthalmic precision instrument management has been greatly improved.

CONCLUSION

To sum up, fine management combined with the PDCA cycle method can improve the qualified rate of disinfection of ophthalmic precision instruments, optimize the performance of instruments, reduce the risk of instrument management, and reduce the incidence of TASS.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

The manuscript was written by FZ and LH was the supervisor of the whole study. All authors of this study have contributed equally and have done work of equal value to this study.

REFERENCES

1. Ling ML, Ching P, Widitaputra A, Stewart A, Sirijindadirat N, Thu LT, et al. A guidelines for disinfection and sterilization of instruments in health care facilities. *Antimicrob Resist Infect Control.* (2018) 7:25. doi: 10.1186/s13756-018-0308-2
2. Southworth PM. Infections and exposures: reported incidents associated with unsuccessful decontamination of reusable surgical instruments. *J Hosp Infect.* (2014) 88:127–31. doi: 10.1016/j.jhin.2014.08.007
3. Murdoch H, Taylor D, Dickinson J, Walker JT, Perrett D, Raven ND, et al. Surface decontamination of surgical instruments: an ongoing dilemma. *J Hosp Infect.* (2006) 63:432–8. doi: 10.1016/j.jhin.2006.02.015
4. Costa DM, Lopes LKO, Hu H, Tipple AFV, Vickery K. Alcohol fixation of bacteria to surgical instruments increases cleaning difficulty and may contribute to sterilization inefficacy. *Am J Infect Control.* (2017) 45:e81–6. doi: 10.1016/j.ajic.2017.04.286
5. Chobin N. Surgical instrument decontamination: a multistep process. *AORN J.* (2019) 110:253–62. doi: 10.1002/aorn.12784
6. Junk AK, Chen PP, Lin SC, Nouri-Mahdavi K, Radhakrishnan S, Singh K, et al. Disinfection of tonometers: a report by the American Academy of Ophthalmology. *Ophthalmology.* (2017) 124:1867–75. doi: 10.1016/j.ophtha.2017.05.033
7. Liu J. [Construction of subspecialty of critical care medicine under centralized and fine management of hospital: subject construction experience of Affiliated Hospital of Guizhou Medical University]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* (2019) 31:400–2. doi: 10.3760/cma.j.issn.2095-4352.2019.04.005
8. Vogel PA, Vassilev G, Kruse B, Cankaja Y. PDCA-Zyklus und Morbiditäts- und Mortalitätskonferenz als Basis der Wundinfektionsreduktion in der Kolorektalchirurgie [PDCA cyclus and morbidity and mortality conference as a basic tool for reduction of wound infection in colorectal surgery]. *Zentralbl Chir.* (2010) 135:323–9. doi: 10.1055/s-0030-1247280
9. Demirel A. Improvement of hand hygiene compliance in a private hospital using the Plan-Do-Check-Act (PDCA) method. *Pak J Med Sci.* (2019) 35:721–5. doi: 10.12669/pjms.35.3.6
10. Evangelista Sde S, dos Santos SG, de Resende Stoianoff MA, de Oliveira AC. Analysis of microbial load on surgical instruments after clinical use and following manual and automated cleaning. *Am J Infect Control.* (2015) 43:522–7. doi: 10.1016/j.ajic.2014.12.018
11. Alfa MJ. Medical instrument reprocessing: current issues with cleaning and cleaning monitoring. *Am J Infect Control.* (2019) 47S:A10–6. doi: 10.1016/j.ajic.2019.02.029
12. St Clair D. How can emerging disinfection technologies gain a foothold in the current culture of hospitals? *World Hosp Health Serv.* (2014) 50:20–2.
13. Sweet W, Snyder D, Raymond M. Design and implementation of the infection prevention program into risk management: managing high level disinfection and sterilization in the outpatient setting. *J Healthc Risk Manag.* (2020) 40:44–9. doi: 10.1002/jhrm.21407
14. Duro M. Surgical instrument tracking system advancements and benefits. *AORN J.* (2014) 100:C7–8. doi: 10.1016/S0001-2092(14)00665-6
15. Kong X, Zhu X, Zhang Y, Wu J. The application of plan, do, check, act (PDCA) quality management in reducing nosocomial infections in endoscopy rooms: it does work. *Int J Clin Pract.* (2021) 75:e14351. doi: 10.1111/ijcp.14351
16. Wang L, Qu X, Yu X. [PDCA Applied in Special Rectification of Medical Instrument Clinical Trial]. *Zhongguo Yi Liao Qi Xie Za Zhi.* (2015) 39:376–9.

17. Loesche AH. Using huddles to improve communication and teamwork in an instrument-processing department. *Nurs Manag.* (2020) 27:34–42. doi: 10.7748/nm.2020.e1958
18. Tan S, Jiang T, Ebrahimi A, Langrish T. Effect of spray-drying temperature on the formation of flower-like lactose for griseofulvin loading. *Eur J Pharm Sci.* (2018) 111:534–9. doi: 10.1016/j.ejps.2017.10.040
19. Huang Y, Huang Y, Chen Y, Pan W, Hu J, Yi L. Factors affecting implementation and pass rates of surgical instrument moistening. *BMC Infect Dis.* (2021) 21:752. doi: 10.1186/s12879-021-06471-3
20. Fukui T. [Patient safety and quality of medical care. Editorial: From evidence-based medicine to PDCA cycle]. *Nihon Naika Gakkai Zasshi.* (2012) 101:3365–7. doi: 10.2169/naika.101.3365
21. Gao Y, Chen X, Kang L. The effect of Plan-Do-Check-Act cycle nursing management of gynecological surgery: a systematic review and meta-analysis. *Ann Palliat Med.* (2021) 10:8072–81. doi: 10.21037/apm-21-1590
22. Qiu H, Du W. Evaluation of the Effect of PDCA in Hospital Health Management. *J Healthc Eng.* (2021) 2021:6778045. doi: 10.1155/2021/6778045

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zeng, Wang, Gao and Hu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 16 March 2022
doi: 10.3389/fsurg.2022.854632

Assessment of the Clinical Diagnosis of Onychomycosis by Dermoscopy

Yan Ma[1,2*†], *Ying Ji*[1,2†], *Wen Cen*[1,2], *Zusha Qiao*[1,2], *Yan Gao*[1,2], *Lu He*[3] *and Wenli Feng*[1,2*]

[1] *Department of Dermatology, The Second Hospital of Shanxi Medical University, Taiyuan, China,* [2] *Key Research Lab of Airway Neuroimmunology, Taiyuan, China,* [3] *Department Social Medicine, School of Public Health, Shanxi Medical University, Taiyuan, China*

Background: As a common clinical superficial fungal infection, the diagnosis of onychomycosis relies on clinical features, traditional KOH direct microscopy and fungal culture. In recent years, dermoscopy has been widely used in the diagnosis and treatment of infectious diseases and has provided new options for the diagnosis of onychomycosis.

Objective: To evaluate the value of dermoscopy in the clinical diagnosis of onychomycosis and to explore the relationship between each clinical subtype and the dermoscopic pattern.

Methods: A retrospective study of 114 cases of clinically suspected onychomycosis was conducted to compare the differences between dermoscopy and fungal pathogenic examination (microscopy and culture) in the diagnostic sensitivity of onychomycosis and to analyze the relationship between nine common dermoscopic modalities and clinical subtypes of onychomycosis.

Results: Among the 114 proposed patients, 87 nails with positive fluorescent staining microscopy and/or positive fungal cultures were diagnosed as onychomycosis. The sensitivity and specificity of dermatoscopy, using the mycological findings as a reference, were 86.21 and 33.33%, respectively. The incidence of common dermatoscopic patterns in the 87 nails with confirmed onychomycosis was as follows: white flocculation in 76 cases (87.35%), longitudinal nail pattern in 72 cases (82.76%), jagged changes in the distal nail plate in 69 cases (79.31%) and yellow staining in 46 cases (52.87%), these four patterns were more commonly seen in the distal lateral subungual onychomycosis and total dystrophic onychomycosis, but there was no statistical difference in the positive dermatoscopic pattern between these two types ($P > 0.05$).

Conclusion: Dermoscopy can be an important aid in the diagnosis of onychomycosis, especially when fungal microscopy or culture is not appropriate, but this method is still not a substitute for fungal microscopy and culture.

Keywords: onychomycosis, dermoscopy, fluorescence microscopy, sensitivity, diagnosis

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Liang Hui,
Hainan General Hospital, China
Feng Qin,
Shanghai Jiao Tong University School of Medicine, China

***Correspondence:**
Yan Ma
mayan197522@163.com
Wenli Feng
fwl92@hotmail.com

†These authors share first authorship

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *14 January 2022*
Accepted: *10 February 2022*
Published: *16 March 2022*

Citation:
Ma Y, Ji Y, Cen W, Qiao Z, Gao Y, He L and Feng W (2022) Assessment of the Clinical Diagnosis of Onychomycosis by Dermoscopy. Front. Surg. 9:854632. doi: 10.3389/fsurg.2022.854632

INTRODUCTION

Onychomycosis is a fungal infection of the fingernails caused by dermatophytes, non-dermatophytes and yeasts, with a global prevalence ranging from 2 to 13% in all age groups (1). Onychomycosis accounts for ∼50% of all nail diseases (2) and 30% of superficial fungal diseases (3), it is also the most common nail disease in the clinic, nail trauma, poor life hygiene habits, and

concomitant autoimmune diseases can easily lead to the development of nail fungus, in addition to its occurrence is also associated with factors such as economic and work stress, social exclusion and reduced quality of life (4, 5). Onychomycosis is mainly characterized by changes in the shape and color of the nail, affecting the patient's image and even secondary social difficulties, and because it is difficult to eradicate it can easily become a source of recurrent infections of other superficial fungal diseases. The rate of positive tests for nail fungal pathogenesis is the lowest of all superficial fungal diseases and is the most difficult type to diagnose and takes longer to administer, while accurate diagnosis is essential for the ongoing treatment and management of nail fungal disease (5, 6). The most widely used diagnostic method for nail fungal disease is still the traditional 10% KOH (potassium hydroxide) direct microscopy and fungal culture, however, its diagnostic sensitivity and specificity depends on the level of the examiner and the examination equipment, and the detection rate is <50% (7). Therefore, the search for other means to diagnose or aid in the diagnosis of the disease is a current clinical concern.

With the development of science and technology, new tests and examinations are emerging (6, 8–10). When comparing the advantages and disadvantages of PAS staining of nail tissue, KOH, and fungal culture in the diagnosis of onychomycosis, Haghani (11) used positive fluorescent staining as the diagnostic criterion for nail fungal infection. Modern dermoscopy, as a non-invasive, easy-to-use, and timely return portable examination tool, is a new and important adjunct to clinical work in dermatology and diagnostic methods, and has been widely used in China in recent years, and more and more physicians are using dermoscopy for onychomycosis in patients who are not suitable for routine fungal microscopy or culture (12, 13). In this study, we observed the use of dermoscopy in the diagnosis of onychomycosis in Shanxi, China.

MATERIALS AND METHODS

We used a retrospective study of patients with a proposed diagnosis of onychomycosis in our outpatient clinic from September 2017 to May 2018. Those who received antifungal medication in the last 6 months were excluded, and the largest lesion area was selected when multiple toenails were involved in the same patient. Each participant was given a detailed medical history, and gender, age, site of onset, number of nails, morphological characteristics and clinical subtypes were recorded separately, and the information recorded was classified and organized. All diseased nails were perfected with clinical staging observations, calcofluor white (CFW) fungal microscopy, fungal culture and dermoscopy. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the local medical ethics committee. All patients were informed about the study and signed an informed consent form.

Dermatoscopic examination and diagnostic basis Macrophotography of the diseased nail and acquisition of dermatoscopic images (×20 non-infiltrating mode) were performed by a dermatoscopic image processing workstation (manufacturer: Guangzhou Chuang Hong Medical Technology Co., Ltd., China, model: CH-DSIS-2000). Selection criteria for dermatoscopic images of onychomycosis: to avoid subjectivity, all dermatoscopic images were analyzed by two physicians and those with consistent results were selected. The diagnosis of onychomycosis was based on two or more of the currently accepted four patterns of dermoscopic examination of onychomycosis: "short spiny pattern, longitudinal striae, distal irregular interrupted pattern and linear pattern" (14). However, in practice, the dermoscopic changes of onychomycosiss were not limited to the above four types. Therefore, the group referred to the dermoscopic patterns of common nail diseases described by Piraccini et al. (14) and Nakamura and Costa (15) and combined with clinical experience, the following nine patterns were selected for observation of the selected diseased nails: serrated distal nail plate changes (**Figure 1**), longitudinal nail striae (**Figure 2**), white flocculent changes (**Figure 3**), subungualhyperkeratosis and debris (**Figure 4**), longitudinal nail fissures (**Figure 2**), bleeding under the nail (**Figure 5**), yellow homogeneous stains, punctate depression deformation (**Figure 6**), and peri nail erythema (**Figure 7**).

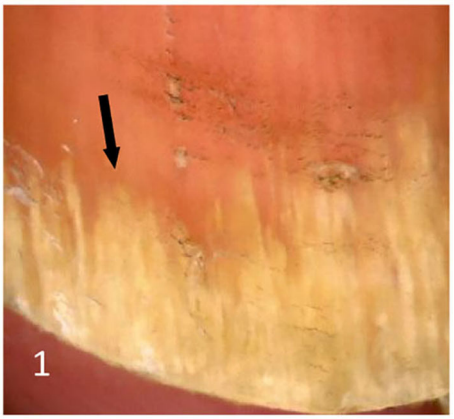


FIGURE 1 | Jagged distal nail plate changes.

Inclusion criteria: (1) patients who had not received antifungal medication in the last 6 months; (2) patients with nail changes and positive mycological microscopy (i.e., clear inky filaments observed under the microscope). Exclusion criteria: (1) Patients with co-morbidities such as psoriasis or chronic nail infection that may lead to nail changes; (2) Patients who were unable to cooperate with the retention of clinical and dermoscopic images.

Fungal examination of nail specimens: disinfected the diseased nail with 75% ethanol and scrape the suspected lesion into two equal parts, one for fungal microscopy and one for fungal culture. The collected nail debris specimens were placed on slides with 1 drop of fungal fluorescence staining sdution (Jiangsu Lifetime Biological Technology Co., Ltd., China) mixed thoroughly and left to stand for about 1–3 min after staining and then the slides were covered and observed under a fluorescent

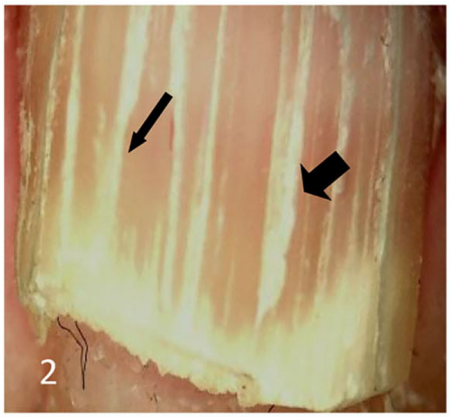


FIGURE 2 | Thin arrows indicate longitudinal striae; thick arrows indicate longitudinal nail fissures.

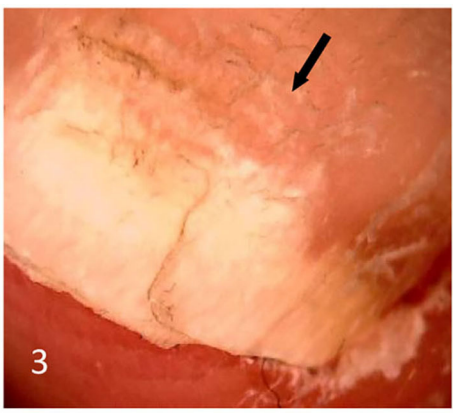


FIGURE 3 | White flocculent nail plate changes.

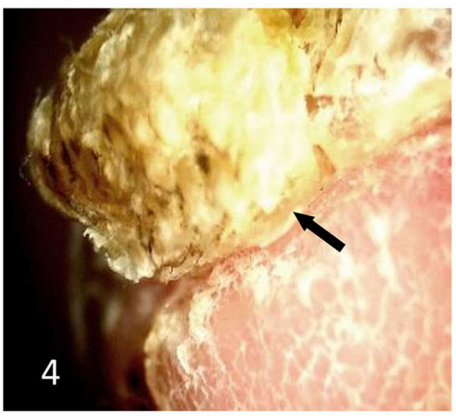


FIGURE 4 | Subungualhyperkeratosis and debris.

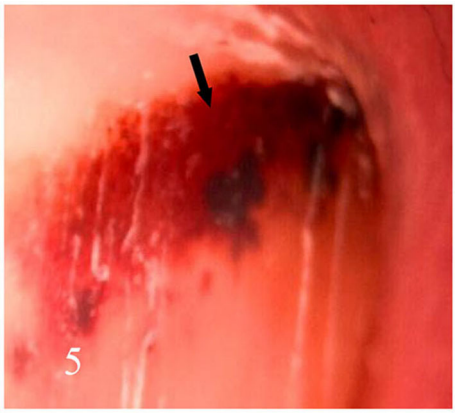


FIGURE 5 | Bleeding under the nail.

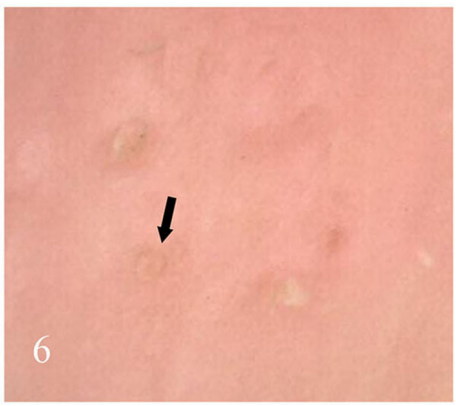


FIGURE 6 | Punctate depression of the nail plate.

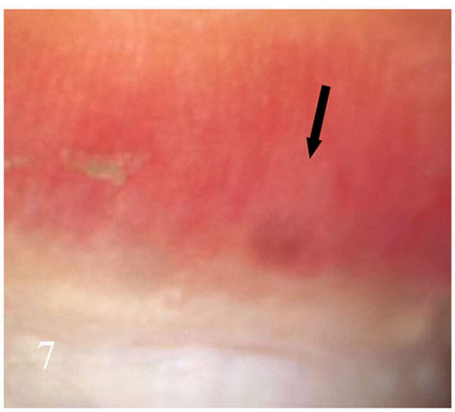


FIGURE 7 | Peri nail erythema.

microscope (Model: Olympus CX23, Japan, wavelength 340–380 nm) and observed under a fluorescent microscope, positive microscopy was diagnosed by the emission of bright blue fluorescent mycelial structures. This was done by two technicians simultaneously and those with consistent results were included in this study. Inoculate nail scraps in Sabouraud's Medium

containing chloramphenicol and actinomycin and incubate at 25°C. Observed and recorded the growth of colonies every other day from the 3rd day after inoculation for a period of 3 weeks.

Statistical methods: The sensitivity and specificity of dermatoscopy and mycological examination were compared with reference to fungal microscopy and culture results. The relationship between dermatoscopic patterns and clinical subtypes was further analyzed in nails diagnosed with onychomycosis. Data were expressed as number of cases and percentages, and all data were expressed as count data, except for the age of the subjects, which was described as mean ± standard deviation. $P < 0.05$ indicated that the difference is statistically significant.

RESULTS

Dermatoscopic and Fungal Findings

A total of 114 patients, 68 women and 46 men, aged 40.24 ± 16.33 years old (6–78 years old), with a clinical diagnosis of nail fungal disease were enrolled based on dermoscopic and fungal examination findings. The positive rates of dermoscopy, CFW fungal microscopy and fungal culture in all cases were: 81.58% (93/114), 71.93% (82/114), and 46.49% (53/114), respectively (see **Table 1**).

Observations of Dermoscopic Sensitivity and Specificity

A positive fungal microscopy and/or culture result of either was used as a positive fungal mycological result to confirm the diagnosis of onychomycosis. This result is also used as a reference to observe the sensitivity and specificity of dermoscopy (**Tables 2**–**4**).

Based on **Table 2**, it is clear that there were 87 cases of onychomycosis, the positive rate of fungal microscopy was 82/87 = 94.25% and the positive rate of fungal culture was 53/87 = 60.92%. Among the 114 patients, 87 had positive mycological results and 27 had negative mycological results.

According to **Table 3**, it can be seen that there were 75 cases with consistent positive dermoscopic and fungal results and 9 cases with consistent negative results, a total of 84 cases, accounting for 96.55% of onychomycosis.

According to **Table 4**, the sensitivity of dermoscopy for onychomycosis was 86.21%, i.e., dermoscopy easily detects onychomycosis but is not very specific and may misdiagnose nails with similar clinical presentation but caused by other causes as onychomycosis. The positive predictive value (PPV), i.e., the ability of dermoscopy to predict onychomycosis, was 80.65%, which is good. However, the kappa values indicated that the agreement between the two methods was not high, i.e., overall, dermoscopy as a diagnostic method for onychomycosis does not appear to be better than microscopy and culture at present.

Distribution of Different Dermoscopic Patterns in Clinical Subtypes of Onychomycosis

As seen in **Table 5**, of the 87 cases with positive CFW microscopy and positive culture confirming the diagnosis of onychomycosis, the number of cases of each clinical subtype was 3 (3.45%) for white superficial onychomycosis (SWO), 59 (67.82%) for distal lateral subungual onychomycosis (DLSO), 6 (6.90%) for proximal subungual onychomycosis (PSO) and 19 (21.83%) for total dystrophic onychomycosis (TDO), with DLSO and TDO being the most common subtypes, which is consistent with previous literature (5).

Intergroup Comparison of Dermoscopic Patterns Between the Two Subtypes of DLSO and TDO

As seen in **Table 5**, of the four common types of onychomycosis, SWO (3 cases) and PSO (6 cases) were not statistically significant for analysis due to the small number of cases. In contrast, the two clinical subtypes of DLSO (59 cases) and TDO (19 cases) totaled 78 cases, accounting for 89.66% of clinically diagnosed onychomycosis. Therefore, we compared the relationship between dermatoscopic patterns and clinical typing for both DLSO and TDO subtypes and found that $P > 0.05$ ($P = 0.239$), i.e., there was no statistical difference in the distribution of dermatoscopic patterns in these two clinical subtypes (**Table 6**). However, further analysis of the relationship between the dermatoscopic pattern and clinical staging revealed that nail white flocculation, longitudinal nail striae, jagged changes in the distal nail plate, yellow nail plate staining, and subcutaneous nail keratin accumulation were all more prevalent in the DLSO subtype and the TDO subtype and were the most common dermatoscopic patterns in the clinical setting.

DISCUSSION

The incidence of onychomycosis is increasing year on year, accounting for 90% of toenail infections and at least 50% of fingernail infections, and the incidence of onychomycosis varies slightly between age groups. The incidence is 10% in the general population, 20% in those aged 60 years and older, and over 50% in those aged 70 years and older (16–18). Onychomycosis mainly manifests as changes in the color and shape of the nail plate, similar to psoriasis. Nail changes due to inflammatory diseases such as lichen planus, pemphigus, viral warts, and chronic nail fungus are similar, and if the diagnosis is inaccurate it is easy to cause misdiagnosis, thus seriously affecting the quality of life of patients, so a clear diagnosis is very important (19). Direct microscopy with 10% potassium hydroxide (KOH), fungal culture, histopathological assessment, CFW examination, enzyme analysis and polymerase chain reaction are all used in the diagnosis of onychomycosis, with fungal microscopy and culture being the most common and widespread methods, but the sensitivity and specificity of these two methods vary considerably between centers due to the varying levels of testers (20). CFW

TABLE 1 | Clinical staging of 114 patients and positivity rate of the three tests.

	SWO		DLSO		PSO		TDO		Total	
	#	%	#	%	#	%	#	%	#	%
Total number of cases	3	2.63	78	68.42	12	10.53	21	18.42	114	
CFW positive	3	2.63	56	49.12	6	5.26	17	14.91	82	71.93
Dermoscopy positive	2	1.75	68	59.65	7	6.14	16	14.04	93	81.58
Culture positive	1	0.88	37	32.45	3	2.63	12	10.53	53	46.49

Among the 114 patients, the positive rates of dermoscopy, CFW microscopy and fungal culture were 81.58, 71.93, and 46.49% respectively.
 # Is the number of cases and % is the percentage of the subtype in the total number of lines.
SWO, white superficial onychomycosis; DLSO, distal lateral subungual onychomycosis; PSO, proximal subungual onychomycosis; TDO, total dystrophic onychomycosis.

TABLE 2 | CFW microscopy and fungal culture results.

	CFW microscopy	Fungal cultures	Number of cases
Positive for both	+	+	48
Positive CFW microscopy only	+	−	34
Positive fungal culture only	−	+	5
Negative for both	−	−	27

TABLE 3 | Dermatoscopic and fungal mycological results.

	Dermatoscopic	Fungal mycological	Number of case
Positive for both	+	+	75
Positive dermoscopy only	+	−	18
Positive fungal examination only	−	+	12
Negative for both	−	−	9

TABLE 4 | Analysis of the value of dermoscopic testing.

	Dermoscope (%)
Sensitivity	86.21
Specificity	33.33
Positive predictive value	80.65
Negative predictive value	42.86
Compliance rate	73.68
Kappa value	21.16

has a strong affinity for chitin chitinous substance and cellulose of the fungal cell wall and fluoresces bright blue under ultraviolet light for easy identification, so its sensitivity and specificity are significantly higher than KOH microscopy whether it is used for dander, body fluids or nail specimens (21), and has been widely used in fungal microscopy for onychomycosis in China in recent years. Dermatoscopy, as a non-invasive testing tool, can identify structures that are not visible to the naked eye or not easily identified clearly, and is widely used for the diagnosis and differential diagnosis of pigmented skin diseases and certain skin tumors.

It has been confirmed by domestic and international studies (12, 15) that dermatoscopy has been shown to be useful in the diagnosis of onychomycosis, especially in the distal lateral subxiphoid nail type where the dermatoscopic presentation is specific. For patients who are not suitable for fungal microscopy or culture, dermatoscopy is increasingly used to assist in the diagnosis of onychomycosis.

In the 114 patients with suspected onychomycosis in our study, the rate of positive CFW microscopy (71.93%) was higher than that of fungal culture (46.49%), in agreement with that reported by Dass et al. (22), and the rate of positive dermoscopy (81.58%) was also slightly higher than that of CFW microscopy. When fungal mycological results were used as a reference, the sensitivity of dermatoscopy was 86.21%, but the specificity was 33.33%, which may be influenced by the combined drawbacks of the respective dermatoscopic and pathogenic examinations. The tendency for false positives in dermatoscopic diagnosis due to the similar clinical presentation of nail damage from various causes and the limitations of nail specimens taken during pathogenic examination are the main reasons for their false negatives. The high positive predictive value and low negative predictive value of dermoscopy further suggest that dermoscopy is comparable to CFW microscopy in terms of sensitivity, although less specificity. However, as a non-invasive diagnostic imaging technique, it is still a good option for patients for whom nail specimen sampling is inconvenient and for primary screening and condition monitoring of onychomycosis.

The dermatoscopic pattern of onychomycosis and its differentiation from other nail diseases has been reported (23, 24), but relatively few studies have addressed the presentation of the dermatoscopic pattern in different clinical subtypes. Piraccini et al. (14) first proposed that the characteristic dermoscopic pattern of DLSO onychomycosis is a serrated edge at the junction of the diseased nail and the normal nail with the tip facing the nail bed, while the characteristic pattern of traumatic nail injury is a wavy edge at the border of the diseased nail and the normal nail. However, the dermatoscopic patterns of the other three clinical subtypes of onychomycosis are still inconclusive. Jesus-Silva et al. (25) analyzed the correlation between KOH microscopy and dermoscopic patterns in 178 diseased nails with clinically suspected onychomycosis and found that longitudinal nail stripes and serrated edges were

TABLE 5 | Clinical typing and dermoscopic pattern distribution of 87 patients with onychomycosis.

	SWO		DLSO		PSO		TDO		TOTAL	
	#	%	#	%	#	%	#	%	#	%
Total	3	3.45	59	67.82	6	6.90	19	21.83	87	100
Distal serration	2	2.30	51	58.62	2	2.3	14	16.09	69	79.31
Longitudinal nail stripe	1	1.15	52	59.77	3	3.45	16	18.39	72	82.76
White flocculation	3	3.45	49	56.32	6	6.90	18	20.69	76	87.35
Sub nail keratin build up	0	0	28	32.18	0	0	13	14.94	41	47.13
Longitudinal nail fissures	0	0	11	12.64	0	0	5	5.75	16	18.39
Bleeding under the nail	0	0	17	19.54	0	0	8	9.19	25	28.74
Yellow stain	0	0	34	39.08	1	1.15	11	12.64	46	52.87
Nail plate depression and deformation	1	1.15	21	24.14	0	0	7	8.05	29	33.33
Erythema around the nail	0	0	0	0	1	1.15	3	3.45	4	4.60

 # Is the number of cases, % is the percentage of cases in this group out of 87 cases of nail fungal disease.
SWO, white superficial onychomycosis; DLSO, distal lateral subungual onychomycosis; PSO, proximal subungual onychomycosis; TDO, total dystrophic onychomycosis.

TABLE 6 | Distribution of dermoscopic dermatoscopic patterns between two subtypes of DLSO and TDO in 78 cases of onychomycosis.

ITEM	DLSO ($n = 59$)	TDO ($n = 19$)	*P*-value
Distal serration	51	14	0.239
Longitudinal nail stripe	52	16	
White flocculation	49	18	
Sub nail keratin build up	28	13	
Longitudinal nail fissures	11	5	
Bleeding under the nail	17	8	
Yellow stain	34	11	
Nail plate depression and deformation	21	7	
Erythema around the nail	0	3	

more commonly associated with DLSO or TDO subtypes, and the incidence of positive distal serrated patterns in nails with pathogenically confirmed DLSO subtypes in this study was only 43.59%, which is inconsistent with Piraccini's et al. (14) who concluded that the sensitivity of the serrated pattern in the DLSO subtype was 100%. The present study also found a high rate of positivity for the distal serrated margin and nail longitudinal pattern in the DLSO subtype and TDO subtype, in agreement with the Jesus-Silva findings (25). However, the statistical analysis of the longitudinal nail striae and the distal serrated edge of the nail plate showed no statistically significant difference between the DLSO and TDO subtypes ($P > 0.05$), in agreement with Jesus-Silva's conclusions (25) but not with Chetana et al. (26), which may be related to the small number of cases included. Since DLSO is most common clinically and can eventually progress to TDO, distal serrated margins and longitudinal nail striae are also highly positive in the TDO subtype (14/19, 16/19). The yellow stain pattern is characterized by a stained yellow homogeneous change in the nail plate, while the subcutaneous keratin accumulation pattern refers to a ruinous accumulation of keratin on the ventral side of the nail plate (27). In the present study these two patterns were also more positive in the DLSO and TDO subtypes, and the statistical difference in dermoscopic pattern between these two subtypes was not statistically significant, which still needs to be confirmed in a large sample study. In addition, white flocculent changes of the nail plate are usually a clinical feature of the SWO type, and we found that this pattern, in addition to being seen in all SWO cases (3/3), also had a high positive rate in the DLSO subtype (49/59) and TDO subtype (18/19), with this dermoscopic pattern accounting for 87.35% of all onychomycosiss, suggesting that the latter two types of onychomycosis are highly susceptible to coexistence with the SWO subtype. We also found a case of PSO subtype with a white nail involving the proximal 4/5 of the nail plate and a serrated edge with the tip toward the free edge of the nail on the lateral edge of the white nail, as reported by Yorulmaz and Yalcin (27). In summary, we suggest that the longitudinal stripe pattern, the distal serrated pattern and the sub nail cuticle accumulation pattern are more likely to occur in the DLSO and TDO subtypes, as in the existing reports (25–27), whereas the yellow stain pattern is mostly used for the microscopic description of onychomycosis in the existing reports, and its diagnostic value is debatable.

This paper is the pioneer in comparing the value of dermoscopy and mycological examination in the diagnosis of onychomycosis, which is less well reported in the existing literature. In addition, the occurrence of nine dermoscopic patterns in different clinical subtypes of onychomycosis was analyzed, and it was concluded that dermoscopy can be a rapid, non-invasive and effective tool for the diagnosis of onychomycosis by combined fungal pathogenesis. The correlation between dermatoscopic patterns and clinical subtypes of onychomycosis needs to be further investigated in large samples.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Medical Ethics Committee. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YM and WF gave sufficient guidance to this study. All authors of this study have made equal contributions, including study design, inclusion of cases, implementation of experiments, statistics of data, and writing of the paper. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the Youth Science and Technology Research Fund of Shanxi Province Applied Basic Research Program (201901D211499) and the New Technology New Project of the Second Hospital of Shanxi Medical University (2017021).

REFERENCES

1. Leung AKC, Lam JM, Leong KF, Hon KL, Barankin B, Leung AAM, et al. Onychomycosis: an updated review. *Recent Pat Inflamm Allergy Drug Discov*. (2020) 14:32–45. doi: 10.2174/1872213X13666191026090713
2. Ricardo JW, Lipner SR. Safety of current therapies for onychomycosis. *Expert Opin Drug Saf*. (2020) 19:1395–408. doi: 10.1080/14740338.2020.1829592
3. Gupta AK, Foley KA, Mays RR, Shear NH, Piguet V. Monotherapy for toenail onychomycosis: a systematic review and network meta-analysis. *Br J Dermatol*. (2020) 182:287–99. doi: 10.1111/bjd.18155
4. Noguchi H, Matsumoto T, Kimura U, Hiruma M, Kano R, Yaguchi T, et al. Onychomycosis caused by Trichosporon cacaoliposimilis. *J Dermatol*. (2020) 47:e193–5. doi: 10.1111/1346-8138.15305
5. Lipner SR, Scher RK. Onychomycosis: treatment and prevention of recurrence. *J Am Acad Dermatol*. (2019) 80:853–67. doi: 10.1016/j.jaad.2018.05.1260
6. Ghannoum M, Mukherjee P, Isham N, Markinson B, Rosso JD, Leal L. Examining the importance of laboratory and diagnostic testing when treating and diagnosing onychomycosis. *Int J Dermatol*. (2018) 57:131–8. doi: 10.1111/ijd.13690
7. Aggarwal R, Targhotra M, Kumar B, Sahoo PK, Chauhan MK. Treatment and management strategies of onychomycosis. *J Mycol Med*. (2020) 30:100949. doi: 10.1016/j.mycmed.2020.100949
8. Méhul B, de Coi N, Grundt P, Genette A, Voegel JJ, Monod M. Detection of Trichophyton rubrum and Trichophyton interdigitale in onychomycosis using monoclonal antibodies against Sub6 (Tri r 2). *Mycoses*. (2019) 62:32–40. doi: 10.1111/myc.12843
9. Cuchí-Burgos E, Rubio-Casino R, Ballestero-Téllez M, Pariente-Jiménez F, Pérez-Jové J, Blanco-Suárez A. Commercial real time PCR implementation for rapid diagnosis of onychomycosis: a new workflow in a clinical laboratory. *Enferm Infecc Microbiol Clin (Engl Ed)*. (2021) 39:326–9. doi: 10.1016/j.eimce.2020.05.019
10. Watanabe S, Okubo A, Miyajima Y, Satoh K, Makimura K. Specific detection of Trichophyton rubrum and Trichophyton interdigitale based on loop-mediated isothermal amplification (LAMP) from onychomycosis specimens. *J Dermatol*. (2019) 46:1179–83. doi: 10.1111/1346-8138.15092
11. Haghani I, Shokohi T, Hajheidari Z, Khalilian A, Aghili SR. Comparison of diagnostic methods in the evaluation of onychomycosis. *Mycopathologia*. (2013) 175:315–21. doi: 10.1007/s11046-013-9620-9
12. Kayarkatte MN, Singal A, Pandhi D, Das S, Sharma S. Nail dermoscopy (onychoscopy) findings in the diagnosis of primary onychomycosis: a cross-sectional study. *Indian J Dermatol Venereol Leprol*. (2020) 86:341–9. doi: 10.4103/ijdvl.IJDVL_100_19
13. Kim YJ, Han SS, Yang HJ, Chang SE. Prospective, comparative evaluation of a deep neural network and dermoscopy in the diagnosis of onychomycosis. *PLoS ONE*. (2020) 15:e0234334. doi: 10.1371/journal.pone.0234334
14. Piraccini BM, Balestri R, Starace M, Rech G. Nail digital dermoscopy (onychoscopy) in the diagnosis of onychomycosis. *J Eur Acad Dermatol Venereol*. (2013) 27:509–13. doi: 10.1111/j.1468-3083.2011.04323.x
15. Nakamura RC, Costa MC. Dermatoscopic findings in the most frequent onychopathies: descriptive analysis of 500 cases. *Int J Dermatol*. (2012) 51:483–5. doi: 10.1111/j.1365-4632.2010.04720.x
16. Aslam R, Hussain T, Yousaf AM, Ghori MU, Khan IU, Rizvi SAA, Shahzad Y. Onychomycosis: current understanding and strategies for enhancing drug delivery into human nail tissue. *Curr Drug Res Rev*. (2021) 13:25–35. doi: 10.2174/2589977512666200731171505
17. Gupta AK, Stec N, Bamimore MA, Foley KA, Shear NH, Piguet V. The efficacy and safety of pulse vs. continuous therapy for dermatophyte toenail onychomycosis. *J Eur Acad Dermatol Venereol*. (2020) 34:580–8. doi: 10.1111/jdv.16101
18. Gupta AK, Venkataraman M, Renaud HJ, Summerbell R, Shear NH, Piguet V. A paradigm shift in the treatment and management of onychomycosis. *Skin Appendage Disord*. (2021) 7:351–8. doi: 10.1159/000516112
19. Nada EEA, El Taieb MA, El-Feky MA, Ibrahim HM, Hegazy EM, Mohamed AE, et al. Diagnosis of onychomycosis clinically by nail dermoscopy versus microbiological diagnosis. *Arch Dermatol Res*. (2020) 312:207–12. doi: 10.1007/s00403-019-02008-6
20. Abdallah NA, Said M, Mahmoud MT, Omar MA. Onychomycosis: correlation between the dermoscopic patterns and fungal culture. *J Cosmet Dermatol*. (2020) 19:1196–204. doi: 10.1111/jocd.13144
21. Prakash R, Prashanth HV, Ragunatha S, Kapoor M, Anitha TK, Krishnamurthy V. Comparative study of efficacy, rapidity of detection, and cost-effectiveness of potassium hydroxide, calcofluor white, and Chicago sky blue stains in the diagnosis of dermatophytoses. *Int J Dermatol*. (2016) 55:e172–5. doi: 10.1111/ijd.13037
22. Dass S. Manick VEV, Pavavni K, Pallam Aishwarya, Rao M. Srinivas. Comparison of KOH, calcofluor white and fungal culture for diagnosing fungal onychomycosis in an urban teaching hospital, Hyderabad. *Indian J Microbiol Res*. (2015) 2:148–53. doi: 10.5958/2394-5478.2015.00004.7
23. Bhat YJ, Mir MA, Keen A, Hassan I. Onychoscopy: an observational study in 237 patients from the Kashmir Valley of North India. *Dermatol Pract Concept*. (2018) 8:283–91. doi: 10.5826/dpc.0804a06
24. Litaiem N, Nakouri I, Bouhlel S, Mansour Y, Bouchakoua M, Zegaloui F. Dermoscopic features of toenail onychomycosis. *J Am Podiatr Med Assoc*. (2020) 110:4. doi: 10.7547/18-102
25. Jesus-Silva MA, Fernandez-Martinez R, Roldan-Marin R, Arenas R. Dermoscopic patterns in patients with a clinical diagnosis of onychomycosis-results of a prospective study including data of potassium hydroxide (KOH) and culture examination. *Dermatol Pract Concept*. (2015) 5:39–44. doi: 10.5826/dpc.0502a05
26. Chetana K, Menon R, David BG. Onychoscopic evaluation of onychomycosis in a tertiary care teaching hospital: a cross-sectional study from South India. *Int J Dermatol*. (2018) 57:837–42. doi: 10.1111/ijd.14008

27. Yorulmaz A, Yalcin B. Dermoscopy as a first step in the diagnosis of onychomycosis. *Postepy Dermatol Alergol.* (2018) 35:251–8. doi: 10.5114/ada.2018.76220

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Ma, Ji, Cen, Qiao, Gao, He and Feng. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 17 March 2022
doi: 10.3389/fsurg.2022.862716

The Mechanism of Downregulation of Twist1 Inhibiting Trophoblast Invasion and Aggravating the Development of Preeclampsia

*Shuangjian Yang, Wenjuan Tong and Yi Li**

The First Affiliated Hospital, Department of Gynecology and Obstetrics, Hengyang Medical School, University of South China, Hengyang, China

To study the expression of under expressed transcription factor Twist1 in preeclampsia (PE) and its effect on the invasion of placental trophoblast cells and to explore its related mechanism on the development of PE by establishing a pregnant rat model. Methods: the villi were collected from the induced abortion in the first trimester (6–8 weeks), the normal placenta (18–20 weeks) induced by the second trimester, the term placenta tissue of normal pregnancy (37–40 weeks), and the placental tissue of patients with PE, to detect the expression of Twist1. Trophoblast cells were subjected to primary culture in placental tissues of normal pregnant women and placental tissues of PE patients. The invasion ability of the two groups of trophoblasts was detected, and the primary cultured trophoblasts were divided into two groups: an experimental group and a control group. Specific Twist1 siRNA was added to the experimental group, and no reagents were added to the control group. The above-mentioned cells were given different interventions. To explore the effect of Twist1 on trophoblast cell invasion, cells were cultivated for 72 h. The SD rats were conceived. After the pregnancy was stable, the SD rats in different groups were treated with different treatments (interference with Twist1), and the average systolic blood pressure and urine protein of the gestational mothers in the different treatment groups were measured at 1 week, 2 weeks, and full-term pregnancy. The expression of Twist1 in the placenta tissue of SD rats with different interventions at full-term pregnancy was detected. The results showed that Twist1 expression is down-regulated in PE, and the invasion ability of placental trophoblast cells in PE patients is weak. After inhibiting Twist1, the mean tail artery pressure and urine protein level of SD pregnant rats increase, showing a trend of PE. The mechanism may be related to the inhibition of the placenta by Twist1 Trophoblast cell invasion.

Keywords: preeclampsia, transcription factor Twist1, placental trophoblast cells, invasion ability, urine protein

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Lihong Chen,
The First Affiliated Hospital of Fujian Medical University, China
Xiaming Pei,
Hunan Cancer Hospital, China

***Correspondence:**
Yi Li
liyi_6256@yeah.net

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *26 January 2022*
Accepted: *15 February 2022*
Published: *17 March 2022*

Citation:
Yang S, Tong W and Li Y (2022) The Mechanism of Downregulation of Twist1 Inhibiting Trophoblast Invasion and Aggravating the Development of Preeclampsia. Front. Surg. 9:862716. doi: 10.3389/fsurg.2022.862716

INTRODUCTION

Preeclampsia (PE) is a special type of hypertensive disorder complicating pregnancy (HDCP). The main characteristics are hypertension, proteinuria, and edema after 20 weeks of pregnancy, and blood pressure returns to normal after delivery (1). Due to differences in geography, society, economy, ethnicity, and culture, the incidence is different in different regions. Worldwide, the

incidence of PE is about 2–8%, while the incidence of PE in our country is relatively high, about 9.4%. Although more and more countries continue to improve the health of mothers and babies, more than 500,000 women die of pregnancy-related diseases every year, and about 10–15% of pregnant women die directly from PE and eclampsia (2–4).

The basic pathophysiological changes of PE are manifested as small vasospasm, vascular endothelial injury, reduced blood perfusion in the patient, multiple organs are damaged by ischemia and hypoxia, and insufficient placental perfusion can lead to fetal injury (5). It is currently believed that shallow placental implantation is the basis for the onset of PE, leading to long-term ischemia and oxidative stress in the placenta, releasing abnormal placental factors into the maternal blood circulation and inducing PE (6). Placental trophoblasts are the performers of the infiltration of the placenta into the endometrium and myometrium. In the first trimester, the placental trophoblast cells are in a physiological hypoxic state, and then the trophoblast cells gradually infiltrate the endometrium to the inner 1/3 of the muscle layer and enter the lumen of the uterine spiral arterioles to replace the vascular endothelium, resulting in enlargement of the lumen. The villi area of the placenta gradually expands, the blood supply resistance of the uterus–placenta decreases, the blood volume increases, and the hypoxic state of placental trophoblast cells is corrected. The increased apoptosis rate of placental trophoblast cells and decreased invasion ability will cause insufficient placental infiltration and uterine vascular remodeling, resulting in insufficient placental blood supply and oxidative stress in trophoblast cells, which ultimately leads to the occurrence of PE (7). Therefore, exploring the factors that regulate the activity and function of trophoblasts and their intervention methods are the key points to clarify the pathogenesis of PE and guide its prevention and treatment.

Abnormal trophoblast cell invasion and spiral artery remodeling disorder cause decreased placental perfusion, ischemia, and hypoxia, which is one of the most important pathogenesis of PE, and Twist1 can regulate cell differentiation and inhibit apoptosis in a variety of human tissues and tumors. Twist1 is widely expressed in placental trophoblasts, and its expression level shows a gestational week-dependent increase (8, 9). It is reported in the literature that Twist1 has the ability to promote the differentiation of trophoblasts (10), so we speculate that it may play an important role in the pathogenesis of placental-related disease-PE during pregnancy, but the correlation between the two needs to be further confirmed. Studies have shown (11) that Twist1 can directly regulate the activity and function of trophoblast cells, but the mechanism of action is unknown. Therefore, this study collected different placental tissues to detect the expression of Twist1 and explored the effect of Twist1 on the invasion of trophoblasts by isolating placental trophoblasts. It also analyzed the effect of Twist1 in SD-conceived rats and explored the relevant mechanism of Twist1's influence on PE. The specific report is as follows.

MATERIALS AND METHODS

Clinical Samples

From July 2018 to July 2020, the experiment collected chorionic villi in the first trimester of pregnancy (6–8 weeks), normal placenta (18–20 weeks), normal pregnancy full-term placenta (37–40 weeks), and placental tissue of PE (34–37 weeks). PE is characterized by hypertension after 20 weeks of pregnancy, blood pressure ≥140/90 mmHg, accompanied by proteinuria (≥300 mg protein/24 h), liver and kidney damage, pulmonary edema, central nervous system abnormalities, or visual impairment. None of the subjects developed thrombocytopenia syndrome. The study excluded patients with smoking, drinking, chronic hypertension, nephritis, cardiovascular disease comorbidities, multiple pregnancies, fetal chromosomal abnormalities, or other fetal abnormalities. All cases were delivered by cesarean section before delivery. All cases signed an informed consent form for the use of placental specimens and the study was approved by the ethics committee of our hospital.

Isolation and Culture of Placental Trophoblasts

The modified density gradient centrifugation method was used to separate and culture the trophoblast cells from the placental tissue of normal pregnancy and the placenta of patients with PE. The chorionic trophoblast tissue was cut and added in equal volumes of trypsin (2.5 g/L) and DNase (100 U/ml) in a 37°C water bath for 3 × 10 min and DMEM/F12 culture medium containing 10% fetal bovine serum was added to terminate the digested part and finally, the centrifugation was performed at 1,200 r/min for 5 min to obtain the cell suspension. The supernatant was discarded and resuspended in the DMEM/F12 medium culture. The cell suspension was divided into 2 parts, the first part was added to the cell Percoll separation solution, and the second part was added in the upper layer of the lymphocyte separation solution, and centrifuged at 1,500 r/min for 30 min with a centrifugal radius of 12 cm. A gray cloud-like cell layer at the junction of the different concentrations of the Percoll separation solution was observed, sucked the cell layer, and the cell layer between the lymphocyte separation solution and the culture solution was also observed. Both layers were washed two times with the culture solution and antibiotic saline and centrifuged at 1,200 r/min for 5 min (centrifugal radius = 12 cm). These cells were resuspended in the DMEM/F12 medium containing 20% fetal bovine serum, inoculated the culture plate at 1.0 × 105/ml, and continued to culture for 72 h in an incubator with 5% CO_2, saturated humidity at 37°C.

Identification of Trophoblasts

An inverted optical microscope (Jinan Jiawan Biotechnology Co., Ltd.) was used to observe the morphology of trophoblast cells; after cells were cultured for 72 h, 500 μl of freshly separated cell suspension was taken, fixed, and ruptured and 2 μl each of mouse anti-human CK-7 monoclonal antibody and goat anti-mouse IgG were added and shaken and incubated at 4°C for 20 min.

Flow cytometry was used to detect the CK-7 expression, and the percentage of CK-7 positive expressing cells was used to identify the purity of the cell.

Cell Transfection

The logarithmic trophoblast cells from normal pregnancy term placenta tissue were taken. When the cells were about 80% of the bottom of the bottle, trypsin digestion and passage and inoculation of 1 × 105 cells per well on a 12-well cell culture plate were performed. At the bottom of the bottle, cells were transfected according to the instructions of the Lipofectamine 2000 kit (Shanghai Duma Biotechnology Co., Ltd.). The Twist1 negative control plasmid and Twist1 interference plasmid were transfected into trophoblast cells, which were the si-NC group and si-Twist1 group, respectively, and the untreated cells were used as the blank control group. Each group has 5 duplicate wells, and the transfection efficiency of the cells was observed 48 h after transfection with a fluorescence microscope.

Detection of Twist1 Expression

The RT-qPCR and Western blotting were used to detect Twist1 mRNA and protein expression levels in tissues and cells. The TRIzol kit (Shanghai Yihui Biotechnology Technology Co., Ltd.) was used to obtain total RNA, which was subsequently reverse transcribed into cDNA and identified by agarose gel electrophoresis, identification, according to the RT-qPCR SYBR II kit (Shanghai Jizhi Biochemical Technology Co., Ltd.) instructions set the total reaction system to 20 μl, reaction conditions: 94°C pre-denaturation 5 min; denaturation at 95°C for 30 s, annealing at 60°C for 30 s, extension at 72°C for 50 s, repeat 40 cycles; and extension at 72°C for 5 min. Using β-actin as the internal reference gene, the $2^{-\Delta\Delta Ct}$method (12) was used to calculate the expression level of Twist1 mRNA in tissues and cells. Primer sequence: Twist1, Forward: 5′-GAGCTGGACTCCAAGATGG-3′, Reverse: 5′-TTAAGAAATCTAGGTCTCCGGC-3′; β-actin, Forward: 5′-GTGCACACGCACTGCACGCTGCACAC-3′, Reverse: 5′-TCGCCACTCACGTG-3′. The experiment was repeated 3 times and the average value was taken. In Western blotting, the following steps were performed: the tissue or cells were lysed on ice for 30 min, centrifuged and the protein was quantified, the sample was mixed with the loading buffer, denatured in a boiling water bath, centrifuged to collect the supernatant, separated by electrophoresis, wet transferred to the membrane, and sealed with 5% skimmed milk powder at room temperature for 2 h. Then, rabbit anti-rat Twist1 monoclonal antibody (1:1000) was added, incubated overnight at 4°C on a shaker, and goat anti-rabbit IgG secondary antibody (1:8000) was added after washing with TBST and incubated at room temperature for 1 h. It was added to the ECL darkroom for visualization, and the ratio of the gray value of the Twist1 protein band to the gray value of the internal reference β-actin band was used to indicate the protein expression level.

Detection of Cell Invasion Ability

A Transwell chamber (Shanghai Yanhui Biotechnology Co., Ltd.) experiment was used to detect the cell invasion ability of each group. Matrigel (diluted with PBS to 1 g/L) was pre-laid in a Transwell chamber with 50 μl per well. Cells with a density of 5.0×10^5/ml were added to the upper chamber, and 600 μl containing 10% fetal bovine serum was added to the lower chamber. RPMI medium, routinely cultured for 28 h until the cells degrade Matrigel, took the bottom filter membrane, washed with PBS, fixed with 0.25% glutaraldehyde, stained with 0.1% crystal violet after 20 min, wiped off the upper cells with a sterile cotton swab after 30 min, washed, dried, observed the staining under a microscope. Five fields were randomly selected and the average number of cells passing through the micropores in each field was calculated. This represents the cell invasion ability. The experiment was repeated 3 times and the average value was taken.

Conception and Grouping of SD Rats

Thirty SD female rats and 60 male rats (Hunan Slike Jingda Laboratory Animal Co., Ltd.) of the same weight and age were selected, and the SD female and male rats were caged together 1:2. The next morning, the vaginal plug was found to be the first day of pregnancy ("vaginal plug," also known as "vaginal suppository" or "mating suppository," is a substance formed after the coagulation of semen existing in the vagina after mating of animals for ∼24 h [short 4–5 h, long 48 h] to fall off automatically). The pregnant rats were divided into two groups, the normal group and the Twist1 inhibition group, with 8 rats in each group. After the pregnancy was stable, SD rats in different groups were given different treatments. The treatment group was given an intravenous injection of Twist1 antibody, and the control group was given an intravenous injection of normal saline.

Detection of Mean Tail Artery Pressure

The BP-2000 blood pressure analysis system was used to detect blood pressure before and after the operation. The rat was fixed in a heating bag in the cage, and after preheating at a temperature of 38°C for 10 min, the rat's tail was passed through a pressure sensor and fixed to the root of the rat's tail. The tail artery of the rat was brought into close contact with the pressure sensor, the waveform of the blood pressure measurement system was observed, and the blood pressure was measured after the waveform stabilized. The blood pressure of rats was detected at 1 week, 2 weeks, and full-term; each time, the measurement was repeated 3 times, the systolic and diastolic blood pressure were measured, the average arterial pressure was obtained, where the average arterial pressure = (systolic blood pressure + diastolic blood pressure × 2)/3.

Detection of Urine Protein Content

The blood pressure was measured and transient urine samples were collected from rats, and urine albumin and creatinine were measured using urine albumin ELISA kit and creatinine detection kit (Shanghai Fantai Biotechnology Co., Ltd.), respectively. The ratio of urine albumin to urine creatinine was used as the criterion for proteinuria. The urinary microalbumin/creatinine ratios of the two groups of rats at 1 week, 2 weeks, and full-term were determined. After the mean tail artery pressure and urine protein were detected at the full

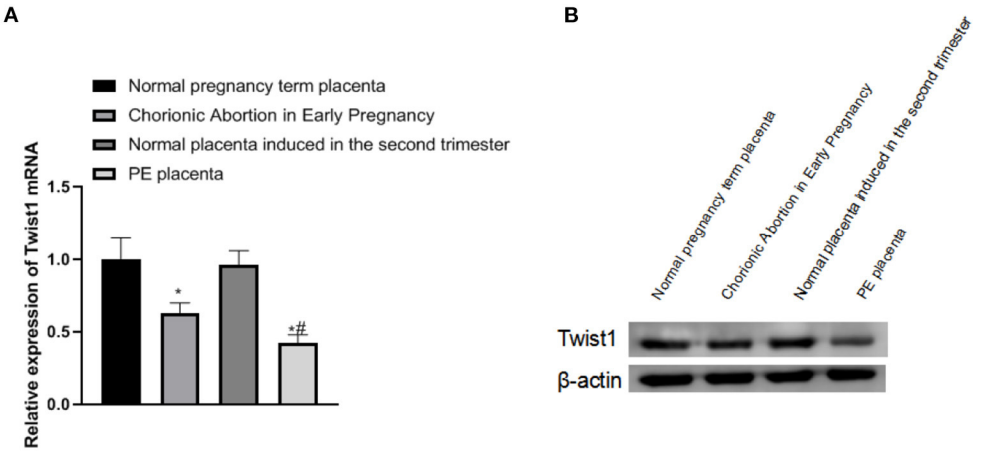


FIGURE 1 | The expression of Twist1 mRNA and protein in different placental tissues. **(A,B)** The expression of Twist1 mRNA and protein; Compared with Normal pregnancy term placenta, $^{*}p < 0.05$; compared with Chorionic Abortion in Early Pregnancy, $^{\#}p < 0.05$.

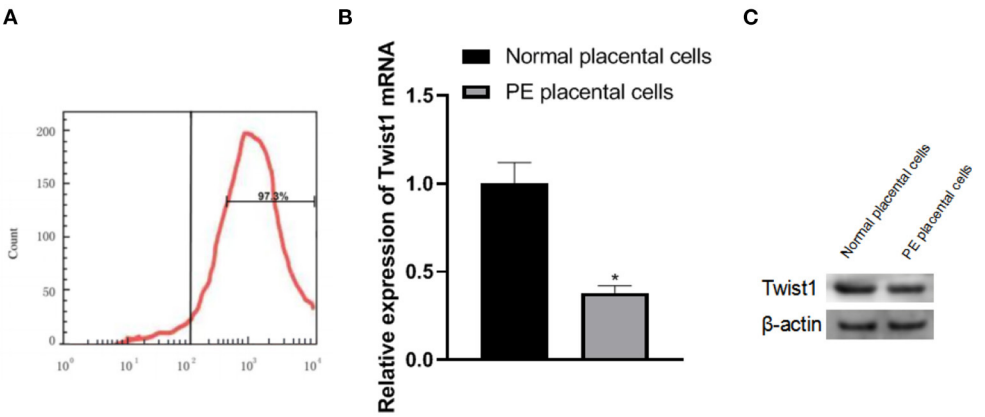


FIGURE 2 | Identification of primary trophoblast cells and the expression of Twist1 mRNA and protein in the cells. **(A)** Identification of Primary Trophoblasts; **(B,C)** The expression of Twist1 mRNA and protein; Compared with Normal placental cells, $^{*}p < 0.05$.

term of pregnancy, the pregnancy of SD rats after different treatments was terminated, and the placental tissue was extracted to detect the expression of Twist1 mRNA and protein in rat placental tissue according to the method described in Detection of Twist1 Expression.

Statistical Methods

The SPSS20.0 statistical software was used for data analysis. All experimental data were normally distributed, and the results were expressed as mean ± *SD*. The comparison between the two groups was performed by an independent sample *t*-test. The difference was statistically significant with $p < 0.05$.

RESULTS

The Expression of Twist1 MRNA and Protein in Different Placental Tissues

Compared with normal pregnancy full-term placenta tissue, the expression of Twist1 mRNA and protein in the placenta tissue of patients with early abortion and PE was significantly reduced, and the changes in placenta tissue of patients with PE were more obvious ($p < 0.05$), as shown in **Figures 1A,B**.

Identification of Primary Trophoblasts and the Expression of Twist1 MRNA and Protein in the Cells

The primary placental trophoblast cells were detected by flow cytometry. The cell surface-expressed abundant CK-7 and the percentage of CK-7 positive expressing cells were 97.3%, as shown in **Figure 2A**. The expression of Twist1 mRNA and protein in PE placental cells was significantly lower than that of normal placental cells ($p < 0.05$), as shown in **Figures 2B,C.**

The Effect of Interference With Twist1 on Trophoblast Cell Invasion

After the trophoblast cells were isolated, it was observed that the trophoblast cells of PE patients had weaker invasion ability than normal pregnant women's trophoblast cells ($p < 0.05$), as shown in **Figure 3A**. The invasion ability was significantly weakened ($p < 0.05$), as shown in **Figures 3B–D**.

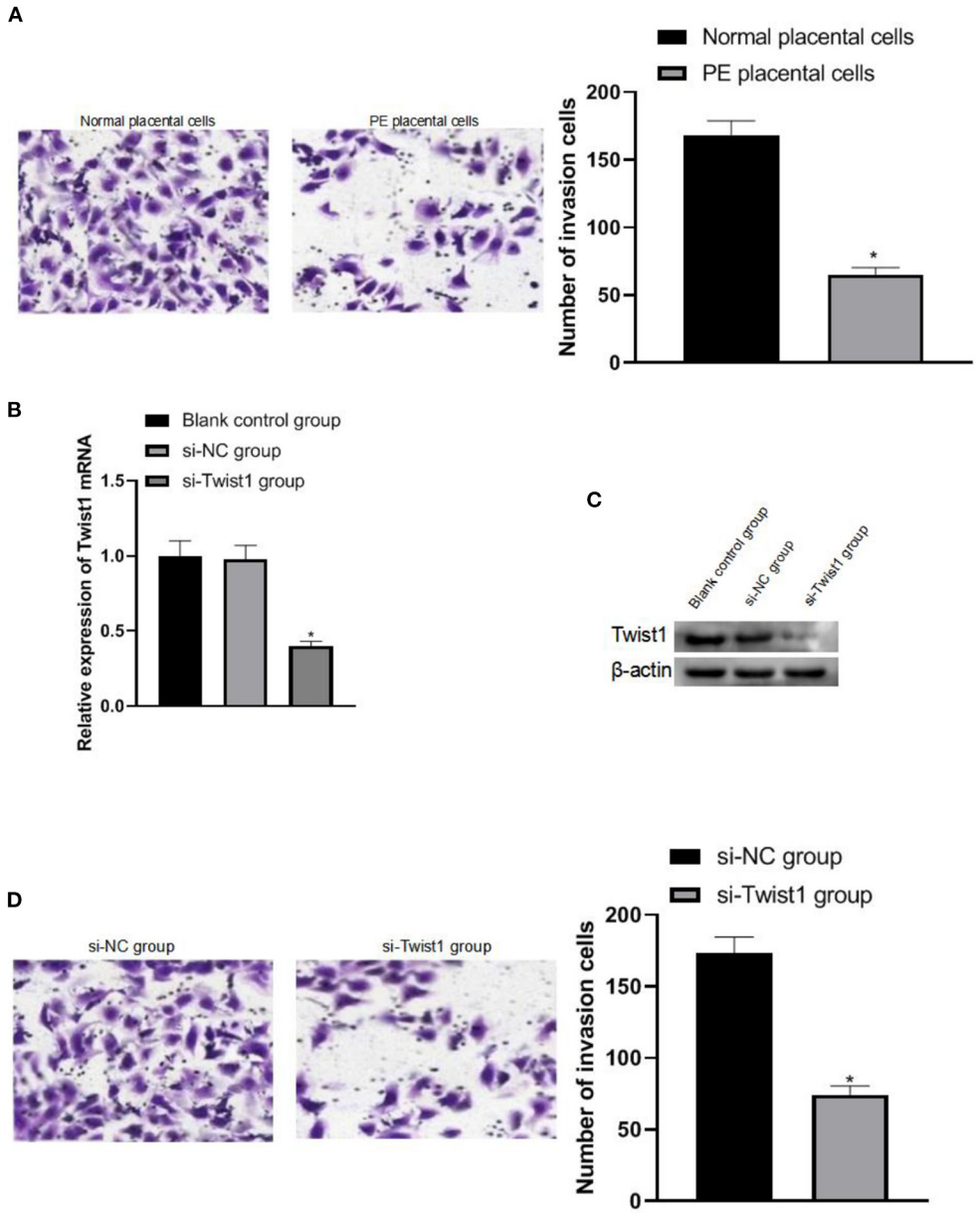


FIGURE 3 | The effect of interference with Twist1 on trophoblast cell invasion. **(A)** Detection of the invasive ability of trophoblasts; **(B,C)** The expression of Twist1 mRNA and protein; **(D)** Detection of the invasive ability of trophoblasts; Compared with Normal placental cells and si-NC group, $^{*}p < 0.05$.

The Effect of Inhibiting Twist1 on Mean Tail Artery Pressure and Urine Protein in Female Mice

The observation of *SD* conceived rats with different treatments found that compared with the normal group, the average tail artery pressure and urine protein level of rats in the Twist1 inhibition group increased significantly at 1, 2, and 3 weeks ($p < 0.05$), as shown in **Figures 4A,B.**

The Expression of Twist1 MRNA and Protein in the Placenta of Two Pregnant Rats

After the term, the expression of Twist1 in the placenta tissue was detected and it was found that the expression of Twist1 mRNA and protein in the placenta tissue of the Twist1 inhibition group was significantly lower than that of the normal group ($p < 0.05$), as shown in **Figures 5A,B**.

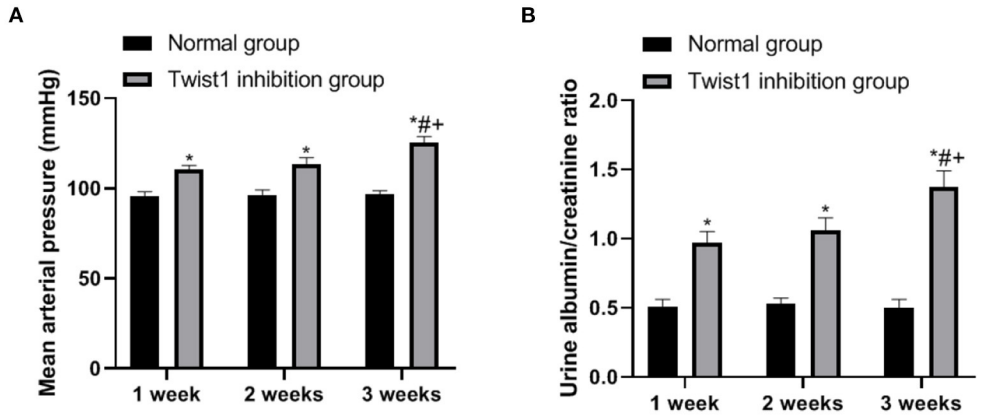


FIGURE 4 | The effect of inhibiting Twist1 on mean tail artery pressure and urine protein in female mice. **(A,B)** Detection of Mean Tail Arterial Pressure and Urine Protein in Female Rats; Compared with Normal group, $^{*}p < 0.05$; compared with Twist1 inhibition group of 1 week, $^{\#}p < 0.05$; compared with Twist1 inhibition group of 2 week, $^{+}p < 0.05$.

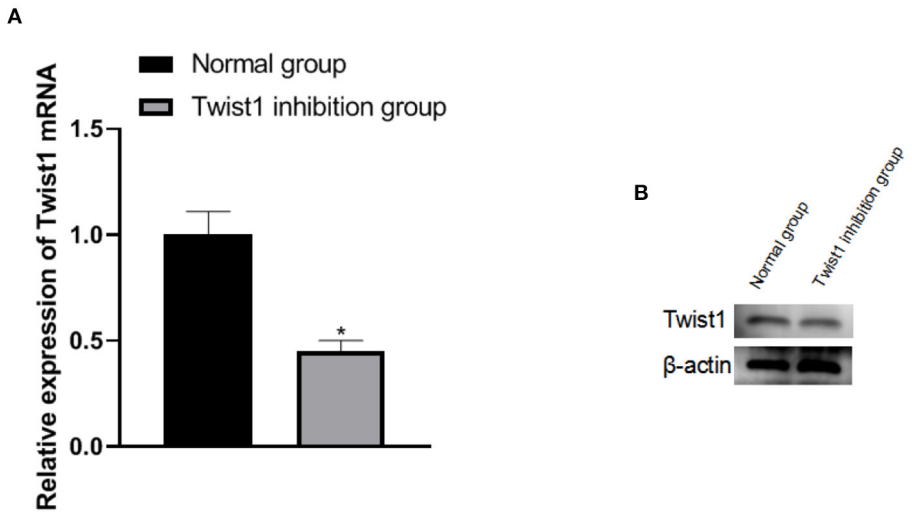


FIGURE 5 | The expression of Twist1 mRNA and protein in the placenta of two pregnant rats. **(A,B)** The expression of Twist1 mRNA and protein; Compared with Normal group, $^{*}p < 0.05$.

DISCUSSION

Preeclampsia manifests as hypertension, proteinuria, and is often accompanied by edema. PE with severe clinical manifestations is called severe PE, including severe hypertension, abnormal nerve, and circulatory and organ dysfunction (13). If PE is not well controlled, it can progress to eclampsia. It is possible to develop a variety of complications that threaten the lives of mothers and children, including hemolysis, elevated creatinine levels, low platelet syndrome, placental abruption, multiple organ dysfunction, diffuse intravascular coagulation, fetal distress, fetal intrauterine growth restriction, and stillbirth (14–16). Worldwide, the incidence of PE fluctuates from 5 to 12%, and the mortality rate of patients with eclampsia can reach 1%. Epidemiological investigations show that high-risk factors for PE include advanced age (≥40 years), diabetes, obesity, multiple pregnancies, family history of PE, and thrombotic vascular disease. The etiology and pathogenesis of PE have not yet been fully elucidated. At present, it is generally believed that the occurrence and development of PE involve a variety of factors, such as abnormal trophoblast cell invasion, abnormal immune regulation, endothelial cell damage, genetic factors, and systemic inflammation (17–19).

Trophoblasts are the main component of the placental structure and play an important role in the formation of the placenta and the maintenance of the normal development of the fetus. In the early stage of blastocyst implantation, trophectoderm cells differentiate into two types of trophoblast cells, namely cytotrophoblast cells and syncytial trophoblast cells (20). In the early stage of blastocyst implantation, trophectoderm

cells differentiate into two types of trophoblast cells, namely cytotrophoblast cells and syncytial trophoblast cells. There are two different differentiation pathways for cytotrophoblast cells: One is to fuse with syncytiotrophoblast cells, and the other one is to differentiate into infiltrating extravillous trophoblast cells (EVTs). Some EVTs infiltrate the deep layer of the endometrium to the inner third of the myometrium and are called interstitial trophoblast cells; some of the trophoblast cells that invade the maternal uterine spiral artery are called intravascular trophoblast cells. There are two stages of EVTs, invasion and placenta formation during pregnancy. In the first stage, 10 weeks before pregnancy, EVTs successfully invaded the decidua tissue of the uterus. If this process is blocked, it will lead to miscarriage. In the second stage, 10–18 weeks, EVTs successfully invade the subdecidual muscle layer and uterine SPA. The endothelial cells and smooth muscle cells of SPA undergo apoptosis, and gradually replace the vascular endothelium and vascular smooth muscle cells (VSMCs). The vascular basement membrane is degraded. The elastic fibers of the tube wall degeneration to form fibrin-like substances, which lead to changes in vascular resistance, forming a high-flow, low-resistance SPA, ensuring that sufficient circulating blood flow is provided for the fetal placenta (21). Therefore, damage to trophoblasts may also lead to the development of PE.

In female reproductive function, Twist1 can regulate the decidualization of uterine stromal cells, embryonic development, and organ differentiation (22). The development of the placenta and tumor growth has very similar characteristics in many aspects, so it can be speculated that the regulatory mechanism of Twist1 on tumor cell apoptosis also acts on trophoblast cells (23). In the study, focusing on the changes and nourish PE contact cell activity and function, by regulating the expression Twist1 detected trophoblast cell invasion ability change, thereby further exploring the role of Twist1 in placental development and pathogenesis of PE. The study found that compared with normal pregnancy full-term placenta tissue, the expression of Twist1 mRNA and protein in the chorionic tissue of early abortion and the placenta of PE patients were significantly reduced, and the chorionic tissue of the placental tissue of PE patients was significantly reduced compared with that of the early stage aborted chorionic tissue, which is partly consistent with the research results of Ma et al. (10). Twist1 is an evolutionarily highly conserved transcription factor, which is widely expressed in a variety of normal tissues and tumor cells and plays a regulatory role (24). Due to insufficient gestational age in abortion patients, the placental tissue of PE patients presents pathological changes. The decrease of Twist1 expression may indicate that it is related to the gestational age and pathological changes.

In order to explore the role of Twist1 in PE, linked it with trophoblasts, after we separated the trophoblasts, we observed that the trophoblasts of PE patients were weaker than the trophoblasts of normal pregnant women, suggesting that impaired trophoblast invasion may be the cause of the development of PE. After interfering with Twist1, it was found that the invasion ability of cells was also significantly weakened, suggesting that Twist1 can regulate the invasion ability of trophoblasts.

This also explains the reason for the low expression of Twist1 in the placental tissues of PE patients. The reduced expression of Twist1 weakens the invasion ability of trophoblasts, hinders the invasion of trophoblasts, and leads to obstacles to SPA remodeling. At the same time, oxygen free radicals are released and the vascular endothelium is damaged, causing the production of PE. Animal experiments were conducted to explore the effects of Twist1 on the body. Observation of SD conceived rats with different treatments found that after Twist1 inhibition, the average tail artery pressure and urine protein levels of the rats increased significantly at 1 week, 2 weeks, and full-term. Hypertension and proteinuria are the main manifestations of PE. After the term, the expression of Twist1 in the placenta tissue was detected, and it was found that the expression of Twist1 mRNA and protein in the placenta tissue of the Twist1 inhibition group was significantly lower than that of the normal group. It shows that the *in vivo* experiment interferes with the success of Twist1, and the insufficient expression of Twist1 can make pregnant female mice show PE morbidity.

CONCLUSION

In summary, the expression of Twist1 is downregulated in PE, and the invasion ability of trophoblast cells in the placental tissue of PE patients is weak. After inhibiting Twist1, the mean tail artery pressure and urine protein level of SD conceived rats increased, showing a trend of PE. The mechanism may be related to the ability of Twist1 to inhibit the invasion of placental trophoblast cells.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by this study was approved by the Ethics Committee of the First Affiliated Hospital, Hengyang Medical School, University of South China. The patients/participants provided their written informed consent to participate in this study. The animal study was reviewed and approved by this study was approved by the Animals Ethics Committee of the First Affiliated Hospital, Hengyang Medical School, University of South China.

AUTHOR CONTRIBUTIONS

WT is responsible for the design of the study and the conduct of the experiment. SY is responsible for the detection of the results, the statistics of the data and the writing of the article, and YL is the supervisor of the whole study. All authors of this study have made equal contributions. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by the 2021 Hunan Provincial Health Commission Scientific Research Project (202105020156).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.862716/full#supplementary-material

REFERENCES

1. Maeda Y, Kaneko K, Ogawa K, Sago H, Murashima A. The effect of parity, history of preeclampsia, and pregnancy care on the incidence of subsequent preeclampsia in multiparous women with SLE. *Mod Rheumatol*. (2021) 31:843–8. doi: 10.1080/14397595.2020.1830466
2. Cheng S, Liu X, Chen A, Li H, Yan L. Exploring the Mechanism of Action of Banxia Baizhu Tianma Decoction against Preeclampsia by a Network Pharmacology Approach. *Evid Based Complemen Altern Med*. (2021) 2021:8843833. doi: 10.1155/2021/8843833
3. Tan S, Chen X, Cui C, Hou Y, Li W, You H. Biodegradation of saline phenolic wastewater in a biological contact oxidation reactor with immobilized cells of Oceanimonas sp. *Biotechnol Lett*. (2017) 39:91–96. doi: 10.1007/s10529-016-2226-9
4. Walsh SW, Strauss JF 3rd. The Road to Low-Dose Aspirin Therapy for the Prevention of Preeclampsia Began with the Placenta. *Int J Mol Sci*. (2021) 22:6985. doi: 10.3390/ijms22136985
5. Xu H, Xie Y, Sun Y, Guo R, Lv D, Li X, et al. Integrated analysis of multiple microarray studies to identify potential pathogenic gene modules in preeclampsia. *Exp Mol Pathol*. (2021) 120:104631. doi: 10.1016/j.yexmp.2021.104631
6. Pinto-Souza CC, Coeli-Lacchini F, Luizon MR, Cavalli RC, Lacchini R, Sandrim VC. Effects of arginase genetic polymorphisms on nitric oxide formation in healthy pregnancy and in preeclampsia. *Nitric Oxide*. (2021) 109–10:20–5. doi: 10.1016/j.niox.2021.02.003
7. Song W, Shi X, Liu K, Li R, Niu L, Su L, Wu H. Detection of mitochondrial coupling factor 6 in placental tissues from preeclamptic pregnancies and its influence on biological behavior of trophoblast cells. *Exp Ther Med*. (2021) 22:1185. doi: 10.3892/etm.2021.10619
8. Hashimoto M, Uesugi N, Osakabe M, Yanagawa N, Otsuka K, Kajiwara Y, et al. Expression Patterns of Microenvironmental Factors and Tenascin-C at the Invasive Front of Stage II and III Colorectal Cancer: Novel Tumor Prognostic Markers. *Front Oncol*. (2021) 11:690816. doi: 10.3389/fonc.2021.690816
9. Zhao T, Yang Y, Yang J, Cui Y, Cao Z, Zuo D, et al. Harmine-inspired design and synthesis of benzo[d]imidazo[2,1-b]thiazole derivatives bearing 1,3,4-oxadiazole moiety as potential tumor suppressors. *Bioorg Med Chem*. (2021) 46:116367. doi: 10.1016/j.bmc.2021.116367
10. Ma L, Zhang Z, Dong K, Ma Y. TWIST1 Alleviates Hypoxia-induced Damage of Trophoblast Cells by inhibiting mitochondrial apoptosis pathway. *Exp Cell Res*. (2019) 385:111687. doi: 10.1016/j.yexcr.2019.111687
11. Zhang L, Wang H, Liu C, Wu Q, Su P, Wu D, et al. MSX2 Initiates and Accelerates Mesenchymal Stem/Stromal Cell Specification of hPSCs by Regulating TWIST1 and PRAME. *Stem Cell Rep*. (2018) 11:497–513. doi: 10.1016/j.stemcr.2018.06.019
12. Wang S, Gao G, He Y, Li Q, Li Z, Tong G. Amidation-Modified Apelin-13 Regulates PPARγ and Perilipin to Inhibit Adipogenic Differentiation and Promote Lipolysis. *Bioinorg Chem Appl*. (2021) 2021:3594630. doi: 10.1155/2021/3594630
13. Tsigas EZ. The Preeclampsia Foundation: the voice and views of the patient and her family. *Am J Obstet Gynecol*. (2021) 226:S1254-S1264.e1. doi: 10.1016/j.ajog.2020.10.053
14. McLaughlin K, Hobson SR, Ravi Chandran A, Agrawal S, Windrim RC, Parks WT, et al. Circulating Maternal Placental Growth Factor Responses to Low Molecular Weight Heparin in Pregnant Patients at Risk of Placental Dysfunction. *Am J Obstet Gynecol*. (2022) 226:S1145-S1156.e1. doi: 10.1016/j.ajog.2021.08.027
15. McCarthy FP, O'Driscoll JM, Seed PT, Placzek A, Gill C, Sparkes J, et al. Multicenter Cohort Study, With a Nested Randomized Comparison, to Examine the Cardiovascular Impact of Preterm Preeclampsia. Hypertension. (2021) 78:1382–94. doi: 10.1161/HYPERTENSIONAHA.121.17171
16. Conrad KP, Von Versen-Höynck F, Baker VL. Potential Role of the Corpus Luteum in Maternal Cardiovascular Adaptation to Pregnancy, and Preeclampsia Risk. *Am J Obstet Gynecol*. (2021) 23:S0002-9378(21)00888-7. doi: 10.1016/j.ajog.2021.08.018
17. Yang X, Meng T. miR-215-5p decreases migration and invasion of trophoblast cells through regulating CDC6 in preeclampsia. *Cell Biochem Funct*. (2020) 38:472–9. doi: 10.1002/cbf.3492
18. Smith TA, Kirkpatrick DR, Kovilam O, Agrawal DK. Immunomodulatory role of vitamin D in the pathogenesis of preeclampsia. *Expert Rev Clin Immunol*. (2015) 11:1055–63. doi: 10.1586/1744666X.2015.1056780
19. Binder NK, MacDonald TM, Beard SA, de Alwis N, Tong S, Kaitu'u-Lino TJ, Hannan NJ. Pre-Clinical Investigation of Cardioprotective Beta-Blockers as a Therapeutic Strategy for Preeclampsia. *J Clin Med*. (2021) 10:3384. doi: 10.3390/jcm10153384
20. Liao S, Wang B, Zeng R, Bao H, Chen X, Dixit R, et al. Recent advances in trophoblast cell-surface antigen 2 targeted therapy for solid tumors. *Drug Dev Res*. (2021) 8:30. doi: 10.1002/ddr.21870
21. Fang L, Wang Z, Wu Z, Yan Y, Gao Y, Li Y, et al. GDF-8 stimulates trophoblast cell invasion by inducing ALK5-SMAD2/3-mediated MMP2 expression. *Reproduction*. (2021) 162:331–8. doi: 10.1530/REP-21-0197
22. Proestling K, Birner P, Balendran S, Nirtl N, Marton E, Yerlikaya G, et al. Enhanced expression of the stemness-related factors OCT4, SOX15 and TWIST1 in ectopic endometrium of endometriosis patients. *Reprod Biol Endocrinol*. (2016) 14:81. doi: 10.1186/s12958-016-0215-4
23. Lai SW, Chen MY, Bamodu OA, Hsieh MS, Huang TY, Yeh CT, et al. Exosomal lncRNA PVT1/VEGFA Axis Promotes Colon Cancer Metastasis and Stemness by Downregulation of Tumor Suppressor miR-152-3p. *Oxid Med Cell Longev*. (2021) 2021:9959807. doi: 10.1155/2021/9959807
24. Jao TM, Fang WH, Ciou SC, Yu SL, Hung YL, Weng WT, et al. PCDH10 exerts tumor-suppressor functions through modulation of EGFR/AKT axis in colorectal cancer. *Cancer Lett*. (2021) 499:290–300. doi: 10.1016/j.canlet.2020.11.017

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Yang, Tong and Li. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 17 March 2022
doi: 10.3389/fsurg.2022.837014

Analysis of the Application Effect of PDCA Cycle Management Combined With Risk Factor Management Nursing for Reducing Infection Rate in Operating Room

*Hong Chen, Ping Wang and Qi Ji**

Operating Room, The First People's Hospital of Lianyungang, Lianyungang, China

Purpose: To explore the application effect of plan-do-check-action (PDCA) cycle management combined with risk factor management nursing in an operating room.

Methods: A total of 150 surgical patients in our hospital from November 2020 to February 2021 were selected as the conventional group, and 150 surgical patients in our hospital from March 2021 to June 2021 were selected as the research group. The conventional group implemented routine infection management, and the research group implemented PDCA cycle management combined with risk factor management. Detection of pathogenic bacteria, incidence of incision infection, infection control, occurrence of irregular events, and nursing quality in the operating room were observed in the two groups.

Results: The detection rate of Gram-negative bacillus and Gram-positive cocci, infection rate of incision, and total incidence of irregular events in the research group were lower than those in the conventional group ($P < 0.05$). The qualified rate of disinfection of object surface, hands of medical staff and air, and nursing quality scores in the research group were higher than those in the conventional group ($P < 0.05$).

Conclusion: Plan-do-check-action (PDCA) cycle management combined with risk factor management nursing can reduce the detection rate of pathogenic bacteria and infection rate of incision in the operating room, reduce the incidence of irregular events, improve the qualified rate of disinfection, and greatly improve the quality of nursing, which can be considered to be widely used in clinical practice.

Keywords: PDCA cycle management, risk factor management, operating room, infection rate, nursing quality

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Yan Zou,
University of South China, China
Fang Wei,
Central South University, China

****Correspondence:***
Qi Ji
jiqicat@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *16 December 2021*
Accepted: *10 February 2022*
Published: *17 March 2022*

Citation:
Chen H, Wang P and Ji Q (2022) Analysis of the Application Effect of PDCA Cycle Management Combined With Risk Factor Management Nursing for Reducing Infection Rate in Operating Room. Front. Surg. 9:837014. doi: 10.3389/fsurg.2022.837014

INTRODUCTION

An operating room is the main place for disease treatment and emergency rescue of surgical patients. The patient's condition in an operating room is complex and changeable, and has a high risk. An operating room is the place where hospital infection is most likely to occur. In an operating room, air, particles, hands of medical staff, and other factors may become the way of infection for patients (1, 2). Once patients are infected in an operating room, it may cause

other diseases, which will affect the therapeutic effect and clinical outcome of an operation, and even threaten the patient's life. At the same time, infection of patients in an operating room will increase hospital dispute rate and increase the workload of medical staff (3, 4). An operating room has a wide range of work, many complicated events, many medical staff, and high risk of infection. Therefore, compared with outpatient and inpatient areas, an operating room has higher requirements for nursing quality management (5). However, at present, there is a big gap between actual infection management status and expected nursing goals in most operating rooms. The quality of infection management in an operating room not only directly affects the life safety of surgical patients but is also closely related to the service quality of the whole surgical system. How to build a high-quality infection control management system, ensure the safety of surgical patients, and improve the quality of operating room environments is the clear goal of operating room managers.

Plan-do-check-action (PDCA) cycle management is an effective management tool. The PDCA cycle divides quality management into four stages: plan, do, check, and action; it also divides quality management into eight steps: asking questions, setting goals, drawing up plans, implementing plans, checking results, finding out problems, solving problems, and putting forward new plans (6). In PDCA cycle management, every link is closely linked, and it is implemented repeatedly without stopping, so management objectives can be achieved step by step (7). PDCA cycle management is a scientific and comprehensive working procedure of quality management. Applying PDCA cycle management to nursing management can obviously improve nursing quality and reduce shortage in management scheme, so as to obtain better overall hospital quality (8). Risk factor management refers to the process of minimizing the probability of risk occurrence by studying the occurrence law of risk and thinking about how to control risk and deal with risk factors in the management system (9). Applying risk factor management to nursing work by risk identification and risk assessment can improve the risk awareness of medical staff, effectively prevent the occurrence of risk factors, reduce harm to patients and hospitals, reduce economic losses, and obtain greatest security (10).

At present, PDCA cycle management and risk factor management have been widely recognized by people in the field of nursing management at home and abroad. However, the effect of applying the above two management methods to infection care in operating rooms is worth considering by medical staff. PDCA cycle management combined with risk factor management nursing is implemented in infection management of operating rooms in our hospital. Detailed intervention methods and intervention effects are summarized as follows.

MATERIALS AND METHODS

Research Object

A total 150 surgical patients in our hospital from November 2020 to February 2021 were selected as the conventional group, and 150 surgical patients in our hospital from March 2021 to June 2021 were selected as the research group. Inclusion criteria were: ① no serious organ diseases, ② no severe anemia, and ③ normal intelligence. Exclusion criteria were: ① an infection existed before admission, ② complicated with immune system diseases, ③ complicated with malignant tumor, and ④ poor compliance. The general data of the two groups were balanced and comparable ($P > 0.05$). See **Table 1** for specific general data.

Research Methods

(1) The conventional group implemented routine infection management, including environmental disinfection of operating room, sterilization of instruments, prevention of incision infection, disinfection and isolation, hand hygiene of medical staff, and management of sterile goods, etc.
(2) The research group implemented PDCA cycle management combined with risk factor management. The specific nursing methods were as follows.

Risk management nursing: we investigated the risk factors of infection in the operating room, such as nurses' lack of awareness of infection risk, inadequate management, personnel turnover, and other factors; we formulated a reasonable and preventable management system according to identified infection risk factors, summarized the risk factors, and gave early warning and feedback to doctors in time for factors that were highly suspected to cause surgical infection. A hospital sense control team was established, which was composed of nurses with working experience > 10 years, and nursing staff with the title of chief nurse or above. The team members discussed the influencing reasons of risk factors together and adjusted the management plan appropriately. We updated various infection rules and regulations according to the actual situation of the hospital, including disinfection, hand washing, sanitation, visit, waste treatment, and other projects; we formulated an infection monitoring record list; regular inspections and supervision of disinfection and isolation of the operating room were carried out, and infection management was carried out under the guidance of PDCA cycle management.

Plan-do-check-action (PDCA) cycle management: ① plan: observed the management status of the operating room, find out core problems at present, establish an infection management plan for the operating room with reference to "Hospital Infection Management Standard", and formulate an investigation table of nursing quality in the operating room, including environmental management, nursing safety, item management, disinfection and isolation, etc; ② do: the department regularly organized training to urge medical staff to master the knowledge of hand hygiene, disinfection and isolation, dressing in the operating room and medical wastes, and implement various rules and regulations; detailed instructions of seven washing techniques and precautions for hand disinfection were pasted above the sink, and monitor whether the operating staff strictly followed the operating rules of hand washing and disinfection; The operating room was scientifically arranged, the passage of medical staff was reasonably arranged, the number of visitors to an operation was limited, the sterile operating room, the general operating room, and the infection operating room were strictly distinguished, inter-surgery was prohibited, the

TABLE 1 | Comparison of general data between the two groups (*n*, %).

Group	Gender		Age (years)				
	Male	Female	<40	≥40	Class I incision	Class II incision	Class III incision
Conventional group ($n = 150$)	89 (59.33%)	61 (40.67%)	68 (45.33%)	82 (54.67%)			
Research group ($n = 150$)	93 (62.00%)	57 (38.00%)	61 (40.67%)	89 (59.33%)			
χ^2value	0.224	0.666					
P-value	0.636	0.414					

flow of items was controlled, and the items and equipment in the operating room were fixed and did not frequently change locations; a chlorinated disinfectant was used to wipe the surface of objects in and the floor of the operating room to ensure that surgical items were dry and sterile. The area above the shoulder of the operator and below the belly button was the area with bacteria. The sterile table cloth sag > 30 cm should be replaced immediately after being touched; the sterilized surgical items were managed by a dedicated person, the sterile validity period of disposable articles should be checked, the sealing property should be checked, and medical wastes should be classified and disposed according to the medical waste specification after use; ③ check: key links of infection control, such as surgical instruments, sterile materials, disinfectants were regularly checked, and various infection management tasks were filled in the supervision record form; the operating room was comprehensively reviewed according to the operating room nursing quality inspection form. In the check, the hospital infection office personnel participated in the supervision, analyzed existing infection prevention and control problems, and negotiated to solve the problems. Methods such as theoretical assessment, operational skill assessment, and random questioning were used to assess the knowledge of nurses on the prevention of infection in the operating room, and spot-checked on infection control has been implemented; ④ action: summarized the problems and risk factors of infection in operating room, found out the inadequacies of management from an objective point of view, adjusted the management plan according to the characteristics of departments, formulated targeted solutions, and rectified deficiencies one by one. Unsolvable problems and improvement goals were put into the next PDCA cycle mode, so that the infection control work in the operating room was continuously and systematically monitored.

Observation Index

① Blood 2 ml was taken from patients in both groups 24 h after operation, and pathogen culture was conducted to observe the detection rate of pathogenic bacteria in the two groups of patients.

② Criteria for determining infection referred to the hospital infection criteria (11), and infection rates of various surgical incisions in the operating room were observed.

③ After the operation, sterile cotton swab was dipped in a sampling solution and evenly smeared on the surface of the object 5 cm × 5 cm back and forth. The cotton swab was placed in a test tube with 5 ml sampling solution and vibrated 80 times. After proper dilution, it was inoculated on a common nutrient agar plate to count the viable bacteria. Six objects were sampled on the surface at a time, with a sampling area of 100 cm^2. The sampling method of medical staff's hands was the same as that of the objects, with six people being sampled at a time, and the sampling area was 60 cm^2 of both hands. Natural sedimentation method was used for environmental sampling, and the diameter of the plate was 9 cm. Five sampling sites were arranged in each operating room, which were exposed for 30 min, with a swab dipped in the sample solution spread evenly over a plate. The qualification of the operating room disinfection was determined according to the sanitary standards for hospital disinfection (12): the operating environment belongs to Class I environment, with the total number of bacterial colonies in the air ≤ 10 cfu/m^3, the total number of bacterial colonies on the surface of objects ≤ 5 cfu/m^2, and the total number of bacterial colonies on the hands of medical staff ≤ 5 cfu/m^2. Disinfectant for sterilization in use: aseptic growth; the amount of bacteria contaminated by skin and mucosal disinfectant in use: ≤ 10 cfu/ml; the amount of bacteria contaminated by other disinfectant in use: ≤ 100 cfu/ml; no pathogenic bacteria detected was considered qualified, and no bacterial growth was considered qualified.

④ Irregular events such as sterilization of instruments were not standardized, hand hygiene was incomplete, and frequent personnel activities and improper disposal of surgical wastes were recorded in the process of surgical nursing.

⑤ Members of the nursing quality monitoring team used the operating room nursing quality evaluation table made by the hospital, including environmental management, nursing safety, item management, disinfection,and isolation. There were 10 items in each dimension, which were recorded as 0∼10 points, and total score was 100 points; the higher the score, the better the nursing quality.

Statistical Methods

The SPSS 22.0 software was used for analysis. The measurement data was mean ± standard deviation ($x \pm s$), the comparison was made by *t*-test, the count data was ratio (%), and the comparison was made by χ^2 test.

RESULTS

Detection of Pathogenic Bacteria in the Two Groups

Detection rates of Gram-negative bacillus and Gram-positive cocci in the research group are lower than those in the conventional group ($P < 0.05$), as shown in **Table 2**.

Incidence of Surgical Incision Infection in the Two Groups

The rate of incision infection in the research group is lower than that in the conventional group ($P < 0.05$), as shown in **Table 3**.

Infection Control in the Two Groups

Qualified rates of disinfection of object surface, hands of medical staff, and air in the research group are higher than those in the conventional group ($P < 0.05$), as shown in **Table 4**.

Occurrence of Irregular Events in the Two Groups

The total incidence of irregular events in the research group is lower than that in the conventional group ($P < 0.05$), as shown in **Table 5**.

Nursing Quality in the Operating Room for the Two Groups

Nursing quality scores of the research group are higher than those of the conventional group ($P < 0.05$), as shown in **Figure 1**.

DISCUSSION

Studies have shown that additional mortality rate caused by patients infected in hospitals is 4∼33%, which not only seriously endangers the life and health of patients but also increases hospitalization days, cost of treatment, and doctor-patient conflicts, causing certain negative impacts on patients and the society (13). With the improvement of people's health awareness, people have a deeper understanding of medical information, patients' requirements for medical care are gradually increasing, and medical institutions are paying more and more attention to bacteria. An operating room is one of the main departments of hospital infection, and there are many risk factors leading to patient infection, such as unqualified air disinfection in the operating room, incomplete sterilization of surgical instruments, nonstandard placement of surgical items, weak awareness of infection prevention and control among medical staff, and frequent walking of visitors (14, 15). The management of infections in operating rooms cannot be ignored for the surgical effect of patients, and reducing infections has become the key concern of operating room services.

Risk management is a management concept with risk prevention awareness. By summarizing the accumulated experience of medical staff for many years, we can identify risk factors that may lead to unsafe nursing events, formulate targeted intervention measures according to screened high-risk factors, and regularly evaluate changes in risk factors, explore items that need improvement, and adjust intervention schemes, so as to avoid the occurrence of adverse phenomena (16, 17). In

TABLE 2 | Detection of pathogenic bacteria in the two groups (*n*, %).

Group	Gram-negative bacillus	Gram-positive cocci
Conventional group ($n = 150$)	14 (9.33%)	11 (7.33%)
Research group ($n = 150$)	5 (3.33%)	3 (2.00%)
χ^2value	4.551	4.795
P-value	0.033	0.029

TABLE 3 | Incidence of surgical incision infection in the two groups (*n*, %).

Group	Class I incision	Class II incision	Class III incision	Total incision infection rate
Conventional group ($n = 150$)	3 (2.00%)	8 (5.33%)	6 (4.00%)	17 (11.33%)
Research group ($n = 150$)	1 (0.67%)	3 (2.00%)	2 (1.33%)	6 (4.00%)
χ^2value				5.698
P-value				0.017

TABLE 4 | Infection control in the two groups (*n*, %).

Group	Qualified rate of disinfection				
	Object surface	Hand of medical staff	Air	Sterile articles	Disinfector
Conventional group ($n = 150$)	138 (92.00%)	128 (85.33%)	135 (90.00%)	149 (99.33%)	146(97.33%)
Research group ($n = 150$)	146 (97.33%)	141 (94.00%)	144 (96.00%)	150 (100.00%)	149(99.33%)
χ^2value	4.225	6.080	4.147	1.003	1.831
P-value	0.040	0.014	0.042	0.317	0.176

TABLE 5 | Occurrence of irregular events in the two groups (*n*, %).

Group	Sterilization of instruments was not standardized	Hand hygiene was incomplete	Frequent personnel activities	Improper disposal of surgical wastes	Total incidence rate
Conventional group ($n = 150$)	3 (2.00%)	4 (2.67%)	6 (4.00%)	2 (1.33%)	15 (10.00%)
Research group ($n = 150$)	1 (0.67%)	1 (0.67%)	2 (1.33%)	1 (0.67%)	5 (3.33%)
χ^2value					5.357
P-value					0.021

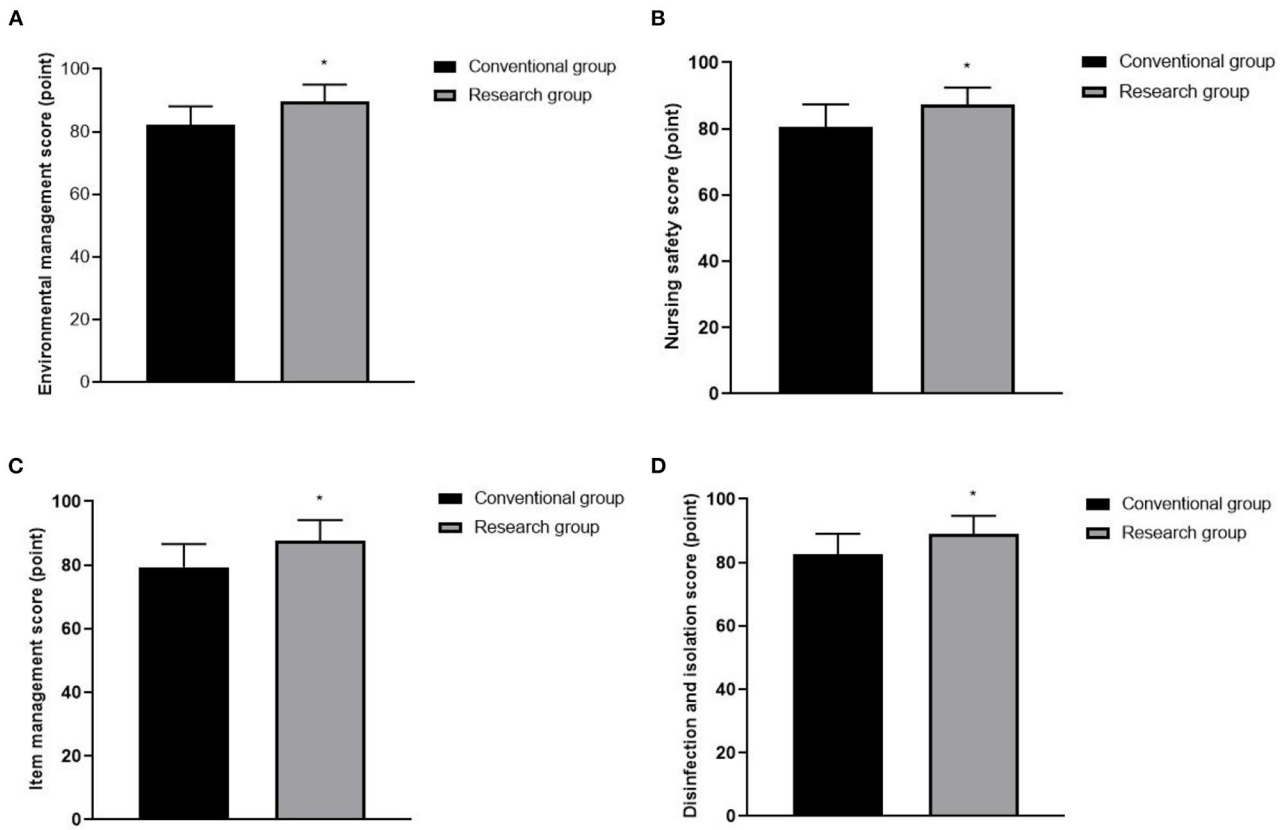


FIGURE 1 | Nursing quality in operating room for the two groups. **(A)** Environmental management score. **(B)** Nursing safety score. **(C)** Item management score. **(D)** Disinfection and isolation score. Compared with the conventional group, $^*P < 0.05$.

this management mode, risk factors are basically factors that can be intervened with and changed, and can be used as the focal point of risk control. By forward-looking analysis, nurses can implement corresponding treatment measures, thus reducing the probability of unsafe events, improving patients' satisfaction, reducing medical disputes, and meeting patients' medical needs with best nursing service (18, 19). In addition, PDCA cycle management is a step-by-step process of dynamic cycle according to the specific situation of each department, making targeted goals and plans, implementing PDCA small cycle and large cycle, gradually improving the quality of nursing work under repeated plan-do-check-action, and, finally, achieving the ideal goal (20). PDCA cycle is a comprehensive cycle, the four stages are inseparable, and the cycle is continuous, with standardization and institutionalization (21). In the PDCA cycle, the small cycle is the decomposition and guarantee of the implementation of the large cycle. Every time the PDCA small cycle is implemented, some management results will be achieved, management level will be improved, and work quality will be improved. After the small cycle ends, it is necessary to summarize, analyze, and update the plan and adjust the scheme, and then enter the next small cycle, which urges the large cycle to keep moving forward (22–24).

According to the actual situation of the operating room, we carried out PDCA cycle management combined with risk factor management nursing. The main intervention items included risk factor assessment, operating room environmental management, goods management, hand hygiene management,

aseptic management, and other measures. After the intervention, the detection rate of pathogenic bacteria, rate of incision infection, and total rate of occurrence of irregular events were lower than those in patients with routine nursing, and disinfection qualified rate and nursing quality score were higher. Risk factor management can supervise and restrict every PDCA link in infection control in operating rooms, and form a reciprocating cycle of risk assessment and risk control, factors that easily lead to infection can be evaluated more objectively, and corresponding interventions targeted at potential risks can be implemented while ensuring the disinfection quality of operating rooms, which has a positive effect on reducing infection in operating rooms and improving the quality of operation (25). The combination of the two management measures could create a virtuous cycle of management improvements in the operating room targeting infection risk factors, and the infection management time of nursing staff can be shortened. At the same time, in the development of PDCA cycle combined with risk factor management, we strengthen the supervision and management of infection control through various forms of disinfection qualification rate assessment and bacterial examination, enhance the disinfection consciousness and aseptic operation consciousness of operating room staff, and realize the management concept of prevention first, thus significantly improving the effect of disinfection and sterilization, reducing irregular events in the operating room, and building a safe operating environment, which is conducive to wound healing of surgical patients and achieving good results in infection nursing in the operating room.

CONCLUSION

To sum up, PDCA cycle management combined with risk factor management nursing can reduce the detection rate of pathogenic bacteria and rate of incision infection in operating rooms, reduce the incidence of irregular events, improve the qualified rate of disinfection, and greatly improve the quality of nursing, which can be considered to be widely used in clinical practice.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the First People's Hospital of Lianyungang. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HC is mainly responsible for the writing of articles. PW is mainly responsible for the design of the research and the statistics of the results. QJ is mainly responsible for the guidance of the entire research process. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Bao J, Li J. The effect of type of ventilation used in the operating room and surgical site infection: a meta-analysis. *Infect Control Hosp Epidemiol.* (2021) 42:931–6. doi: 10.1017/ice.2020.1316
2. Parvizi J, Barnes S, Shohat N, Edmiston CE Jr. Environment of care: is it time to reassess microbial contamination of the operating room air as a risk factor for surgical site infection in total joint arthroplasty? *Am J Infect Control.* (2017) 45:1267–72. doi: 10.1016/j.ajic.2017.06.027
3. Wistrand C, Söderquist B, Falk-Brynhildsen K, Nilsson U. Exploring bacterial growth and recolonization after preoperative hand disinfection and surgery between operating room nurses and non-health care workers: a pilot study. *BMC Infect Dis.* (2018) 18:466. doi: 10.1186/s12879-018-3375-3
4. Moszkowicz D, Hobeika C, Collard M, Bruzzi M, Beghdadi N, Catry J, et al. Operating room hygiene: clinical practice recommendations. *J Visc Surg.* (2019) 156:413–22. doi: 10.1016/j.jviscsurg.2019.07.010
5. Mujagic E, Hoffmann H, Soysal S, Delko T, Mechera R, Coslovsky M, et al. Teaching in the operating room: a risk for surgical site infections? *Am J Surg.* (2020) 220:322–7. doi: 10.1016/j.amjsurg.2019.12.029
6. Gao Y, Chen X, Kang L. The effect of Plan-Do-Check-Act cycle nursing management of gynecological surgery: a systematic review and meta-analysis. *Ann Palliat Med.* (2021) 10:8072–81. doi: 10.21037/apm-21-1590
7. Huang L, Lu C, Pang M, Li L, Zhang Y, Su A, et al. Effect of PDCA-based nursing intervention on activities of daily living, neurological function and self-management in acute cerebral stroke. *Am J Transl Res.* (2021) 13:5315–21.
8. Lu Y, Zhou Q, Wang LN, Wang DJ, Wang N, Hou J, et al. [Application of Plato analysis combined with plan-do-check-act cycle in scientific research management of nurses with primary position title]. *Zhonghua Shao Shang Za Zhi.* (2019) 35:752–6.
9. Silva RP, Valente GSC, Camacho ACLF. Risk management in the scope of nursing professionals in the hospital setting. *Rev Bras Enferm.* (2020) 73:e20190303. doi: 10.1590/0034-7167-2019-0303
10. Dionisi S, DI Muzio M, Giannetta N, DI Simone E, Gallina B, Napoli C, et al. Nursing students' experience of risk assessment, prevention and management: a systematic review. *J Prev Med Hyg.* (2021) 62:E122–31.
11. Palomar M, Vaque J, Alvarez Lerma F, Pastor V, Olaechea P, Fernández-Crehuet J. Indicadores de infección nosocomial [Nosocomial infection indicators]. *Med Clin.* (2008) 131(Suppl 3):48–55. doi: 10.1016/S0025-7753(08)76461-3
12. Hernández-Navarrete MJ, Celorrio-Pascual JM, Lapresta Moros C, Solano Bernad VM. Fundamentos de antisepsia, desinfección y esterilización [Principles of antisepsis, disinfection and sterilization]. *Enferm Infecc Microbiol Clin.* (2014) 32:681–8. doi: 10.1016/j.eimc.2014.04.003
13. Gaines S, Luo JN, Gilbert J, Zaborina O, Alverdy JC. Optimum operating room environment for the prevention of surgical site infections. *Surg Infect.* (2017) 18:503–7. doi: 10.1089/sur.2017.020
14. De Simone B, Sartelli M, Coccolini F, Ball CG, Brambillasca P, Chiarugi M, et al. Intraoperative surgical site infection control and prevention: a position paper and future addendum to WSES intra-abdominal infections guidelines. *World J Emerg Surg.* (2020) 15:10. doi: 10.1186/s13017-020-0288-4
15. Lo Giudice D, Trimarchi G, La Fauci V, Squeri R, Calimeri S. Hospital infection control and behaviour of operating room staff. *Cent Eur J Public Health.* (2019) 27:292–5. doi: 10.21101/cejph.a4932
16. Griebling TL. Re: risk factors for nursing- and healthcare-associated urinary tract infection. *J Urol.* (2019) 201:9. doi: 10.1097/01.ju.0000550107.09271.03
17. Slemon A, Jenkins E, Bungay V. Safety in psychiatric inpatient care: the impact of risk management culture on mental health nursing practice. *Nurs Inq.* (2017) 24:e12199. doi: 10.1111/nin.12199

18. Ashby MA, Morrell B. To your good health! going to the pub with friends, nursing dying patients, and 'ER' receptionists: the ubiquitous rise of risk management and maybe a 'Prudential' Bioethics? *J Bioeth Inq.* (2019) 16:1–5. doi: 10.1007/s11673-019-09912-6
19. Reuben DB, Gazarian P, Alexander N, Araujo K, Baker D, Bean JF, et al. The strategies to reduce injuries and develop confidence in elders intervention: falls risk factor assessment and management, patient engagement, and nurse co-management. *J Am Geriatr Soc.* (2017) 65:2733–9. doi: 10.1111/jgs.15121
20. Demirel A. Improvement of hand hygiene compliance in a private hospital using the Plan-Do-Check-Act (PDCA) method. *Pak J Med Sci.* (2019) 35:721–5. doi: 10.12669/pjms.35.3.6
21. Kong X, Zhu X, Zhang Y, Wu J. The application of plan, do, check, act (PDCA) quality management in reducing nosocomial infections in endoscopy rooms: it does work. *Int J Clin Pract.* (2021) 75:e14351. doi: 10.1111/ijcp.14351
22. Tan S, Wang D, Chi Z, Li W, Shan Y. Study on the interaction between typical phthalic acid esters (PAEs) and human haemoglobin (hHb) by molecular docking. *Environ Toxicol Pharmacol.* (2017) 53:206–11. doi: 10.1016/j.etap.2017.06.008
23. Omar I, Shirazy M, Omar M, Chaari A. Controlling nosocomial infection in adult intensive treatment unit: a quality improvement project. *Int J Risk Saf Med.* (2020) 31:267–73. doi: 10.3233/JRS-190028
24. Yang Z, Ma X, Chen Y, Cao Y, Li Q, Pan X, et al. Effects of a quality improvement program to reduce central venous catheter-related infections in hemodialysis patients. *Am J Med Sci.* (2021) 361:461–8. doi: 10.1016/j.amjms.2020.10.018
25. Bartolomé Benito E, Miquel Gómez A, Sánchez Perruca L, Jiménez Carramiñana J, López Romero A, Sánchez Suárez JL. Impulso de la seguridad del paciente a partir del contrato programa de centro [Boost for patient safety with the centre agreement program]. *Rev Calid Asist.* (2011) 26:343–52. doi: 10.1016/j.cali.2011.07.006

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Chen, Wang and Ji. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 17 March 2022
doi: 10.3389/fsurg.2022.856446

Identification of Prostate Cancer Risk Genetics Biomarkers Based on Intergraded Bioinformatics Analysis

*Xiangdong Liang, Yanchao Wang, Long Pei, Xiaoliang Tan and Chunhui Dong**

Department of Urology, The Fourth Hospital of Hebei Medical University, Shijiahzuang, China

Background: Prostate cancer (PCa) is one of the most popular cancer types in men. Nevertheless, the pathogenic mechanisms of PCa are poorly understood. Hence, we aimed to identify the potential genetic biomarker of PCa in the present study.

Methods: High-throughput data set GSE46602 was obtained from the comprehensive gene expression database (GEO) for screening differentially expressed genes (DEGs). The common DEGs were further screened out using The Cancer Genome Atlas (TCGA) dataset. Functional enrichment analysis includes Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) to study related mechanisms. The Cox and Lasso regression analyses were carried out to compress the target genes and construct the high-risk and low-risk gene model. Survival analyses were performed based on the gene risk signature model. The CIBERSORT algorithm was performed to clarify the correlation of the high- and low-risk gene model in risk and infiltration of immune cells in PCa.

Results: A total of 385 common DEGs were obtained. The results of functional enrichment analysis show that common DEGs play an important role in PCa. A three-gene signature model (*KCNK3*, *AK5*, and *ARHGEF38*) was established, and the model was significantly associated with cancer-related pathways, overall survival (OS), and tumor microenvironment (TME)-related immune cells in PCa.

Conclusion: This new risk model may contribute to further investigation in the immune-related pathogenesis in progression of PCa.

Keywords: prostate cancer (PCa), bioinformatics analysis, immune cell infiltration, survival analysis, ARHGEF38, KCNK3, AK5

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Shenghui Yang,
Hainan Provincial People's Hospital, China
Meifeng Lv,
Jinan Second Maternal and Child Health Hospital, China

****Correspondence:***
Chunhui Dong
chunhuizheyu@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *17 January 2022*
Accepted: *09 February 2022*
Published: *17 March 2022*

Citation:
Liang X, Wang Y, Pei L, Tan X and Dong C (2022) Identification of Prostate Cancer Risk Genetics Biomarkers Based on Intergraded Bioinformatics Analysis. Front. Surg. 9:856446. doi: 10.3389/fsurg.2022.856446

INTRODUCTION

Prostate cancer is regarded as the second foremost reason of death from cancer in men that affects men's health worldwide (1–3), especially in European and American countries (4–6). Surgery and radiotherapy are considered to be the most effective treatment strategies at an early stage (7). Androgen deprivation therapy (ADT) is the main treatment for advanced prostate cancer (8). Although the incidence rate of prostate cancer is low in China, the life span and the dietary structure change are also increasing year by year, with poor differentiation, high malignancy, and poor prognosis (9). Metastatic events are the main cause of death for men with prostate cancer for the reason that PCa can spread to multiple organs in the body (10). The 5 year survival ratio

of metastatic prostate cancer is only about 30%. Nevertheless, androgen-deprivation therapy, in general, is not curative. Patients can develop to castration-resistant prostate cancer, which is lethal (10, 11). Therefore, timely diagnosis of PCa is of great importance for treatment and prognosis.

As a heterogeneous disease, the progression of PCa is closely associated with genome instability (12). Studies have indicated that PCa includes a complicated pathogenesis driven by multiple molecular pathways that are highly associated with the survival, metabolic, and metastatic characteristics of aggressive cancers (13). The genes are considered as loci of susceptibility to tumorigenesis in humans (14). Alterations in expression of genetic biomarker have been reported in various tumors (15, 16). However, in the current study, the development and progression of PCa are poorly understood at molecular and genetic levels.

Tumor immunotherapy is becoming a pillar of the cancer therapy armamentarium (17, 18). A growing number of studies suggest that immune responses may be involved in the clinical outcome of prostate cancer (19–21). As we know, tumor-infiltrating immune cells play a very important regulatory role in the tumor microenvironment and are an attractive therapeutic target (22). PCa has been shown to be significantly associated with immune infiltration in several clinical and genomic trials (23, 24). Multiple genes, such as *COL3A1*, *RAC1*, *FN1*, *SDC2*, and *TNB-585*, have been proved to be associated with high infiltration immune cells in prostate cancer (25, 26).

Bioinformatics analysis based on high-throughput next-generation sequencing technology enhances our understanding of gene expression function in cancer (27). In addition, transcriptomic data analysis is a useful method to identify DEGs at the genome-wide level, which is beneficial for our better understanding of the potential molecular mechanisms of the regulatory role of gene expression (28). Hence, the application of bioinformatics is useful for the investigation into the underlying mechanism of molecular cell biology in PCa.

In this study, through the integrated analysis of PCa data from the public databases, we screened out the potential genetic biomarkers that play a vital role in PCa. Functional enrichment analysis was performed to study the related underlying mechanism and signaling pathways, including gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG). The Cox regression and Lasso regression analyses were conducted to construct the high- and low-risk gene model. The CIBERSORT algorithm was utilized to clarify the correlation of high-risk and low-risk gene model in risk and infiltration of immune cells in PCa. Integrated analysis for identifying novel biomarkers might be beneficial to PCa treatment and has a better understanding of the pathological mechanism.

MATERIALS AND METHODS

Data Preparation and Processing

The high-throughput datasets GSE46602 (29) of PCa was acquired from the public GEO database (https://www.ncbi.nlm.nih.gov/geo). The GSE46602 dataset contains 36 tumor tissues and 14 normal prostate biopsies. In addition, the RNA-sequencing data of PCa and normal control tissues were obtained from the The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/). The PCa samples were analyzed using integrated bioinformatics methods, and samples without complete clinical information were excluded. In addition, the RNA-seq data and clinical information of 492 PCa samples were obtained from the TCGA database.

Identification of Differential Expression Genes (DEGs) in PCa

The RNA expression profile carried out normalization with the Affy package. The RNA expression profile was analyzed by the limma R package (30). The DEGs were displayed in the form of the volcano plot and heat maps and identified old change of $\log_2 > 1.5$ and p-value < 0.05. The R ggplot2 package in the R analysis platform was plotted to present the heat maps and clustering of DEGs.

Functional Enrichment Analysis

To evaluate the potential role of common DEGs in PCa development, GO functional enrichment analyses were used to analyze the biological process (BP), cellular component (CC), and molecular function (MF) of DEGs. In the current study, GO analysis of DEGs was performed by DAVID (31, 32) (https://david.ncifcrf.gov/conversion.jsp). Functional enrichment analysis of KEGG was mainly used to analyze the signaling/metabolic pathway through which differentially expressed genes may perform their biological functions (33). P-value < 0.05 was considered as the critical value for screening the significant enrichment pathway.

Cox Regression and Lasso Regression Analysis

Lasso regression was performed to characterize the high frequency features (34). Then, the univariate Cox regression analysis was performed to screen out the genes with significant correlation ($p < 0.05$). Next, the least absolute shrinkage and selection operator (lasso) regression was carried out to further reduce the number of genes. We used the glmnet3 package (35) to conduct Lasso cox regression analysis based on machine learning to identify the optimal prognostic signature. In the next step, multivariate regression analysis was carried out, step function was used for stepwise regression screening, and finally, the model constructed by the three genes was obtained. Based on the expression of 3 genes in the constructed model, a new risk scoring model was constructed by multivariate Cox regression evaluation. The risk score was then determined, and the sample was stratified into high- and low-risk groups according to the median risk score to verify whether the risk score was an independent predictor.

Immune Infiltration by the Cibersort Analysis

CIBERSORT algorithm (36) was a mean to discriminate a signature between twenty-two human immune cell phenotypes, including memory B cells, activated CD4+ T cells, neutrophils, and so on. The CIBERSORT algorithm was used to quantify the proportion of immune cells in PCa. PCa gene expression profiles

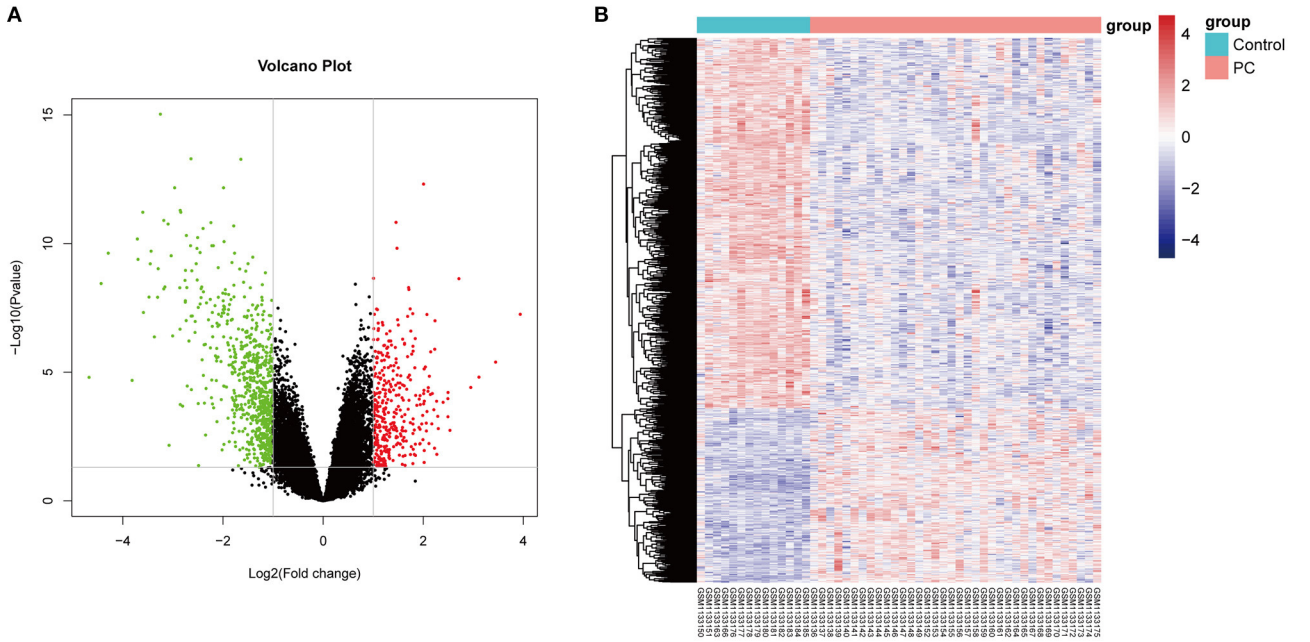


FIGURE 1 | The differentially expressed genes (DEGs) in prostate cancer. **(A)** The Volcano plot shows the differentially expressed genes in the dataset GSE46602. The red color indicates the upregulated genes in prostate cancer, and the green color indicates the downregulated genes in prostate cancer. **(B)** The heat map shows the DEGs between prostate cancer tissue and normal controls.

from the TCGA database were uploaded to the CIBERSORT, and 1,000 permutations were run. Data with p-value < 0.05 after the CIBERSORT were performed for the analysis to improve the accuracy of the deconvolution method. The CIBERSORT software package in R software was used for data analysis. Wilcox test was used to compare the relative abundance of the TIIC between high- and low-risk groups.

Survival Analysis

Correlation between 3 genes and the overall survival of patients with PCa were analyzed utilizing the GEPIA database (37). According to each hub gene's best-separation cutoff value, samples of patients with PCa within the dataset were divided into two groups to obtain the Kaplan–Meier (K–M) survival curves. ROC curves were carried out to investigate the prognostic value in 1, 3, and 5 years by utilizing the survival ROC package (v1.0.34) based on the GSE46602 dataset.

Gene Set Enrichment Analysis (GSEA) of High- and Low-Risk Patients With Pc

GSEA (Version 4.1.0) was used to screen for gene clusters associated with risk score phenotypes, which were overrepresented in large groups of genes. Enriched P-values were calculated based on 1,000 permutations; FDR values were calculated using the Benjamini–Hochberg multiple test correction program ($p < 0.05$). In addition, the enrichment pathways of each phenotype were classified by nominal P-value and standard enrichment score (NES) (38).

RESULTS

Identification of Differentially Expressed Genes

Firstly, in order to find out the difference in genetic expression between PC tissue and normal tissue, DEGs were identified based on the RNA-Seq dataset (GSE46602) ($p < 0.05$ and log2 FC > 1.5). As seen in **Figure 1A**, a total of 841 DE-pcRNAs were identified, which include 269 upregulated DEGs and 572 downregulated DE-pcRNAs. What is more, to have a clearer understanding of the expression distribution of differential genes in the ischemic stroke group and the normal group, we performed heat map cluster analysis on DEGs (**Figure 1B**). Besides, we also screened out the TCGA database for DEGs in PCa and took the intersection with DEGs in the GEO database. A total of 385 common DEGs were obtained.

Functional Enrichment Analysis of Common DEGs

Thereafter, to further uncover the function and pathways of common DEGs in PCa, functional enrichment analysis, including GO and KEGG functional enrichment analysis, was conducted. The top 10 significantly enriched terms of biological processes (BP), cell component (CC), and molecular function (MF) were shown. As seen in **Figure 2A**, terms like response to oxidative stress and epithelial cell morphogenesis were significantly enriched in BP (**Figure 2A**), collagen–containing extracellular matrix and basement membrane were significantly enriched in CC (**Figure 2B**), extracellular matrix structural

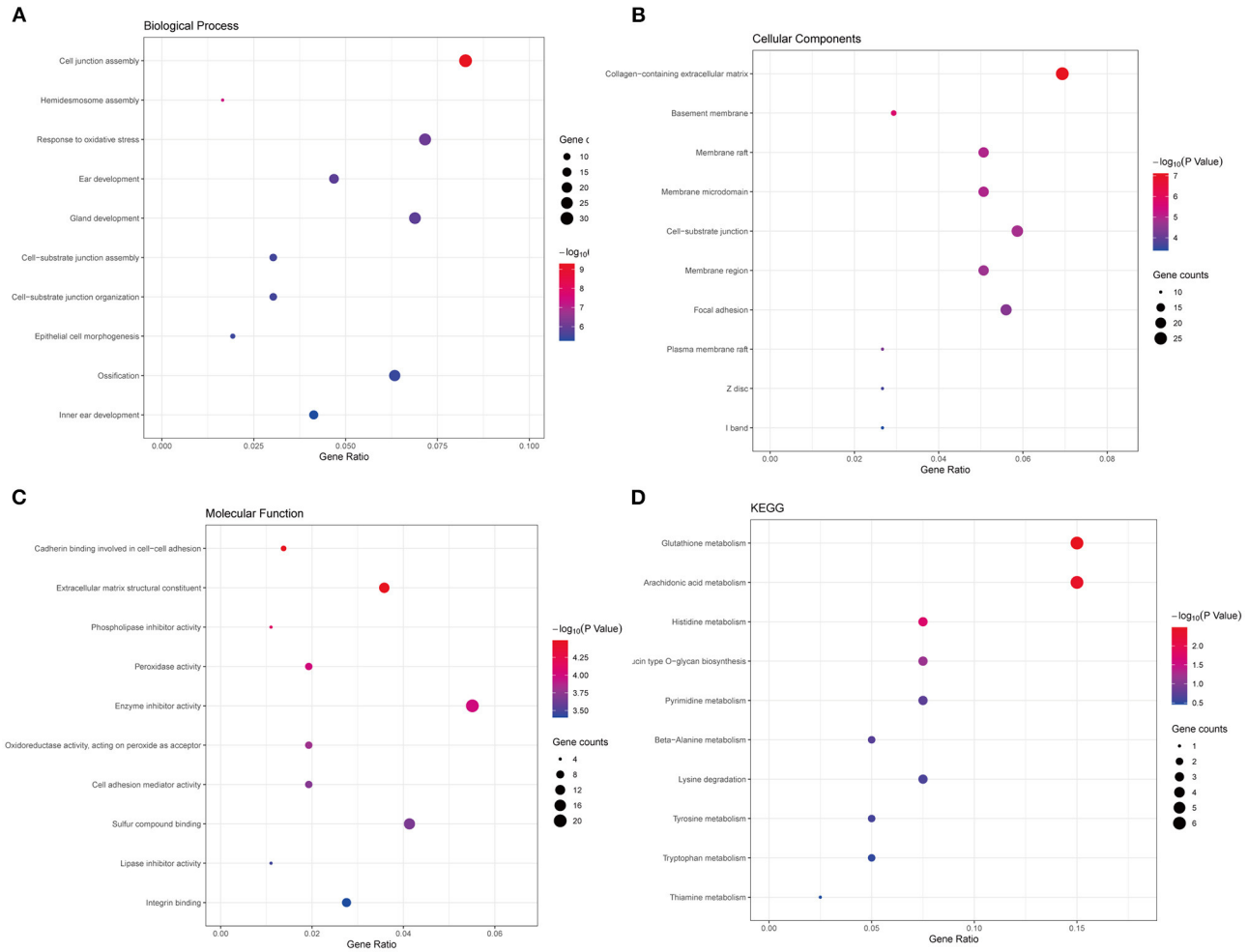


FIGURE 2 | Functional enrichment analyses of the common DEGs. **(A)** The top 10 significantly enriched biological process terms. **(B)** The top 10 significantly enriched cellular component terms. **(C)** The top 10 significantly enriched molecular function terms. **(D)** The KEGG pathway analysis of the common DEGs.

constituent and peroxidase activity were significantly enriched in CC (**Figure 2C**). What is more, the results of the KEGG pathways analysis of DEGs showed that signaling pathways like glutathione metabolism, histidine metabolism, and so on were significantly enriched (**Figure 2D**). The functional enrichment results revealed that the common DEGs are vital to the progress of PCa.

Cox Regression and Lasso Regression Analysis

In the next step, to further compress the target gene and construct immune gene models, Cox regression analysis was carried out with a threshold of $p < 0.05$. Lasso regression, a kind of compression estimation (39), was further compressed to reduce the number of genes (**Figures 3A,B**), and six genes were obtained. Then, multivariate regression analysis was performed. Step function was used to screen by the stepwise regression method, and finally, the risk model constructed by three genes (*KCNK3*, *AK5*, and *ARHGEF38*) was obtained. Next, the samples were divided into high-risk and low-risk groups based on the risk model for the following analysis. The expression level of *KCNK3*, *AK5*, and *ARHGEF38* in primary tumor and solid normal tissue is shown in **Figure 3C**. *AK5* and *ARHGEF38* have lower expression in the solid normal tissue compared to primary tumor. The expression of *KCNK3* is higher in the primary tumor. Besides, the relative expression of *KCNK3*, *AK5*, and *ARHGEF38* in low-risk and high-risk samples is presented in **Figure 3D**. The sensitivity and specificity of the risk score model were demonstrated by constructing an ROC curve. The area under the curve (AUC) was calculated to be 0.6 at 1 year, 0.87 at 3 years, and 0.88 at 5 years (**Figure 3E**).

Survival Analysis of the Risk Model

To investigate the clinical significance of the risk model, the survival analyses were performed. Overall survival (OS) analysis was conducted to assess the effectiveness of the *KCNK3*, *AK5*, and *ARHGEF38*. As seen in **Figures 4A–C**, the high expression

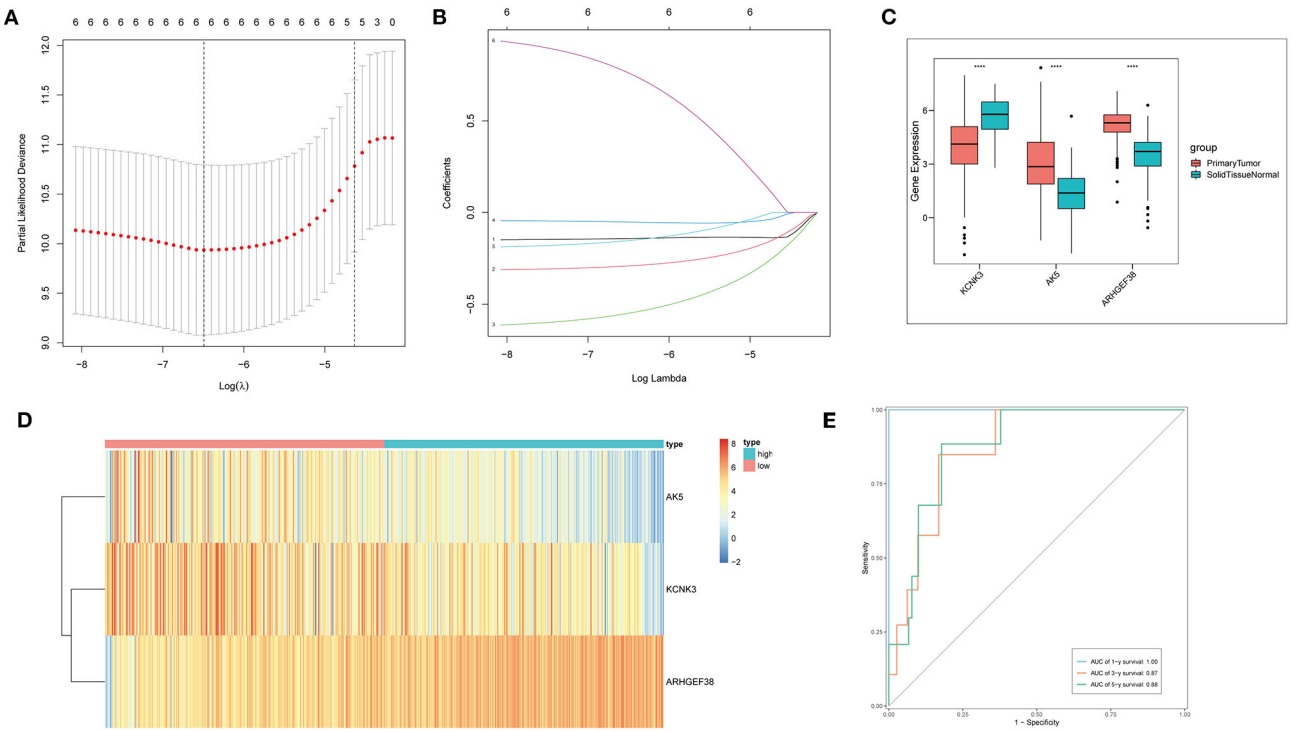


FIGURE 3 | Cox regression and lasso regression analysis. **(A,B)** Cox regression and Lasso regression were performed to obtain six genes. **(C)** The relative expression of AK5, KCNK3, and ARHGEF38 in primary tumor and normal solid tissue. **(D)** The heat map of AK5, KCNK3, and ARHGEF38 expression profiles. **(E)** Time-dependent ROC curves.

of *ARHGEF38* was associated with a lower survival probability ($p = 0.00226$), while the high expression of *KCNK3* ($p = 0.0339$) and *AK5* ($p = 0.0382$) was related to a better survival probability. The results indicated that gene changes of *KCNK3*, *AK5*, and *ARHGEF38* were significantly related to the OS of patients with PCa. What is more, patients with high-risk (red line) PCa presented remarkably worse OS than low-risk ones (blue line). As shown in the survival risk heat map, patients with PCa with higher risk scores had higher mortality (**Figures 4E,F**).

Immune Cell Infiltration Analysis

The immune microenvironment is highly correlated with its overall survival (40). In order to study the correlation between immune microenvironment and the risk model, CIBERSORT algorithm, to evaluate the infiltration of twenty-two kinds of immune cells in PCa tissues, was performed (**Figure 5A**). Infiltration of plasma cells, mast cells resting, M0 macrophages, B cells memory, NK cells activated, M2 macrophages, dendritic cells activated, eosinophils was remarkably different in the high-risk and low-risk groups (**Figure 5B**). Other types of immune cells did not differ significantly between the two groups. The above results demonstrated that macrophages may be significant in the development and progression of PCa. The estimated method was utilized to predict tumor purity, stromal score, and immune. Significantly different in the high-risk and low-risk groups were shown in in **Figures 5C–E**. What is more, in order to distinguish the gene expression profiles between high-risk and low-risk PCa samples, GSEA analysis was performed to characterize important functional phenotypes and different gene sets between the high-risk and low-risk score groups. GSEA indicated enrichment of gene sets associated with aminoacyl-tRNA biosynthesis, chemical carcinogenesis—DNA adducts, drug metabolism-cytochrome P450, Fanconi anemia pathway, glycosphingolipid biosynthesis-ganglio series, histidine metabolism, nucleocytoplasmic transport, Ribosome biogenesis in eukaryotes, RNA degradation, staphylococcus aureus infection (**Figure 5F**).

DISCUSSION

Prostate cancer (PCa) is one of the pervasive carcinoma occurring in men and a large health burden worldwide (41). The lethality of PCa is due to the lack of treatment options that can produce a lasting response at the genetic and cellular biological levels (42, 43). The progression and pathogenic mechanisms of PCa remain unclear. Currently, analysis used for gene expression has benefit analysis for oncological research with the development in sequencing technologies. In this study, the high-throughput dataset of PCa (GSE46602) was obtained from the GEO database for further comprehensive bioinformatics analyses.

The PCa-related DEGs were screened out and explored, and the related biological processes and signaling pathways

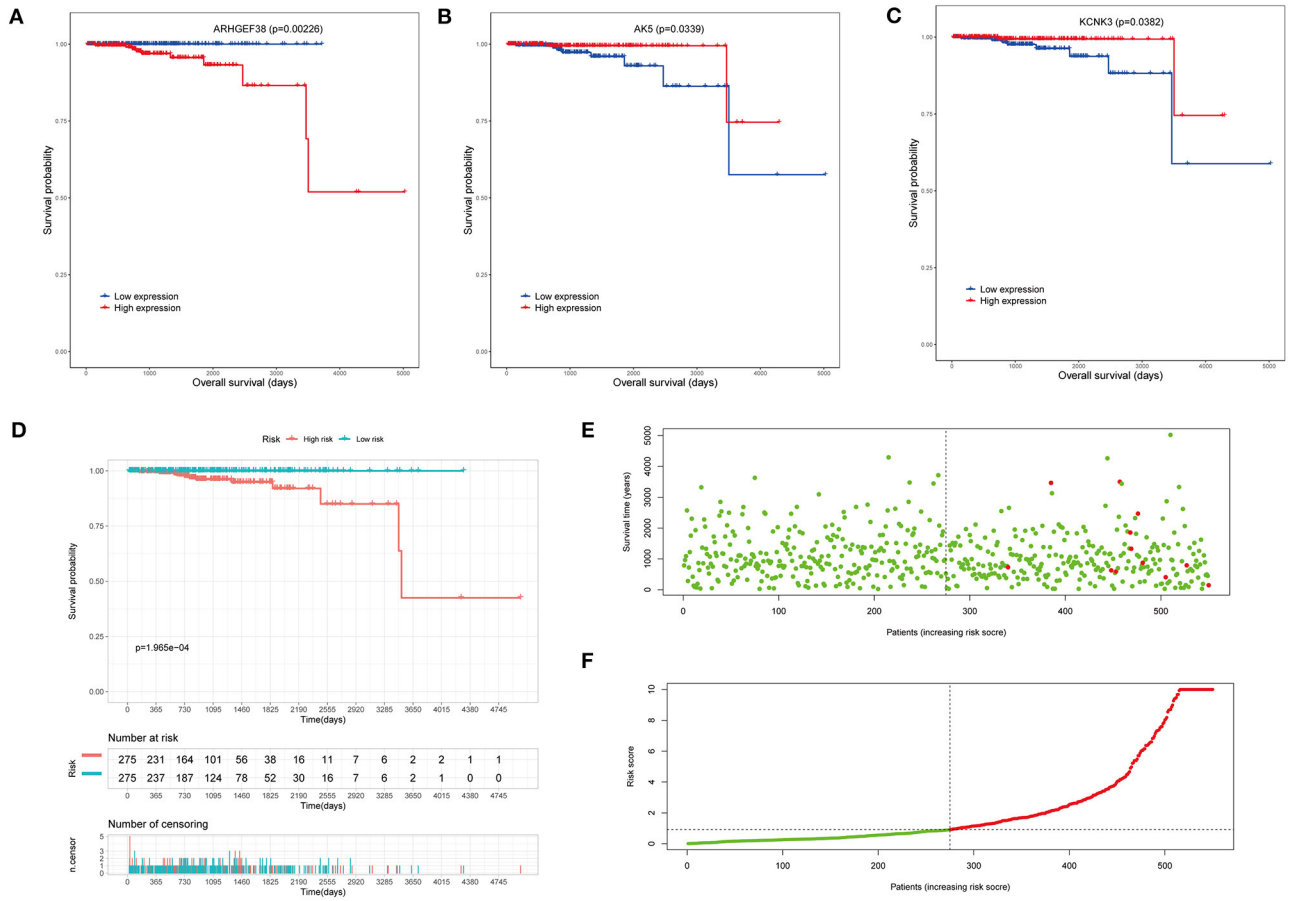


FIGURE 4 | Survival analysis of the risk model. **(A–C)** The overall survival (OS) analysis in high and low *AK5*, *KCNK3*, and *ARHGEF38* expression samples. **(D)** Kaplan–Meier survival analyses show the OS of patients in the high-risk score and the low-risk score groups. **(E,F)** The risk plot between the high- and low-risk score groups.

that make a better understanding of their functions were also studied. Terms like response to oxidative stress were significantly enriched in BP. Oxidative stress referred to the increase in the formation of reactive oxygen species, which destroys the body's antioxidant protection and causes a variety of diseases, including various cancers (44). Mukha et al. indicated that PCa cells can be radiosensitized by glutamine deprivation, resulting in DNA damage, oxidative stress, and epigenetic modifications (45). Glutathione-related metabolism is the main mechanism of cellular resistance to oxidative stress factors (46). The results of the KEGG analysis of DEGs demonstrated that glutathione metabolism and histidine metabolism were significantly enriched. The functional enrichment results suggest that the common DEGs were a vital regulator in the procession of PCa.

About 15% of patients with PCa are diagnosed with high-risk disease (47). Therefore, through utilizing univariate Cox and iterative lasso Cox regression analyses, a 3-gene (*KCNK3*, *AK5*, and *ARHGEF38*) risk signature model in PCas was constructed. The ROC curves further approved the accuracy of our risk model. It is reported that *KCNK3* influenced physiological processes, ranging from vascular tone to metabolic diet through inflammation (48). Also, *KCNK3* was correlated with prolonged survival after surgery in colorectal cancer (49). *AK5* was reported as a new prognosis marker that promotes autophagy and proliferation in human gastric cancer (33). Interestingly, *ARHGEF3* was proved to be an oncogene and may be a novel biomarker for predicting invasive PCa (50).

The 3-gene risk signature model emerges clinical significance. The results indicated that gene changes of *KCNK3*, *AK5*, and *ARHGEF38* were remarkedly associated with the overall survival of patients with PCa. What is more, patients with high-risk PCa have remarkably worse OS than low-risk ones. Dysregulated expression of *ARHGEF38* is associated with poor prognosis in nasopharyngeal carcinoma (51). Currently, immunotherapy has not been utilized in advanced PCa, and more novel methods are needed to overcome immune rejection and suppressive tumor microenvironment (52). As for the immune microenvironment, 8 kinds of immune related cells were remarkably various between the high-risk and low-risk

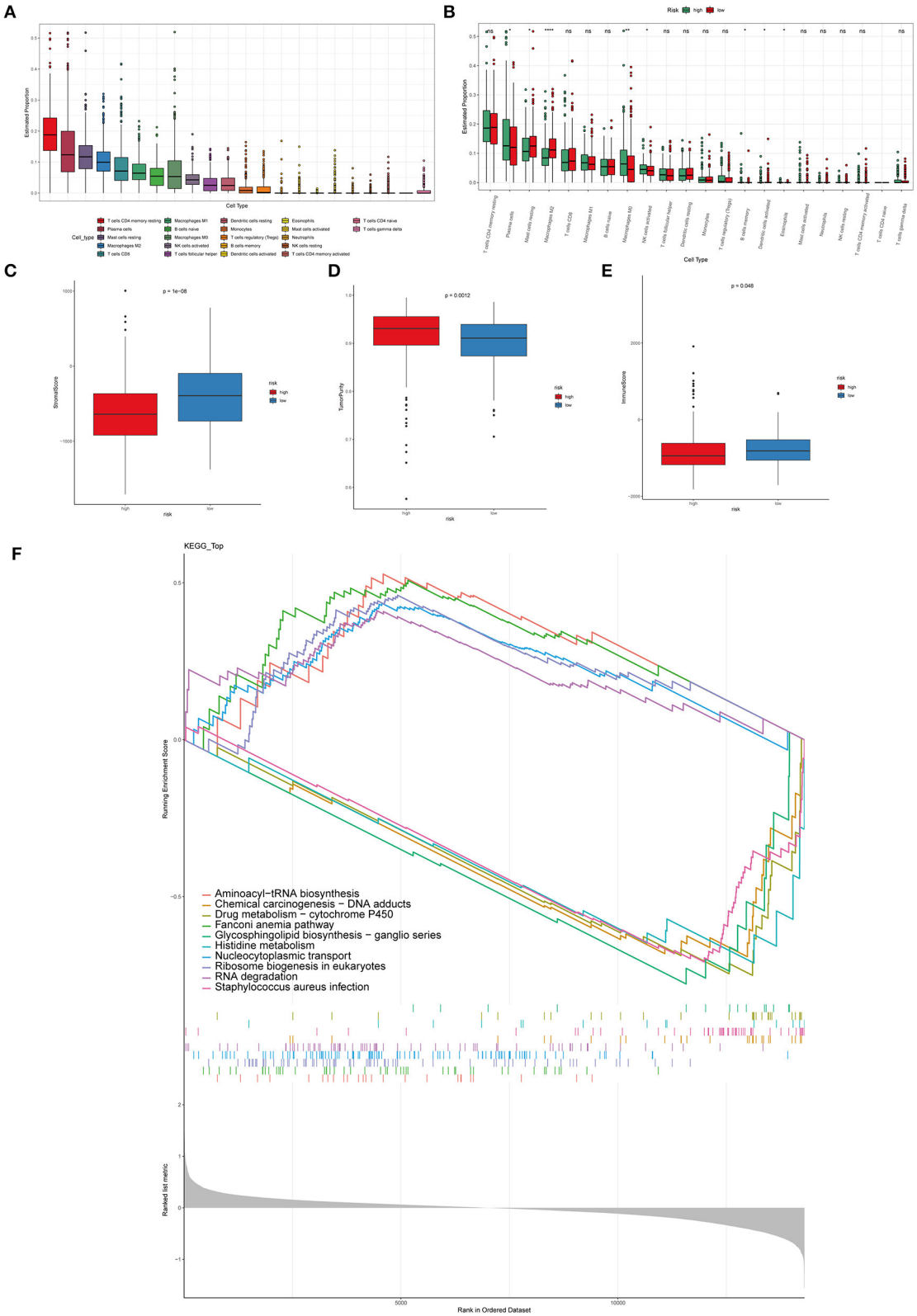


FIGURE 5 | Immune cell infiltration in PCa tissues of high- and low-risk patients. **(A)** The distribution of 22 types of immune cells between primary and metastatic PCa tissues. **(B)** Comparisons between immune cells in the high- and low-risk groups in TCGA. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{****}p < 0.0001$. The stromal score **(C)**, tumor purity **(D)**, immune score **(E)** in the high- and low-risk groups. **(F)** The GSEA analysis was performed to characterize important functional phenotypes and different gene sets between the high-risk and low-risk score groups.

score groups, including plasma cells, mast cells resting, M0 macrophages, M2 macrophages, NK cells activated, B cells memory, dendritic cells activated, and eosinophils. The risk model could further illuminate the immune-related pathogenesis of the therapeutic method by permitting early diagnosis and prognosis of PCa.

CONCLUSION

In this study, we unraveled the DEGs in PCa from GEO datasets, which were further verified by TCGA data and identified the common DEGs. The functional enrichment results suggest that the common DEGs play an important role in the progress of PCa. A three-gene signature model (*KCNK3*, *AK5*, and *ARHGEF38*) was constructed, and the model was significantly related to cancer-related pathways, overall survival, and TME cells in PCa. This new risk model might benefit the further elucidation about the immune-related progression in PCa.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

XL and CD designed the research. YW and LP carried out the analyses. XT performed visualization. XT and CD wrote the manuscript. All the authors reviewed and approved the final manuscript.

FUNDING

This project was supported by the Youth Science and Technology Project of Hebei Provincial Health Commission (No. 20201098).

REFERENCES

1. Zeng XZ, Huang ZS, Fang HP, Wu JY, Huang QX, Zhuang CB, et al. Coexpression of TLR9 and VEGF-C is associated with lymphatic metastasis in prostate cancer. *Asian J Androl.* (2021). doi: 10.4103/aja202167
2. Nguyen-Nielsen M, Borre M. Diagnostic and therapeutic strategies for prostate cancer. *Semin Nucl Med.* (2016) 46:484–90. doi: 10.1053/j.semnuclmed.2016.07.002
3. Zuo W, Wang ZZ, Xue J. Artesunate induces apoptosis of bladder cancer cells by miR-16 regulation of COX-2 expression. *Int J Mol Sci.* (2014) 15:14298. doi: 10.3390/ijms150814298
4. Kenfield SA, Van Blarigan EL, Panchal N, Bang A, Zhang L, Graff RE, et al. Chan, feasibility, safety, and acceptability of a remotely monitored exercise pilot CHAMP: a clinical trial of high-intensity Aerobic and resistance exercise for Metastatic castrate-resistant Prostate cancer. Cancer Med. (2021) 10:8058–70. doi: 10.1002/cam4.4324
5. Vetrichelvan O, Gorjala P, Goodman O Jr, Mitra R. Bergamottin a CYP3A inhibitor found in grapefruit juice inhibits prostate cancer cell growth by downregulating androgen receptor signaling and promoting G0/G1 cell cycle block and apoptosis. *PloS ONE.* (2021) 16:e0257984. doi: 10.1371/journal.pone.0257984
6. Zou Z, Liu R, Liang Y, Zhou R, Dai Q, Han Z, et al. Identification and validation of a PPP1R12A-related five-gene signature associated with metabolism to predict the prognosis of patients with prostate cancer. *Front Genet.* (2021) 12:703210. doi: 10.3389/fgene.2021.703210
7. Liu B, Jiang HY, Yuan T, Luo J, Zhou WD, Jiang QQ, et al. Enzalutamide-induced upregulation of PCAT6 promotes prostate cancer neuroendocrine differentiation by regulating miR-326/HNRNPA2B1 axis. *Front Oncol.* (2021) 11:650054. doi: 10.3389/fonc.2021.650054
8. Azad AA, Eigl BJ, Murray RN, Kollmannsberger C, Chi KN. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. *Eur Urol.* (2015) 67:23–9. doi: 10.1016/j.eururo.2014.06.045
9. Xu H, Mo F, Zhou J, Hao Z, Chen X, Liang C. Lack of Association between Common Polymorphisms in Selenoprotein P Gene and Susceptibility to Colorectal Cancer. Breast Cancer, and Prostate Cancer: A Meta-Analysis. *BioMed Res Int.* (2021) 2021:6525449. doi: 10.1155/2021/6525449
10. Wang Y, Wu N, Jiang N. Autophagy provides a conceptual therapeutic framework for bone metastasis from prostate cancer. *Cell Death Dis.* (2021) 12:909. doi: 10.1038/s41419-021-04181-x
11. Miller DR, Ingersoll MA, Teply BA, Lin MF. Combination treatment options for castration-resistant prostate cancer. In: Bott SRJ, Ng KL, editors. *Prostate Cancer, Brisbane (AU).* (2021). doi: 10.36255/exonpublications.prostatecancer.combinationtreatment.2021
12. Hawley JR, Zhou S, Arlidge C, Grillo G, Kron KJ, Hugh-White R, et al. Reorganization of the 3D genome pinpoints non-coding drivers of primary prostate tumors. *Cancer Res.* (2021) 81:5833–48. doi: 10.1158/0008-5472.CAN-21-2056
13. Bai B, Chen Q, Jing R, He X, Wang H, Ban Y, et al. Molecular basis of prostate cancer and natural products as potential chemotherapeutic and chemopreventive agents. *Front Pharmacol.* (2021) 12:738235. doi: 10.3389/fphar.2021.738235
14. Pezeshki S, Hashemi P, Salimi A, Ebrahimi S, Javanzad M, Monfaredan A. NUF2Evaluation of and expression in prostate cancer: potential biomarkers for prostate cancer screening. *Rep Biochem Mol Biol.* (2021) 10:224–32. doi: 10.52547/rbmb.10.2.224
15. Sun Z, Mao Y, Zhang X, Lu S, Wang H, Zhang C, et al. Identification of ARHGEF38, NETO2, GOLM1, and SAPCD2 associated with prostate cancer progression by bioinformatic analysis and experimental validation. *Front Cell Develop Biol.* (2021) 9:718638. doi: 10.3389/fcell.2021.718638
16. Ye Z, Zheng M, Zeng Y, Wei S, Wang Y, Lin Z. et al. Bioinformatics analysis reveals an association between cancer cell stemness, gene mutations, and the immune microenvironment in stomach adenocarcinoma. *Front Genet.* (2020) 11:595477. doi: 10.3389/fgene.2020.595477
17. Shi Y, Lammers T. Combining nanomedicine and immunotherapy. *Acc Chem Res.* (2019) 52:1543–54. doi: 10.1021/acs.accounts.9b00148
18. Boone CE, Wang L, Gautam A, Newton IG, Steinmetz NF. Combining nanomedicine and immune checkpoint therapy for cancer immunotherapy. *Wiley Interdiscip Rev Nanomed Nanobiotechnol.* (2021) 14:e1739. doi: 10.1002/wnan.1739
19. Adamaki M, Zoumpourlis V. Immunotherapy as a precision medicine tool for the treatment of prostate cancer. *Cancers.* (2021) 13:173. doi: 10.3390/cancers13020173
20. Bansal D, Reimers MA, Knoche EM, Pachynski RK. Immunotherapy and Immunotherapy Combinations in Metastatic Castration-Resistant Prostate Cancer. *Cancers (Basel).* (2021) 13:334. doi: 10.3390/cancers13020334
21. Antonarakis ES. Combining active immunotherapy with immune checkpoint blockade for the treatment of advanced prostate cancer. *Asian J Androl.* (2012) 14:520–1. doi: 10.1038/aja.2012.45
22. Zhang S, Zhang E, Long J, Hu Z, Peng J, Liu L. et al. Immune infiltration in renal cell carcinoma. *Cancer Sci.* (2019) 110:1564–72. doi: 10.1111/cas.13996
23. Xu N, Dong RN, Lin TT, Lin T, Lin YZ, Chen SH, et al. Development and validation of novel biomarkers related to M2 macrophages infiltration by

weighted gene co-expression network analysis in prostate cancer. *Front Oncol*. (2021) 11:634075. doi: 10.3389/fonc.2021.634075
24. Andersen LB, Nørgaard M, Rasmussen M, Fredsøe J, Borre M, Ulhøi BP, et al. Immune cell analyses of the tumor microenvironment in prostate cancer highlight infiltrating regulatory T cells and macrophages as adverse prognostic factors. *J Pathol*. (2021) 255:155–65. doi: 10.1002/path.5757
25. Dang K, Castello G, Clarke SC, Li Y, Balasubramani A, Boudreau A, et al. Attenuating CD3 affinity in a PSMAxCD3 bispecific antibody enables killing of prostate tumor cells with reduced cytokine release. *J Immunother Cancer*. (2021) 9:e002488. doi: 10.1136/jitc-2021-002488
26. Meng F, Han X, Min Z, He X, Zhu S. Prognostic signatures associated with high infiltration of Tregs in bone metastatic prostate cancer. *Aging (Albany NY)*. (2021) 13:17442–61. doi: 10.18632/aging.203234
27. Zeng X, Sanalkumar R, Bresnick EH, Li H, Chang Q, Keleş S. jMOSAiCS: joint analysis of multiple ChIP-seq datasets. *Genome Biol.* (2013) 14:R38. doi: 10.1186/gb-2013-14-4-r38
28. To KY. Identification of differential gene expression by high throughput analysis. *Comb Chem High Throughput Screen*. (2000) 3:235–41. doi: 10.2174/1386207003331616
29. Mortensen MM, Hoyer S, Lynnerup AS, Orntoft TF, Sorensen KD, Borre M, Dyrskjot L. Expression profiling of prostate cancer tissue delineates genes associated with recurrence after prostatectomy. *Sci Rep*. (2015) 5:16018. doi: 10.1038/srep16018
30. Smyth GK. *Limma: Linear Models for Microarray Data*. New York: Springer (2005).
31. Huang da W, Sherman BT, Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. *Nat Protoc*. (2009) 4:44–57. doi: 10.1038/nprot.2008.211
32. Huang da W, Sherman BT, Lempicki RA. Bioinformatics enrichment tools: paths toward the comprehensive functional analysis of large gene lists. *Nucleic Acids Res.* (2009) 37:1–13. doi: 10.1093/nar/gkn923
33. Ogata H, Goto S, Sato K, Fujibuchi W, Kanehisa M. KEGG: kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Res.* (1999) 27:29–34. doi: 10.1093/nar/27.1.29
34. Xu C, Chen H. A ferroptosis-related gene model predicts prognosis and immune microenvironment for cutaneous melanoma. *Front Genet.* (2021) 12:697043. doi: 10.3389/fgene.2021.697043
35. Li N, Zhan X. Identification of pathology-specific regulators of mA RNA modification to optimize lung cancer management in the context of predictive, preventive, and personalized medicine. *EPMA J.* (2020) 11:485–504. doi: 10.1007/s13167-020-00220-3
36. Chen B, Khodadoust MS, Liu CL, Newman AM, Alizadeh AA. Profiling tumor infiltrating immune cells with CIBERSORT. *Methods Mol Biol*. (2018) 1711:243–59. doi: 10.1007/978-1-4939-7493-1_12
37. Tang Z, Li C, Kang B, Gao G, Li C, Zhang Z. GEPIA: a web server for cancer and normal gene expression profiling and interactive analyses. *Nucleic acids Res*. (2017) 45:W98–102. doi: 10.1093/nar/gkx247
38. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci USA*. (2005) 102:15545–50. doi: 10.1073/pnas.0506580102
39. Sunil L. A least absolute shrinkage and selection operator (LASSO) for nonlinear system identification. Syst Identification (2006).
40. Wang Z, Wu Y, Zhao Z, Liu C, Zhang L. Study on transorgan regulation of intervertebral disc and extra-skeletal organs through exosomes derived from bone marrow mesenchymal stem cells. *Front Cell Dev Biol.* (2021) 9:741183. doi: 10.3389/fcell.2021.741183
41. Hou Y, Hu J, Zhou L, Liu L, Chen K, Yang X. Integrative analysis of methylation and copy number variations of prostate adenocarcinoma based on weighted gene co-expression network analysis. *Front Oncol.* (2021) 11:647253. doi: 10.3389/fonc.2021.647253
42. Wang G, Zhao D, Spring D, DePinho R. Genetics and biology of prostate cancer. Genes Develop. (2018) 32:1105–40. doi: 10.1101/gad.315739.118
43. Yu C, Niu, Li L, Li T, Duan L, He Z, et al. Identification of the metabolic signatures of prostate cancer by mass spectrometry-based plasma and urine metabolomics analysis. *Prostate*. (2021) 81:1320–1328. doi: 10.1002/pros.24229
44. Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. *Toxicology*. (2011) 283:65–87. doi: 10.1016/j.tox.2011.03.001
45. Mukha A, Kahya U, Dubrovska A. Targeting glutamine metabolism and autophagy: the combination for prostate cancer radiosensitization. *Autophagy*. (2021) 17:3879–81. doi: 10.1080/15548627.2021.1962682
46. Hayes JD, McLellanLI. Glutathione and glutathione-dependent enzymes represent a co-ordinately regulated defence against oxidative stress. *Free Radical Res.* (1999) 31:273–300. doi: 10.1080/10715769900300851
47. Chang AJ, Autio K, Roach M, Scher H. High-risk prostate cancer-classification and therapy. *Nat Rev Clin Oncol.* (2014) 11:308–23. doi: 10.1038/nrclinonc.2014.68
48. West JD, Austin ED, Rizzi EM, Yan L, Tanjore H, Crabtree AL, et al. KCNK3 mutation causes altered immune function in pulmonary arterial hypertension patients and mouse models. *Int J Mol Sci.* (2021) 22:5014. doi: 10.3390/ijms22095014
49. Cavalieri D, Dolara P, Mini E, Luceri C, Castagnini C, Toti S. et al. Analysis of gene expression profiles reveals novel correlations with the clinical course of colorectal cancer. *Oncol Res.* (2007) 16:535–48. doi: 10.3727/096504007783438376
50. Liu QW, Li JY, Zhang XC, Liu Y, Liu QY, Xiao L, et al. Human amniotic mesenchymal stem cells inhibit hepatocellular carcinoma in tumour-bearing mice. *J Cell Mol Med*. (2020) 24:10525–41. doi: 10.1111/jcmm.15668
51. Liu TH, Zheng F, Cai MY, Guo L, Lin HX, Chen JW, et al. The putative tumor activator ARHGEF3 promotes nasopharyngeal carcinoma cell pathogenesis by inhibiting cellular apoptosis. *Oncotarget*. (2016) 7:25836–48. doi: 10.18632/oncotarget.8283
52. Dorff TB, Narayan V, Forman SJ, Zang PD, Fraietta JA, June CH, et al. Novel redirected T cell immunotherapies for advanced prostate cancer. *Clinical Cancer Res.* (2021). doi: 10.1158/1078-0432.CCR-21-1483

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Liang, Wang, Pei, Tan and Dong. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 18 March 2022
doi: 10.3389/fsurg.2022.863273

Complete Video-Assisted Thoracoscopic Surgery and Traditional Open Surgery for Elderly Patients With NSCLC

*Yi Mao, Zhaojia Gao and Yajun Yin**

Department of Thoracic Surgery, The Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University, Changzhou, China

Objective: To observe the efficacy of complete video-assisted thoracoscopic surgery (CVATS) and traditional open surgery (TOS) in the treatment of elderly patients with non-small cell lung cancer (NSCLC) and their influence on cardiopulmonary function.

Methods: A total of 120 elderly patients with primary NSCLC who were treated surgically in our hospital from January 2018 to January 2021 were selected and divided into the study group and the control group according to the different surgical procedures, 60 patients in each group. CVATS was used in the observation group and TOS in the control group. The surgical indexes and cardiopulmonary function indexes were observed and compared between the two groups. The serum C-reactive protein (CRP) level and visual analog scale's (VAS) score of the patients at different time points were detected. The incidence of postoperative complications was compared between the two groups.

Results: The perioperative indexes such as operation time were significantly different between the two groups ($p < 0.05$), but the number of lymph node dissection was not significantly different ($p > 0.05$). The serum CRP level and VAS score of the observation group were significantly lower than those of the control group on the 1st, 3rd, and 7th postoperative days ($p < 0.05$). There were significant differences in cardiopulmonary function between the two groups on the 7th postoperative day ($p < 0.05$). The incidence of adverse reactions in the observation group was significantly lower than that in the control group ($p > 0.05$).

Conclusion: CVATS is effective in the treatment of NSCLC. Compared with TOS therapy, CVATS has less damage to cardiopulmonary function and fewer complications, which is conducive to the rehabilitation of elderly patients. It is a safe and reliable scheme for the treatment of elderly patients with NSCLC.

Keywords: non-small cell lung cancer, complete video-assisted thoracoscopic surgery, traditional open surgery, cardiopulmonary function, lymph node dissection

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Jiangang Liu,
The Second Affiliated Hospital of Shandong First Medical University, China
Yang Liu,
The First Medical Center of Chinese PLA General Hospital, China

****Correspondence:***
Yajun Yin
maoyiyinyajun@njmu.edu.cn

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *27 January 2022*
Accepted: *17 February 2022*
Published: *18 March 2022*

Citation:
Mao Y, Gao Z and Yin Y (2022) Complete Video-Assisted Thoracoscopic Surgery and Traditional Open Surgery for Elderly Patients With NSCLC. Front. Surg. 9:863273. doi: 10.3389/fsurg.2022.863273

INTRODUCTION

Due to the popularity of low-dose chest CT physical examination in recent years, the detection rate of early lung cancer manifested as lung ground-glass nodule has greatly improved. At the same time, with the aging of the population and the serious pollution of the surrounding environment, the proportion of elderly patients is also increasing gradually (1, 2). Non-small cell lung cancer

(NSCLC) is a common malignant tumor disease, which has no specific typical symptoms in the early stage, and is usually diagnosed in the middle or late stage. At this time, it has lost the best treatment opportunity for surgical resection. For some early patients, at this time, the tumor focus is small, and there is no sign of diffusion or metastasis. At this point, surgical resection is still the main treatment for patients. Pulmonary lobectomy is currently the most commonly used treatment for early-stage NSCLC in clinics. Most of the traditional treatments are traditional open surgery (TOS). However, due to the weak constitution and poor lung function of elderly patients, there are many complications after lobectomy, and the early mortality is high (3).

CVATS is suitable for biopsy of nodular masses in lung, resection of benign masses in lung and lobectomy, etc. Compared with the TOS, the CVATS has the advantages of clearer tissue display of surgical field tissue, stronger advantages of minimally invasive and more precise operation. Complete video-assisted thoracoscopic surgery (CVATS) is performed through a small thoracotomy incision and two or three small incisions. It does not need chest support or ribs cutting during the operation and has little influence on the structure of the chest and the function of respiratory muscle, thus reducing the trauma and promoting postoperative recovery (4, 5). However, the effect and the prognosis of lymph node dissection need further study. In this study, we compared the clinical efficacy of CVATS and TOS in the treatment of elderly patients with NSCLC and the impact on the cardiopulmonary function of the patients in order to explore whether CVATS can bring better surgical outcomes for the elderly patients.

DATA AND METHODS

General Information

A total of 120 elderly patients with primary NSCLC who were treated surgically in our hospital from January 2018 to January 2021 were selected and divided into a study group and a control group according to the different surgical procedures, 60 patients in each group. CVATS was used in the observation group, and TOS was used in the control group. Inclusion criteria: all the patients were diagnosed with NSCLC by imaging and pathology before operation and had clinical stages of stage I-III a; all the patients can tolerate the surgical treatment and have good compliance after preoperative evaluation. Exclusion criteria: the patients with preoperative radiotherapy and chemotherapy or dysfunction of important organs, such as heart, liver and brain; exclusion of other types of lung tumors and distant metastasis; the patients with previous thoracic surgery were excluded.

Research Methods

TOS was adopted in the control group. After tracheal intubation and general anesthesia, a 20–25-cm incision was made in the fifth intercostal space. After anatomical lobectomy, the lymph nodes were systematically cleaned. After the operation, a drainage tube was placed through the midline of the armpit of the seventh intercostal space.

CVATS was used in the observation group. After general anesthesia, the patient was placed in the healthy lateral position, and an incision of about 1.5–2 cm in length was made between the 7th rib at the midline level of armpit, which was inserted into thoracoscope. A surgical incision was made in the 4th or 5th intercostal space at the level of axillary front line as the main surgical incision, with the length of about 2–3 cm, and a surgical incision was made in the 7th intercostal space at the level of scapular downline as the auxiliary surgical incision with the length of about 1.5–2 cm. The operation of the surgical instruments was completely supervised by video-assisted thoracoscopy. The patient's thoracic adhesion, lesion site, tumor size, infiltration range, enlargement, and metastasis of mediastinal lymph nodes in thoracic cavity were investigated, and then lobectomy was performed. Sequentially dissect the hilar structure to continuously cut off the pulmonary vessels, bronchi, and pulmonary fissure, and then free the pulmonary veins and artery branches. Lung lobes were removed through the main operation hole, and the thoracic and mediastinal lymph nodes were cleaned systematically. After the surgery, the drainage tube was inserted through the axillary midline of the 7th intercostal space.

Both groups of the patients were given routine nursing and symptomatic treatment after the operation.

Observation Indicators

(1) The operation indexes of the patients in the two groups, such as operation time, bleeding volume, number of lymph node cleanings, postoperative drainage volume, and hospital stay, were observed and compared.
(2) The peripheral venous blood samples of the patients in the two groups were collected preoperatively and on the 1st, 3rd, and 7th postoperative days, and the serum C-reactive protein (CRP) levels were detected and compared.
(3) The visual analog scale (VAS) was applied to evaluate and compare the pain severity on the 1st, 3rd, and 7th postoperative days. VAS scoring criteria: 0 point means no pain, 10 points mean the most pain, < 3 points mean good analgesia, and ≥ 5 points mean poor analgesic effect.
(4) Perioperative cardiopulmonary indicators [heart rate (HR), forced expiratory volume in 1 s (FEV_1), maximum voluntary ventilation (MVV), diffusion of lung CO (DLCO)] of the two groups were compared and analyzed.
(5) The incidence of postoperative complications was observed and compared between the two groups.

Statistical Methods

SPSS22.0 software was used for processing. The measurement data of the experimental data were expressed as mean standard deviation ($\overline{x} \pm s$). All the data were in normal distribution, and the means between the two groups were compared by independent sample t-test. ANOVA was used to compare multiple time points. The count data were expressed as (%), and the comparison was performed using χ^2 test. The test level was $\alpha = 0.05$, and $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

Patients With General Data Comparison

There was no significant difference in general information, such as gender, age, disease type, pathological type, clinical stage, and differentiation degree between the two groups ($p > 0.05$), indicating that they were comparable, as shown in **Table 1**.

Comparison of Surgical Indicators Between the Two Groups

The operation time, bleeding volume, drainage volume, and hospital stay of the patients in the observation group were lower than those in the control group ($p < 0.05$). There was no significant difference in the number of lymph node dissection between the two groups ($p > 0.05$), as shown in **Table 2**.

Comparison of CRP Levels Between the Two Groups

Serum CRP levels preoperative between the two groups had no significant difference ($p > 0.05$), but it peaked on the 1st postoperative day and began to decline on the 3rd and 7th postoperative days. In addition, serum CRP levels of the patients in the observation group at each time point in postoperative were significantly lower than those in the control group ($p < 0.05$), as shown in **Figure 1**.

Comparison of VAS Scores Postoperative Between the Two Groups

The VAS scores of the patients in the two groups decreased sequentially at each time point postoperatively, and the VAS scores of the patients in the observation group at each time point at the 1st, 3rd, and 7th postoperative days were significantly lower than those in the control group ($p < 0.05$), as shown in **Figure 2**.

Comparison of Cardiopulmonary Function Indexes During Postoperative Between the Two Groups

After the operation, the HR and DLCD in the observation group were higher than those in the control group, while FEV_1 and MVV were lower than those in the control group. These differences were statistically significant ($p < 0.05$), as shown in **Figures 3–6**.

TABLE 1 | Comparison of general data of patients between the two groups (n, $\bar{x} \pm s$).

Group	Gender		Disease type		Pathological type		
	Male	Female	Central type	Peripheral type	Glandular cancer	Squamous carcinoma	Other
Control group ($n = 60$)	37 (61.67)	23 (38.33)	31 (51.67)	29 (48.33)	22 (36.67)	35 (58.33)	3 (5.00)
Observation group ($n = 60$)	35 (58.33)	25 (41.67)	33 (55.00)	27 (45.00)	20 (33.33)	36 (60.00)	4 (6.67)
χ^2 *value*	0.139		0.134			0.252	
P value	0.709		0.714			0.882	

Group	Age (years)	Clinical stages			Differentiation degree		
		Stage I	Stage II	Stage IIIa	Poorly differentiated	Intermediate differentiation	Highly differentiated
Control group ($n = 60$)	67.83 ± 2.14	29 (48.33)	21 (35.00)	10 (16.67)	12 (20.00)	39 (65.00)	9 (15.00)
Observation group ($n = 60$)	68.18 ± 2.87	27 (45.00)	22 (36.67)	11 (18.33)	14 (23.33)	41 (68.33)	5 (8.33)
t/χ^2 *value*	0.757		0.142			1.347	
P value	0.450		0.931			0.510	

TABLE 2 | Comparison of surgical indexes between the two groups (n, $\bar{x} \pm s$).

Group	N	Operation time (min)	Bleeding volume (ml)	Number of lymph node dissection (units)	Drainage volume (ml)	Hospital stay (d)
Control group	60	179.62 ± 31.25	372.91 ± 70.28	18.06 ± 4.12	2086.61 ± 427.63	12.36 ± 2.95
Observation group	60	120.48 ± 33.94	246.83 ± 69.82	18.53 ± 3.92	1394.52 ± 357.19	7.05 ± 1.83
t value		9.929	9.858	0.640	9.621	11.848
P value		<0.001	<0.001	0.523	<0.001	<0.001

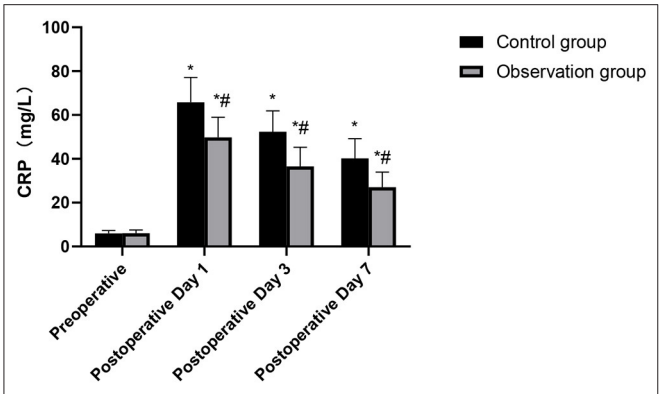


FIGURE 1 | Comparison of CRP levels in the patients of the two groups. Compared with preoperative, $^{*}p < 0.05$. Compared with the control group, $^{\#}p < 0.05$.

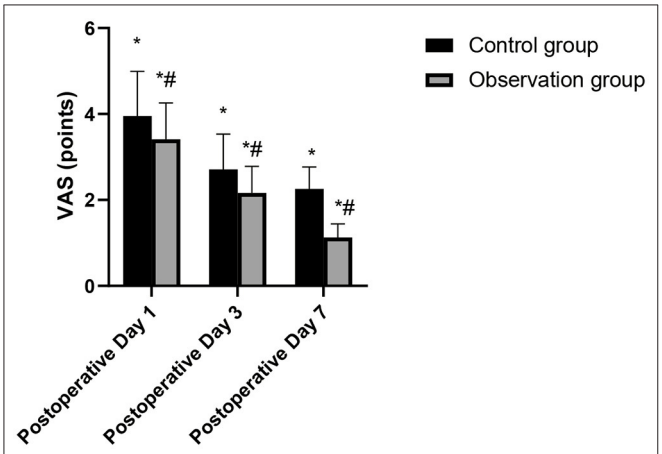


FIGURE 2 | Comparison of VAS scores in the patients of the two groups. Compared with postoperative, $^{*}p < 0.05$. Compared with the control group, $^{\#}p < 0.05$.

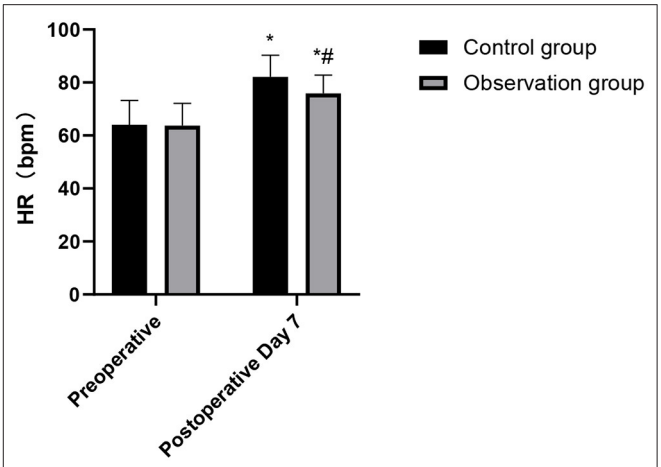


FIGURE 3 | Comparison of HR changes in the patients of the two groups. Compared with preoperative, $^{*}p < 0.05$. Compared with the control group, $^{\#}p < 0.05$.

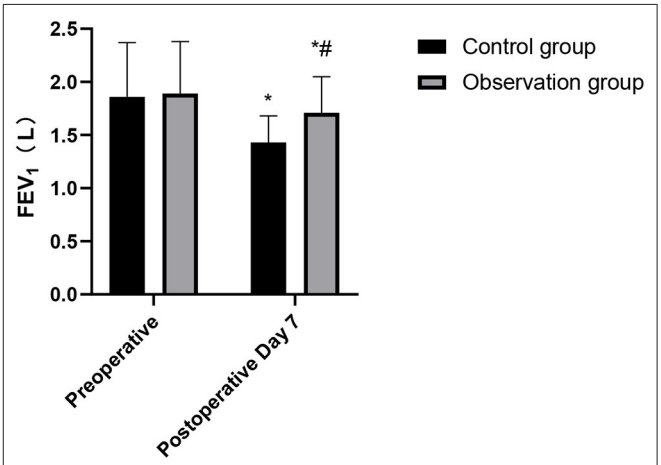


FIGURE 4 | Comparison of FEV_1 changes in the patients of the two groups. Compared with preoperative, $^{*}p < 0.05$. Compared with the control group, $^{\#}p < 0.05$.

Comparison of the Incidence of Adverse Reactions Between the Two Groups

The incidence of adverse reactions in the observation group was significantly lower than that in the control group ($p > 0.05$), as shown in **Figure 7**.

DISCUSSION

Because of the abundant blood supply to the lungs, blood metastasis can occur in the early stage, and there is no specific clinical manifestations. The main reason for poor treatment effect is the low early diagnosis rate (6). Although radiotherapy, chemotherapy, and biotherapy can prolong the survival time of patients with lung cancer, surgery is still the only way to achieve radical cure (7, 8). The objective of surgery is to remove as many lesions and lymph nodes as possible, and, at the same time, to maximize the preservation of intact lung tissue so as to ensure surgical effect and bring long-term survival benefits for patients. Elderly patients with lung cancer are a special group. Because of physiological factors and physical function degradation, young people are often diagnosed at an early stage, but they give up radical lobectomy because they cannot tolerate lobectomy. On the other hand, the elderly often have other diseases, which makes the treatment of elderly patients with lung cancer much more complicated (9, 10).

With the development of video-assisted thoracoscopic surgery and the skill of surgeons, it provides another option for elderly patients with lung cancer. Previous studies have shown that, compared with TOS, CVATS for patients with early NSCLC can relieve postoperative pain, have better postoperative lung function, shorter hospital stay, and a similar long-term survival rate (11, 12). CVATS has a clear vision and no blind spots, which is conducive to the accurate operation of doctors. To a greater

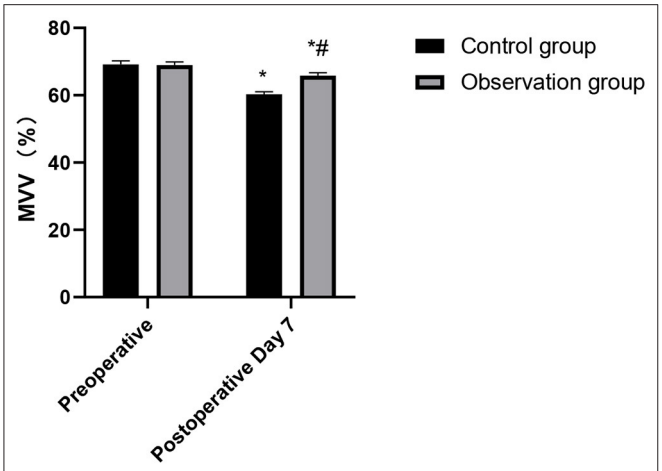


FIGURE 5 | Comparison of MVV changes in the patients of the two groups. Compared with preoperative, $^{*}p < 0.05$. Compared with the control group, $^{\#}p < 0.05$.

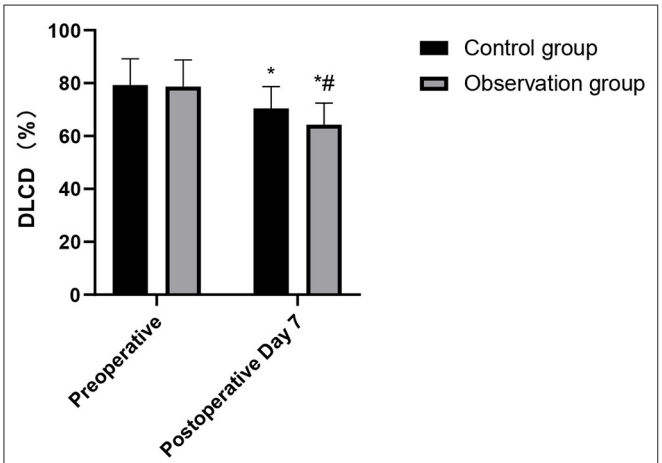


FIGURE 6 | Comparison of DLCD changes in the patients of the two groups. Compared with preoperative, $^{*}p < 0.05$. Compared with the control group, $^{\#}p < 0.05$.

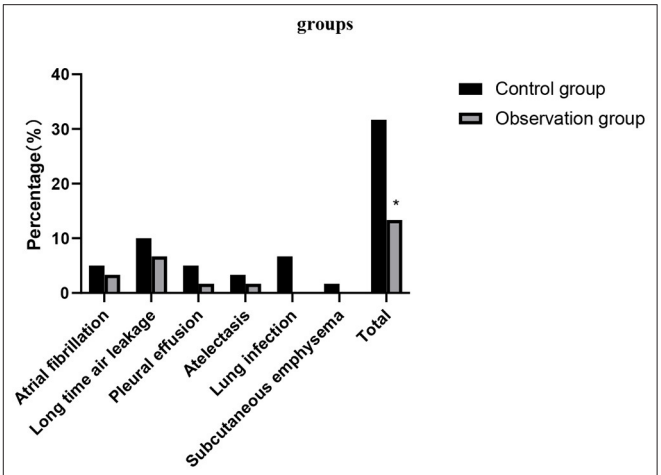


FIGURE 7 | Comparison of the incidence of adverse reactions between the two groups. Compared with the control group, $^{*}p < 0.05$.

extent, the accidental injuries during the surgery were reduced, and the amount of bleeding and postoperative drainage was further reduced. Besides, the surgical instruments are mature, accurate, and limited, which are convenient for lobectomy and lymph node dissection (13, 14). In this study, the perioperative indicators such as operation time were significantly different between the two groups of the patients, but the number of lymph node dissection was not significantly different. It is suggested that CVATS can not only achieve the lymph node dissection effect of traditional TOS but also can be safe and reliable, which accords with the principle of radical resection of tumor. CVATS requires a high degree of surgery, and the operator must be familiar with the skills of thoracic anatomy and endoscopy. The amount of bleeding and operation time are a comprehensive response of the operator to the degree of operation proficiency, and also a response of the operation to the degree of injury of the patient. The advantages of CVATS also lie in the fact that the surgical incision is small, and it is not necessary to cut off the intercostal muscles and ribs, so it has little effect on the muscular nerves and thoracic structure, which is conducive to reducing the degree of pain after surgery and has certain positive significance for the rehabilitation of patients after surgery (15, 16). This study showed that the VAS scores of the observation group at each time point postoperative were significantly lower than those in the control group.

At present, the comparison between CVATS and TOS is mostly based on some indexes such as clinical efficacy. In fact, in addition to the macroscopic indexes of clinical trauma, the evaluation of the effects of the two kinds of surgery can also be analyzed in the macroscopic aspect. In the case of infection or some tissue damage, CRP content usually increases rapidly, and it is a non-specific inflammatory marker (17, 18). In this study, the serum CRP levels in the observation group at each time point postoperative were significantly lower than those in the control group. The above results show that, compared with TOS, CVATS can reduce the patients' early injury, reduces the level of postoperative stress reaction, and relieves the body's inflammatory reaction, thus promoting the postoperative rehabilitation process (19).

Cardiopulmonary function of the human body can directly affect the activities of other organs and muscles. Cardiopulmonary function represents whether the patient's cardiopulmonary function is suitable for operation or not, and it is closely related to the occurrence of postoperative cardiopulmonary complications. If surgical trauma causes great damage to the cardiopulmonary function, the probability of postoperative cardiopulmonary complications will increase (20). It has been pointed out that CVATS is minimally invasive, and it has little influence on patients' immunity and cardiopulmonary function, thus contributing patients' rapid recovery (21). The results of this study showed that the cardiopulmonary function

of the observation group was significantly better than that of the patients in the control group. TOS can damage thoracic integrity, causing damage to the intercostal nerves and great invasive damage to cardiopulmonary function in the early postoperative period. In contrast, CVATS does not need to divide muscles and ribs, and has less damage to the surrounding normal lung tissue, thus retaining the integrity of the patient's chest to the maximum extent. At the same time, CVATS can avoid the excessive injury to respiratory muscles (such as serratus anterior, latissimus dorsi, and intercostal muscles), which is of great clinical significance for the protection of postoperative cardiopulmonary function and is conducive to reducing the occurrence of postoperative cardiopulmonary complications (22, 23). Therefore, the cardiopulmonary function of the elderly patients using CVATS is better than TOS. The study also showed that the incidence of adverse reactions in the observation group was significantly lower than that in the control group. This shows that CVATS is safe for the elderly, and the incidence of complications can be controlled within an acceptable range (24, 25).

In summary, CVATS has a reliable curative effect on the treatment of NSCLC. Compared with TOS treatment, CVATS has less damage to cardiopulmonary function and fewer complications, which is conducive to the rehabilitation of elderly patients. CVATS is a safe and reliable scheme for the treatment of elderly patients with NSCLC. However, due to the small number of observations cases and short follow-up time, we still need to continue to explore in future studies to optimize the choice of surgical methods and realize the principle of optimal patient benefits.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Affiliated Changzhou No. 2 People's Hospital of Nanjing Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YY was the supervisor of the entire study. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Duma N, Santana-Davila R, Molina JR. Non-small cell lung cancer: epidemiology, screening, diagnosis, and treatment. *Mayo Clin Proc.* (2019) 94:1623–40. doi: 10.1016/j.mayocp.2019.01.013
2. Alexander M, Kim SY, Cheng H. Update 2020: management of non-small cell lung cancer. *Lung.* (2020) 198:897–907. doi: 10.1007/s00408-020-00407-5
3. Yang HX, Woo KM, Sima CS, Bains MS, Adusumilli PS, Huang J, et al. Long-term survival based on the surgical approach to lobectomy for clinical stage I nonsmall cell lung cancer: comparison of robotic, video-assisted thoracic surgery, and thoracotomy lobectomy. *Ann Surg.* (2017) 265:431–7. doi: 10.1097/SLA.0000000000001708
4. Mun M, Nakao M, Matsuura Y, Ichinose J, Nakagawa K, Okumura S. Video-assisted thoracoscopic surgery lobectomy for non-small cell lung cancer. *Gen Thorac Cardiovasc Surg.* (2018) 66:626–31. doi: 10.1007/s11748-018-0979-x
5. Tsou KC, Hsu HH, Tsai TM, Chen KC, Chen JS. Clinical outcome of subcentimeter non-small cell lung cancer after VATS resection: Single institute experience with 424 patients. *J Formos Med Assoc.* (2020) 119:399–405. doi: 10.1016/j.jfma.2019.07.004
6. Hung WT, Cheng YJ, Chen JS. Video-assisted thoracoscopic surgery lobectomy for lung cancer in nonintubated anesthesia. *Thorac Surg Clin.* (2020) 30:73–82. doi: 10.1016/j.thorsurg.2019.09.002
7. Ujiie H, Gregor A, Yasufuku K. Minimally invasive surgical approaches for lung cancer. *Expert Rev Respir Med.* (2019) 13:571–8. doi: 10.1080/17476348.2019.1610399
8. Pennathur A, Brunelli A, Criner GJ, Keshavarz H, Mazzone P, Walsh G, et al. Definition and assessment of high risk in patients considered for lobectomy for stage I non-small cell lung cancer: The American Association for Thoracic Surgery expert panel consensus document. *J Thorac Cardiovasc Surg.* (2021) 162:1605–18.e6. doi: 10.1016/j.jtcvs.2021.07.030
9. Jia J, Guo B, Yang Z, Liu Y, Ga L, Xing G, et al. Outcomes of local thoracic surgery in patients with stage IV non-small-cell lung cancer: a SEER-based analysis. *Eur J Cancer.* (2021) 144:326–40. doi: 10.1016/j.ejca.2020.12.002
10. Cao J, Yuan P, Wang Y, Xu J, Yuan X, Wang Z, et al. Survival rates after lobectomy, segmentectomy, and wedge resection for non-small cell lung cancer. *Ann Thorac Surg.* (2018) 105:1483–91. doi: 10.1016/j.athoracsur.2018.01.032
11. Batihan G, Ceylan KC, Usluer O, Kaya SÖ. Video-assisted thoracoscopic surgery vs thoracotomy for non-small cell lung cancer greater than 5 cm: is VATS a feasible approach for large tumors? *J Cardiothorac Surg.* (2020) 15:261. doi: 10.1186/s13019-020-01305-w
12. Ikeda N. Updates on minimally invasive surgery in non-small cell lung cancer. *Curr Treat Options Oncol.* (2019) 20:16. doi: 10.1007/s11864-019-0614-9
13. Drevet G, Maury JM, Ginoux M, Tronc F. Morbi-mortalité de la résection pulmonaire pour cancer par chirurgie vidéo-assistée chez l'octogénaire [Short-term results of video-assisted lung cancer surgery in octogenarians]. *Rev Mal Respir.* (2020) 37:293–8. doi: 10.1016/j.rmr.2020.01.007
14. Tuminello S, Liu B, Wolf A, Alpert N, Taioli E, Flores RM. Comparison of in-hospital and long-term outcomes of sublobar lung cancer surgery by VATS and open techniques. *Am J Clin Oncol.* (2018) 41:1149–53. doi: 10.1097/COC.0000000000000440
15. Raman V, Yang CJ, Deng JZ, D'Amico TA. Surgical treatment for early stage non-small cell lung cancer. *J Thorac Dis.* (2018) 10:898–904. doi: 10.21037/jtd.2018.01.172
16. Zhao R, Shi Z, Cheng S. Uniport video assisted thoracoscopic surgery (U-VATS) exhibits increased feasibility, non-inferior tolerance, and equal efficiency compared with multiport VATS and open thoracotomy in the elderly non-small cell lung cancer patients at early stage. *Medicine (Baltimore).* (2019) 98:16137. doi: 10.1097/MD.0000000000016137
17. Motono N, Iwai S, Iijima Y, Usuda K, Uramoto H. Operative invasiveness does not affect the prognosis of patients with non-small cell lung cancer. *BMC Pulm Med.* (2020) 20:265. doi: 10.1186/s12890-020-01264-x
18. Matsuoka K, Yamada T, Matsuoka T, Nagai S, Ueda M, Miyamoto Y. Video-assisted thoracoscopic surgery for lung cancer after induction therapy. *Asian Cardiovasc Thorac Ann.* (2018) 26:608–14. doi: 10.1177/0218492318804413
19. Oda R, Okuda K, Osaga S, Watanabe T, Sakane T, Tatematsu T, et al. Long-term outcomes of video-assisted thoracoscopic surgery lobectomy vs. thoracotomy lobectomy for stage IA non-small cell lung cancer. *Surg Today.* (2019) 49:369–77. doi: 10.1007/s00595-018-1746-4

20. Gao Y, Zhang H, Li Y, Wang D, Ma Y, Chen Q. Preoperative pulmonary function correlates with systemic inflammatory response and prognosis in patients with non-small cell lung cancer: results of a single-institution retrospective study. *Oncotarget*. (2017) 8:27489–501. doi: 10.18632/oncotarget.14225
21. Bongiolatti S, Gonfiotti A, Vokrri E, Borgianni S, Crisci R, Curcio C, et al. Thoracoscopic lobectomy for non-small-cell lung cancer in patients with impaired pulmonary function: analysis from a national database. *Interact Cardiovasc Thorac Surg*. (2020) 30:803–11. doi: 10.1093/icvts/ivaa044
22. Zhang Y, Gao Y. Effects of VATS lobectomy, VATS anatomic segmentectomy, and open thoracotomy on pulmonary function of patients with non-small cell lung cancer. *Zhongguo Fei Ai Za Zhi*. (2016) 19:700–4. doi: 10.3779/j.issn.1009-3419.2016.10.15
23. Shi Q, Diao Y, Qian J. Application of single-hole thoracoscopic surgery combined with ERAS concept for respiratory function exercise in perioperative period of lung cancer. *Zhongguo Fei Ai Za Zhi*. (2020) 23:667–72. doi: 10.3779/j.issn.1009-3419.2020.101.26
24. Watanabe A, Miyajima M, Mishina T, Tsuruta K, Takahashi Y, Maki R, et al. Video-assisted thoracoscopic surgery node dissection for lung cancer treatment. *Surg Today*. (2017) 47:1419–28. doi: 10.1007/s00595-017-1494-x
25. Deng HY, Qiu XM, Zhu DX, Tang X, Zhou Q. Video-assisted thoracoscopic sleeve lobectomy for centrally located non-small cell lung cancer: a meta-analysis. *World J Surg*. (2021) 45:897–906. doi: 10.1007/s00268-020-05877-5

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Mao, Gao and Yin. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 18 March 2022
doi: 10.3389/fsurg.2022.857877

Nursing Practice Based on Evidence-Based Concepts to Prevent Enteral Nutrition Complications for Critically Ill Neurosurgical Patients

Jia Jiao[1†], Yu Chen[2†], Lijian Yang[1], Wei Li[1], Zhiwei Zhou[1], Lan Li[1], Yinghong Xiao[1], Jiasha Zhao[1], Linzhi Li[1] and You Xia[2]*

[1] Department of Neurosurgery, Changsha First Hospital, Changsha, China, [2] Department of Nursing Teaching and Research Office, Changsha First Hospital, Changsha, China

OPEN ACCESS

Edited by:
Weiguo Li,
Harbin Institute of Technology, China

Reviewed by:
Li Zhu,
Central South University, China
Qiang Wang,
Guizhou University, China

***Correspondence:**
You Xia
166812637@qq.com

[†] These authors share first authorship

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: 19 January 2022
Accepted: 11 February 2022
Published: 18 March 2022

Citation:
Jiao J, Chen Y, Yang L, Li W, Zhou Z, Li L, Xiao Y, Zhao J, Li L and Xia Y (2022) Nursing Practice Based on Evidence-Based Concepts to Prevent Enteral Nutrition Complications for Critically Ill Neurosurgical Patients. Front. Surg. 9:857877. doi: 10.3389/fsurg.2022.857877

Purpose: To explore the practical value of enteral nutrition care guided by evidence-based concepts in preventing enteral nutritional complications in critically ill neurosurgical patients.

Methods: Three hundred critically ill patients from March 2020 to October 2021 from our neurosurgery department were included in the study. Patients were divided into a control group (March to December 2020, $n = 150$) and a study group (January to October 2021, $n = 150$) according to the order of their admission. The control group received conventional enteral nutrition care, and the study group received enteral nutrition care based on evidence-based concept guidance. The levels of serum nutritional indicators [hemoglobin (Hb), albumin (ALB), and total protein (TP)], feeding compliance rate, the incidence of complications (gastric retention, bloating, diarrhea, reflux, vomiting, aspiration, stress ulcers, etc.), and prognosis during the observation period were compared between the two groups. The scores of the questionnaire of knowledge, attitude, and practice on nutrition among neurosurgical nurses before and after the implementation of evidence-based care were compared among nursing staff in the study group.

Results: At 1 and 2 weeks after enrollment, Hb, ALB, and TP levels were lower in both groups than before enrollment in the same group ($P < 0.05$). At 2 weeks after enrollment, Hb, ALB, and TP levels were higher in both groups than at 1 week after enrollment in the same group ($P < 0.05$). At 1 and 2 weeks after enrollment, Hb, ALB, and TP levels were higher in the study group than in the control group ($P < 0.05$). At 7 days after feeding, the feeding compliance rate was higher in the study group (94.67%) than in the control group (70.00%) ($P < 0.05$). The total complication rate was lower in the study group (8.00%) than in the control group (16.00%) ($P < 0.05$). The percentage of good prognosis was higher in the study group (34.00%) than in the control group (23.33%) ($P < 0.05$). After the implementation of evidence-based

care, caregivers in the study group scored higher on nutrition knowledge, nutrition attitudes, and nutrition practices than those before the implementation ($P < 0.05$).

Conclusion: The implementation of evidence-based nursing interventions in critically ill neurosurgical patients based on evidence-based concepts is of great clinical value in correcting their nutritional status, preventing enteral nutritional complications, improving prognosis, and enhancing the nutritional knowledge, attitudes, and practices of nursing staff.

Keywords: neurosurgery, critically ill patients, evidence-based concepts, enteral nutritional complications, serum nutritional indicators

INTRODUCTION

The scope of neurosurgery treatment mainly includes critically ill patients who suffer from severe craniocerebral injury and hypertensive cerebral hemorrhage and require microsurgical treatment of various craniocerebral and spinal cord tumors (1). It has been reported that, after severe trauma to the brain, the body may be accompanied by stress-induced hyperglycemia and negative nitrogen balance, which can accelerate the metabolism and decomposition of the body, resulting in malnutrition (2). In the process of treating such patients, a certain amount of enteral nutrition support is often needed in the clinic to combat high stress, high metabolism, and high decomposition state of the body of critically ill patients (3). Early enteral nutrition support is an effective treatment method to correct the nutritional status of patients and improve their immunity. However, all systems in critically ill neurosurgical patients are more fragile. Also, the functions of various systems in critically ill neurosurgical patients are relatively fragile and tend to be less tolerant of enteral nutrition. During enteral nutrition supply, patients are prone to common complications and intolerance of the digestive tract and the respiratory system, such as gastric retention (4), bloating (5), diarrhea (6), reflux (7), vomiting (8), aspiration pneumonia (9), and stress ulcers (10). The above not only affects the effectiveness of nutritional supply in patients but also causes suffering to their physical and mental health. How to reduce the complications of enteral nutrition in critically ill neurosurgical patients has become a major and difficult problem that needs to be solved urgently by neurosurgical healthcare professionals.

In recent years, enteral nutrition guidelines and expert consensus for critically ill patients have been established from different perspectives at home and abroad (11–13). It is used to relieve the nursing confusion of clinical nurses during the feeding process, standardize the safe feeding plan, and reduce the intolerance and complications of the gastrointestinal tract and the respiratory tract of patients. This study investigates the value of enteral nutrition care based on evidence-based concepts to prevent enteral nutritional complications in critically ill neurosurgical patients by integrating the best evidence-based medical evidence that is available, the actual situation of the patient, and the personal skills and clinical experience of the caregiver, with the aim of obtaining better care outcomes.

MATERIALS AND METHODS

Research Object

Three hundred critically ill patients from March 2020 to October 2021 in our neurosurgery department were included in the study. Inclusion criteria: time from onset to rescue $\leq$12 h; Glasgow coma scale (GCS) score $\leq$8 scores; neurosurgical severe cases such as craniocerebral trauma, cerebral hemorrhage, and intracranial tumor diagnosed by imaging; those who were expected to be fed *via* nasogastric or nasoenteric tube for $\geq$7 days; those who did not have obvious important organ lesions; and those who had signed the informed consent. Exclusion criteria: Those with a previous history of intestinal obstruction; those with previous severe nutritional disorders or digestive insufficiency, intestinal dysfunction, or cirrhosis; those with combined symptoms of gastrointestinal bleeding; and those with combined endocrine diseases. Patients were divided into a control group (March to December 2020, $n = 150$) and a study group (January to October 2021, $n = 150$) according to the order of their admission. Comparison of the general conditions such as age, GCS score, and primary disease between the two groups in **Table 1** was not statistically significant and was comparable ($p > 0.05$).

Research Methods

Control Group

Nursing care was implemented according to the assessment and observation points, operation points, and precautions specified in the nursing practice guidelines (2011 version) issued by the National Health and Wellness Commission on enteral nutrition support. Within 24 h of patient enrollment, nutritional screening was completed using the Nutritional Risk Screening Assessment Form (NRS 2002) (14). The patient was given parenteral nutrition support 24 h after the injury. Patients were given enteral nutritional support 48 h after injury or after the recovery of postoperative bowel sounds. During the period, the patient's oral care should be done. If gastric retention, diarrhea, vomiting, and other discomforts occurred, the enteral nutrition support was stopped or the enteral nutrition formula was changed or the medication was administered as prescribed by the doctor, and the enteral nutrition supply was restarted after the symptoms were relieved or disappeared.

TABLE 1 | Comparison of general conditions of two groups.

Items	Control group ($n = 150$)	Study group ($n = 150$)	t/χ^2 value	*P*-value
Age (years old)	57.52 ± 6.33	58.01 ± 6.07	0.684	0.494
GCS score (scores)	6.07 ± 0.83	6.05 ± 0.86	0.205	0.838
Gender [*n* (%)]			0.120	0.729
Male	81 (54.00)	78 (52.00)		
Female	69 (46.00)	72 (48.00)		
Primary disease [*n* (%)]			1.400	0.706
Craniocerebral trauma	56 (37.33)	53 (35.33)		
Cerebral hemorrhage	47 (31.33)	49 (32.67)		
Intracranial tumors	25 (16.67)	20 (13.33)		
Others	22 (14.67)	28 (18.67)		
Treatment modality [*n* (%)]			2.377	0.123
Surgery	145 (96.67)	139 (92.67)		
Conservative treatment	5 (3.33)	11 (7.33)		

Study Group

Patients were treated with enteral nutrition care guided by evidence-based concepts. (1) Establishing an evidence-based care team: It consisted of nurse leaders and specialist nurses from the Department of Neurosurgery who had undergone evidence-based care learning and training, a total of 10 people. (2) Screening for evidence-based care evidence: First, keywords such as "neurosurgery," "critically ill patients," "enteral nutrition," and "evidence-based care" were searched through Chinese and foreign databases to find evidence supported by evidence-based medicine (50 documents were searched). Then, the evidence-based care team selected high-quality, authentic, reliable, and practical evidence combined with the clinical experience and skills of the caregivers to form an enteral nutrition support program for neurosurgical patients with severe illnesses. (3) Evidence-based care for enteral nutrition time: Early enteral nutrition solution (Peptison) was given to patients after injury or 24 h after surgery, and a gastrointestinal drug (Metoclopramide) was administered. (4) Evidence-based care for nutrition programs: On days 1 to 2, calories were supplied at 500 kcal/d and nutritional preparations were pumped at a rate of 20 ml/h. On days 3 to 5, calories were supplied at 25–30 kcal/(kg·d), pumped at a rate of 30–50 ml/h, with parenteral nutrition supplementation as appropriate during this period. After the 5th day, calories were supplied at 25–30 kcal/(kg·d), pumped at a rate of 80–100 ml/h, and supported entirely by enteral nutrition. (5) Evidence-based care for nutritional modalities: Nasoenteric tube placement was used. The placement depth was 110–120 cm for men and 105–110 cm for women. After placement, the position of the bowel canal was determined by a chest radiograph. (6) Evidence-based care for the prevention of complications: Before feeding, the patient's nasoenteric tube position was determined, the patient's degree of consciousness impairment, choking reflex, and other feeding conditions were assessed, and an individualized feeding plan for the patient was developed accordingly. During feeding, the head of the bed was elevated $\geq 30^{\circ}$ if not contraindicated; if the patient vomited, the head was tilted to the side and nasal feeding was suspended; and if the patient had abdominal distention or poor digestion, appropriate gastrointestinal drugs were given. A stable pumping rate was maintained, starting from a minimum rate of 20 ml/h and not exceeding a maximum of 120 ml/h. Appropriate abdominal massage was given to the patient after feeding. Feeding was suspended before extubation of tracheal intubation or before lumbar puncture. The researcher used gentle movements when performing suction, turning, etc. After the patients' vital signs were stabilized, respiratory function and swallowing function training were started as early as possible; constipated patients were given glycerol enema as appropriate.

Observation Index

Before enrollment and at 1 and 2 weeks after enrollment, fasting venous blood was drawn from patients in both groups to measure serum nutritional index [hemoglobin (Hb), albumin (ALB), and total protein (TP)] levels. Hb and ALB were measured by enzyme-linked immunosorbent assay, and TP was measured by biuret colorimetry. Hb and ALB detection kits were purchased from Wuhan Cloud Clone Technology Co., Ltd., and TP detection kits were purchased from Shanghai Yuanye Biotechnology Co., Ltd.

The feeding compliance rate at 7 days after feeding between the two groups was compared, i.e., the percentage of the actual feeding amount and the planned feeding amount of the patient. The planned feeding amount was calculated using the Nutritional Risk Screening Assessment Form (NRS 2002), and at the same time, the actual daily feeding amount of the patient was monitored and recorded.

The incidence of complications, such as gastric retention, bloating, diarrhea, reflux, vomiting, aspiration, and stress ulcers, during feeding was compared between the two groups.

The prognostic status of both groups was assessed according to the Oxford Handicap Score (OHS) and the Glasgow Outcome Score (GOS). There were four grades of prognostic status: good prognosis, moderate disability, severe disability or vegetative survival, and death. The grading criteria of the two tables are shown in **Table 2**.

The scores of the caregivers on the questionnaire on nutrition knowledge, attitude, and practice of surgical nurses before and after implementation of evidence-based care were compared. The scale was publicly published by Kobe (15) in 2006 and was Chineseized by domestic scholars in 2009. A total of 3 entries were included: nutrition knowledge (0–30 scores), nutrition attitude (20–100 scores), and nutrition practice (12–60 scores). A total of 20 questionnaires were distributed in this study and 20 were validly returned, with a valid return rate of 100%.

TABLE 2 | The Oxford Handicap Score (OHS) and the Glasgow Outcome Score (GOS) grading standards.

Prognostic status	OHS (score)	GOS (score)
Good prognosis	≤1	=5
Moderate disability	2-3	=4
Severe disability or vegetative survival	4-5	2-3
Death	6	=1

Statistical Methods

SPSS 22.0 software was applied, and the measurement data were expressed as mean±standard deviation (M ± SD) and were compared by *t*-test. Count data were expressed as a ratio (%), and the χ^2 test was used for comparison. $P < 0.05$ was considered statistically significant.

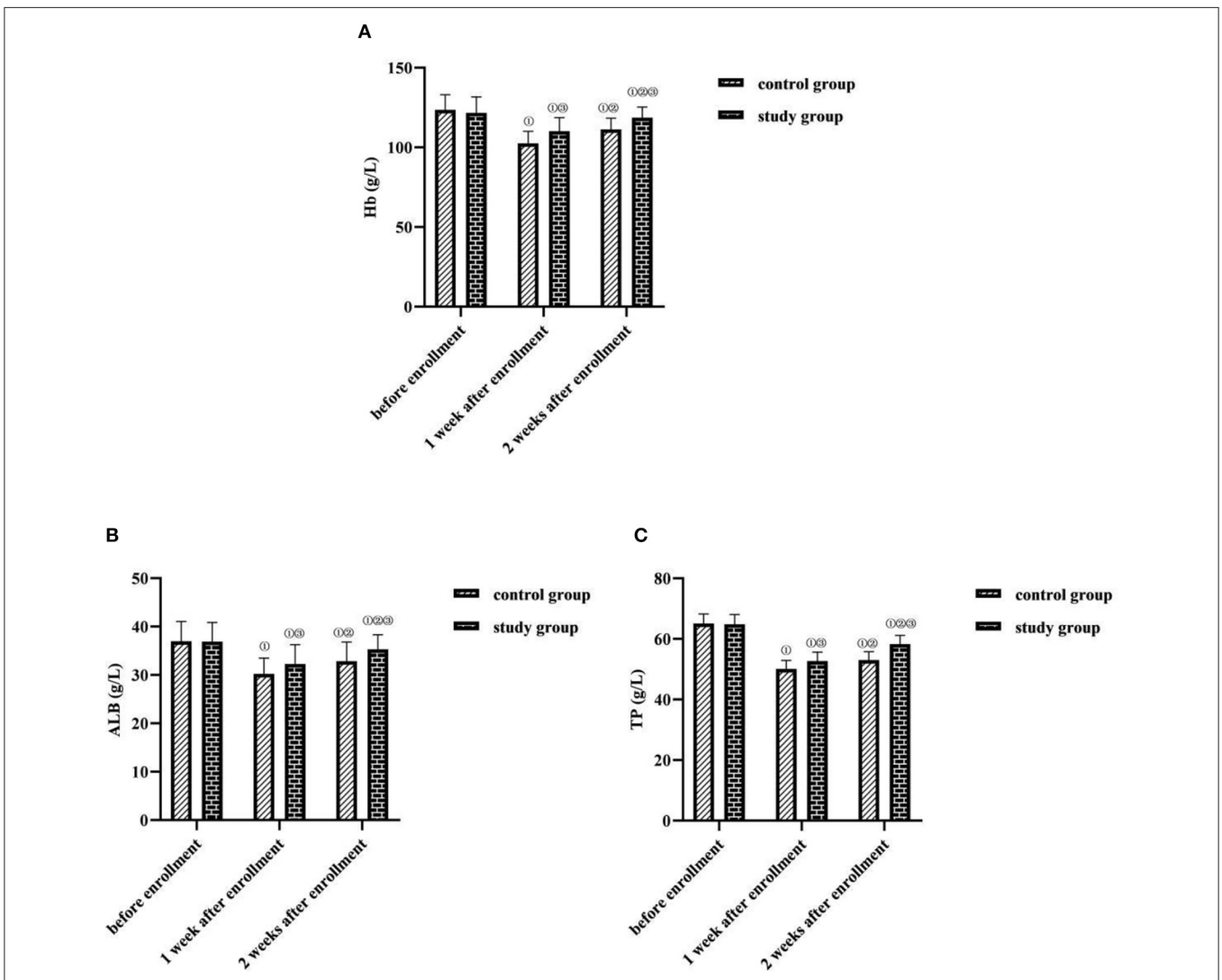


FIGURE 1 | Comparison of serum nutritional index levels between the two groups ($M \pm SD$, g/L). **(A)** Hb levels (g/L). **(B)** ALB levels (g/L). **(C)** TP levels (g/L). Compared with the same group before enrollment, ①$P<0.05$; compared with the same group at 1 week after enrollment, ②$P<0.05$; compared with the control group at the same time point, ③$P < 0.05$.

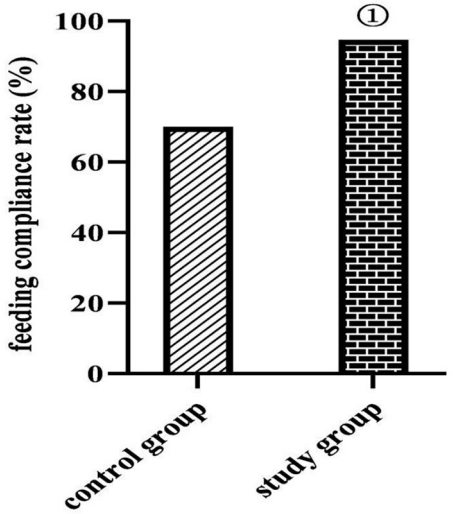


FIGURE 2 | Comparison of feeding compliance rates between the two groups (*n*, %). Compared with the control group, ①$P < 0.05$.

RESULTS

Comparison of Serum Nutritional Index Levels Between the Two Groups

At 1 and 2 weeks after enrollment, Hb, ALB, and TP levels were lower in both groups than before enrollment in the same group ($P < 0.05$). At 2 weeks after enrollment, Hb, ALB, and TP levels were higher in both groups than at 1 week after enrollment in the same group ($P < 0.05$). At 1 and 2 weeks after enrollment, Hb, ALB, and TP levels were higher in the study group than in the control group ($P < 0.05$) (**Figure 1**).

Comparison of Feeding Compliance Rates Between the Two Groups

At 7 days after feeding, the feeding compliance rate was higher in the study group (94.67%) than in the control group (70.00%) ($P < 0.05$) (**Figure 2**).

Comparison of Complication Rates Between the Two Groups

The total complication rate was lower in the study group (8.00%) than in the control group (16.00%) ($P < 0.05$) (**Figure 3**).

Comparison of Prognostic Status Between the Two Groups

The percentage of good prognosis was higher in the study group (34.00%) than in the control group (23.33%) ($P < 0.05$) (**Figure 4**).

Comparison of Nutrition Knowledge, Attitude, and Practice Scores of Caregivers in the Study Group Before and After Care Implementation

After the implementation of evidence-based care, caregivers in the study group scored higher on nutrition knowledge, nutrition attitudes, and nutrition practices than before the implementation ($P < 0.05$) (**Figure 5**).

DISCUSSION

It has been demonstrated that early enteral nutrition support applied to critically ill patients can effectively prevent their secondary injuries and circumvent the occurrence of disability and death (16). Nevertheless, there are controversies regarding the nutrition time, the nutrition program, the nutrition approaches, and the nutrition complications on how to effectively and safely give early enteral nutrition support (17). Evidence-based care is an important application of evidence-based medicine in the field of nursing as a way to improve nursing practice. It contains four continuums of evidence-based questions, evidence-based support, evidence-based observation, and evidence-based application (18). It requires nursing staff to organically combine the best nursing research evidence currently available with the personal experience, and skills of the nursing staff, the actual situation, and the nursing needs of patients. Through research to guide practice, through research to drive practice, and then formulate a scientific, effective and complete nursing program. This study explored the practical value of enteral nutrition nursing under the guidance of evidence-based concepts in preventing enteral nutritional complications in critically ill neurosurgical patients.

According to the evidence of evidence-based medicine (19), when the intestinal function permits, enteral nutrition support is given to patients after injury or 1 to 2 days after surgery, which helps to maintain their intestinal barrier function; according to the difference in the energy metabolism of patients, the necessary energy supply is given to the body, which helps to ensure the nutritional status and immune function of patients. However, the specific implementation of all these measures is more difficult. In this study, based on the evidence-based concept, the evidence-based care team screened high-quality, authentic, reliable, and practical evidence-based medical evidence through data retrieval and combined their own clinical experience and skills to develop and form an enteral nutrition support program for critically ill neurosurgical patients.

In the study results, at 1 and 2 weeks after enrollment, Hb, ALB, and TP levels were lower in both the groups than before enrollment in the same group ($P < 0.05$); at 2 weeks after enrollment, Hb, ALB, and TP levels were higher in both groups than at 1 week after enrollment in the same group ($P < 0.05$); at 1 and 2 weeks after enrollment, Hb, ALB, and TP levels were higher in the study group than in the control group ($P < 0.05$) l and at 7 days after feeding, the feeding compliance rate was higher in the study group (94.67%) than in the control group (70.00%) ($P < 0.05$). This

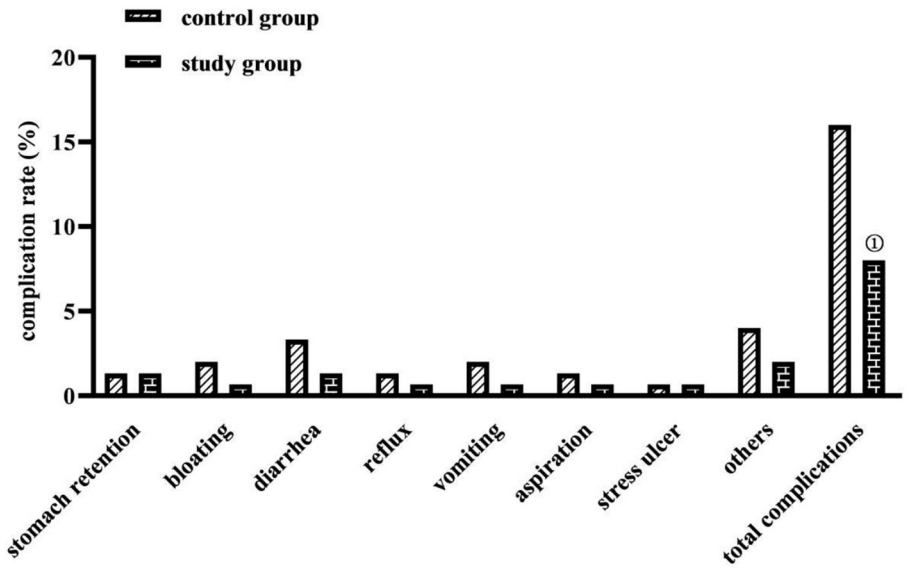


FIGURE 3 | Comparison of complication rates between the two groups (*n*, %). Comparison with the control group on the same parameters, ①$P < 0.05$.

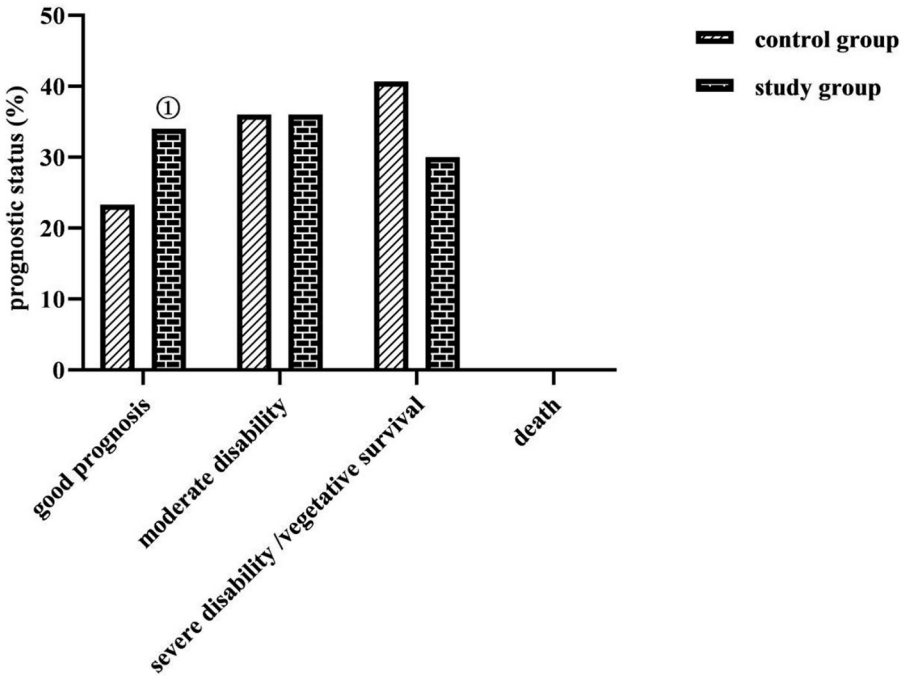


FIGURE 4 | Comparison of prognostic status between the two groups (*n*, %). No death prognosis in both groups. Comparison with the control group on the same parameters, ①$P < 0.05$.

suggests that enteral nutrition support based on evidence-based concepts can help correct the nutritional status of critically ill neurosurgical patients. To analyze the possible reasons: the organs and systems of neurosurgical patients are fragile, but the function of their small bowel is in a relatively normal state, so the use of the nasoenteric tube feeding method based on the evidence-based concept in this study would be more helpful to promote the effect of enteral nutrition supply than nasogastric tube feeding method; and the early administration of enteral nutrition solution and progastric motivational drugs after injury or 24 h postoperatively in evidence-based care helps maintain the structural and functional integrity of the gastrointestinal mucosa

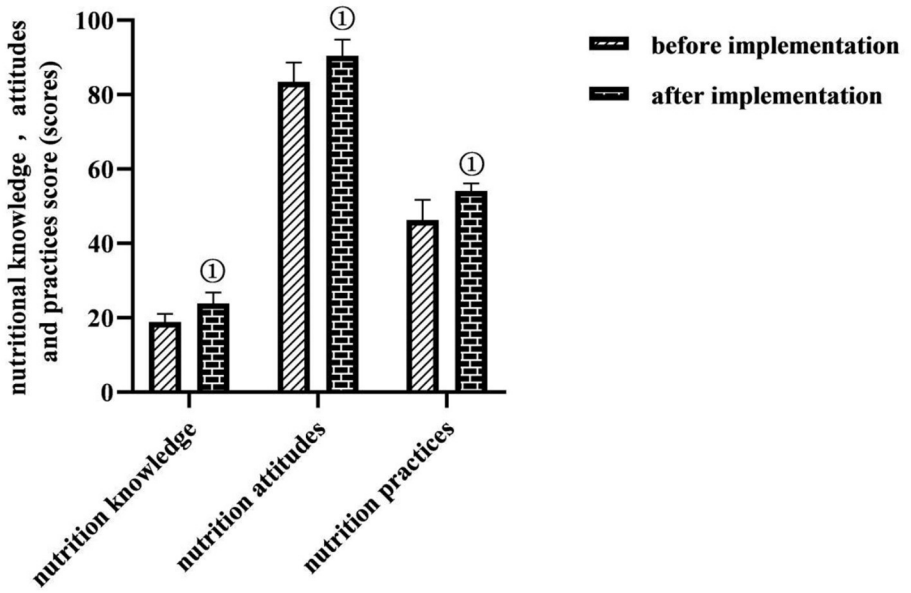


FIGURE 5 | Comparison of nutrition knowledge, attitude, and practice scores of caregivers in the study group before and after care implementation ($M \pm SD$, scores). Comparison with the same dimension before implementation, $^{①}P < 0.05$.

of patients; in terms of nutritional programs, evidence-based care can provide patients with scientific and reasonable energy supply programs and contribute to the stabilization of the metabolic level of the organism and the maintenance of immune function by enhancing nutritional risk assessment, calculating energy expenditure and basal consumption at different time points according to energy metabolic differences of patients, and controlling the drip rate of nutritional fluids (20).

The application of nasogastric tube feeding for enteral nutrition support in critically ill neurosurgical patients is universally effective, but the complications it causes are manifold (21). It is common to have gastric retention, nausea, vomiting, reflux, and aspiration, all of which are among the main causes of feeding intolerance and poor prognosis in patients. In this study, the total complication rate of the study group was lower than that of the control group, the percentage of good prognosis was higher than that of the control group ($P < 0.05$), the incidence of moderate and severe disability or vegetative survival was comparable in both groups, and no death occurred in either group ($P > 0.05$). This indicates that the enteral nutrition method based on an evidence-based concept contributes to the reduction of enteral nutritional complications and the improvement of prognosis in critically ill neurosurgical patients. Analyzing the reasons for this may be related to the fact that this study took a nasoenteric tube as the nutritional support route based on evidence-based concepts and was supplemented with comprehensive care measures for preventing complications. The application of the nasoenteric tube in this study, which was delivered to the duodenum and jejunum of the patient through the pylorus of the stomach, could prevent complications such as reflux, gastric retention, and aspiration pneumonia. Elevating the patient's head could also prevent regurgitation, and controlling the pumping speed and temperature of the nutrient solution could protect gastrointestinal function, prevent bloating, prevent diarrhea, etc. (22). There is also evidence that the start time of early enteral nutrition support in patients with severe traumatic brain injury positively correlated with the degree of neurological improvement and survival (23). In this study, based on evidence-based concepts, early enteral nutrition given to patients after injury or 24 h after surgery could promote the early recovery of nutritional status and neurological function of patients, so the clinical prognosis was good. In addition, according to the survey, clinical nurses in China have inadequate knowledge of nutrition screening and a biased understanding of the effectiveness of enteral nutrition support. The results of this study showed that, after the implementation of evidence-based care, caregivers in the study group scored higher on nutrition knowledge, nutrition attitudes, and nutrition practices than before the implementation. This shows that enteral nutrition nursing under the guidance of the evidence-based concept has a certain effect in improving the nutritional knowledge, attitude, and practice level of nursing staff. This may be because, before the implementation of evidence-based nursing, nurses lacked relevant nursing knowledge of enteral nutritional complications, and there were irregular operating procedures, whereas, after the establishment of the evidence-based care team in the study, a manual on enteral nutrition for critically ill neurosurgical patients based on evidence-based evidence was formed, which provided both evidence resources and dissemination tools for the management of enteral nutritional complications for critically ill patients and met the needs of clinical nurses to obtain knowledge and information.

CONCLUSION

The implementation of evidence-based nursing interventions in critically ill neurosurgical patients based on evidence-based concepts is of great clinical value in correcting their nutritional status, preventing enteral nutritional complications, improving prognosis, and enhancing the nutritional knowledge, attitudes, and practices of nursing staff.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Changsha First Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YoX was the instructor for the entire study. All authors of this study made equal contributions and collaborated on the design of the protocol, the implementation of the experiments, the detection of the results, the statistics of the data, and the writing of the article.

REFERENCES

1. Liu J, Gormley N, Dasenbrock HH, Aglio LS, Smith TR, Gormley WB, et al. Cost-benefit analysis of transitional care in neurosurgery. *Neurosurgery*. (2019) 85:672–9. doi: 10.1093/neuros/nyy424
2. Mousavian SZ, Pasdar Y, Ranjbar G, Jandari S, Akhlaghi S, Almasi A, et al. Randomized controlled trial of comparative hypocaloric vs full-energy enteral feeding during the first week of hospitalization in neurosurgical patients at the intensive care unit. *JPEN J Parenter Enteral Nutr.* (2020) 44:1475–83. doi: 10.1002/jpen.1782
3. Qiu C, Chen C, Zhang W, Kou Q, Wu S, Zhou L, et al. Fat-modified enteral formula improves feeding tolerance in critically ill patients: a multicenter, single-blind, randomized controlled trial. *JPEN J Parenter Enteral Nutr.* (2017) 41:785–95. doi: 10.1177/0148607115601858
4. Zhang H, Gu Y, Mi Y, Jin Y, Fu W, Latour JM. High-energy nutrition in paediatric cardiac critical care patients: a randomized controlled trial. *Nurs Crit Care.* (2019) 24:97–102. doi: 10.1111/nicc.12400
5. Fan M, Wang Q, Fang W, Jiang Y, Li L, Sun P, et al. Early enteral combined with parenteral nutrition treatment for severe traumatic brain injury: effects on immune function, nutritional status and outcomes. *Chin Med Sci J.* (2016) 31:213–20. doi: 10.1016/S1001-9294(17)30003-2
6. Zhao R, Wang Y, Huang Y, Cui Y, Xia L, Rao Z, et al. X. Effects of fiber and probiotics on diarrhea associated with enteral nutrition in gastric cancer patients: a prospective randomized and controlled trial. *Medicine*. (2017) 96:e8418. doi: 10.1097/MD.0000000000008418
7. Castel H, Tiengou LE, Besancon I, Joubert C, Fatome A, Piquet MA. What is the risk of nocturnal supine enteral nutrition? *Clin Nutr.* (2005) 24:1014–8. doi: 10.1016/j.clnu.2005.08.001
8. Martos-Benítez FD, Gutiérrez-Noyola A, Soto-García A, González-Martínez I, Betancourt-Plaza I. Program of gastrointestinal rehabilitation and early postoperative enteral nutrition: a prospective study. *Updates Surg.* (2018) 70:105–12. doi: 10.1007/s13304-018-0514-8
9. Tabei I, Tsuchida S, Akashi T, Ookubo K, Hosoda S, Furukawa Y, et al. Effects of a novel method for enteral nutrition infusion involving a viscosity-regulating pectin solution: a multicenter randomized controlled trial. *Clin Nutr ESPEN.* (2018) 23:34–40. doi: 10.1016/j.clnesp.2017.11.005
10. El-Kersh K, Jalil B, McClave SA, Cavallazzi R, Guardiola J, Guilkey K, et al. Enteral nutrition as stress ulcer prophylaxis in critically ill patients: a randomized controlled exploratory study. *J Crit Care.* (2018) 43:108–13. doi: 10.1016/j.jcrc.2017.08.036
11. McClave SA, Taylor BE, Martindale RG, Warren MM, Johnson DR, Braunschweig C, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: society of critical care medicine (SCCM) and American society for parenteral and enteral nutrition (ASPEN). *JPEN J Parenter Enteral Nutr.* (2016) 40:159–211. doi: 10.1177/0148607115621863
12. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr.* (2019) 38:48–79. doi: 10.1016/j.clnu.2018.08.037
13. Reintam Blaser A, Starkopf J, Alhazzani W, Berger MM, Casaer MP, Deane AM, et al. Early enteral nutrition in critically ill patients: ESICM clinical practice guidelines. *Intensive Care Med.* (2017) 43:380–98. doi: 10.1007/s00134-016-4665-0
14. Jie B, Jiang ZM, Nolan MT, Efron DT, Zhu SN, Yu K, et al. Impact of nutritional support on clinical outcome in patients at nutritional risk: a multicenter, prospective cohort study in Baltimore and Beijing teaching hospitals. *Nutrition.* (2010) 26:1088–93. doi: 10.1016/j.nut.2009.08.027
15. Kobe JA. *Aspects of Nutritional Knowledge, Attitudes and Practices of Nurses Working at the Surgical Division at the Kenyatta National Hospital, Kenya*. Stellenbosch: University of Stellenbosch (2006-12). Available online at: https://scholar.sun.ac.za/handle/10019.1/1514
16. TARGET Investigators, for the ANZICS Clinical Trials Group, Chapman M, Peake SL, Bellomo R, Davies A, et al. Energy-dense versus routine enteral nutrition in the critically ill. *N Engl J Med*. (2018) 379:1823–34. doi: 10.1056/NEJMoa1811687
17. Yuan F, Yang F, Zhang W, Jia Y, Ma Y, Qu Y, et al. Optimizing early enteral nutrition in severe stroke (OPENS): protocol for a multicentre randomized controlled trial. *BMC Neurol.* (2019) 19:24. doi: 10.1186/s12883-019-1253-2
18. Rostamnia L, Ghanbari V, Shabani F, Farahani A, Dehghan-Nayeri N. Evidence-based practice for cardiac intensive care unit nurses: an educational intervention study. *J Contin Educ Nurs.* (2020) 51:167–73. doi: 10.3928/00220124-20200317-06
19. Xu XD, Sun YS, Shao QS, Hu JF, Qian ZY, Zhou YL, et al. Effect of early enteral nutrition supplemented with glutamine on postoperative intestinal mucosal barrier function in patients with gastric carcinoma. *China J Gastr Surg.* (2011) 14:436–9. doi: 10.3760/cma.j.issn.1671-0274.2011.06.013
20. Taberna DJ, Navas-Carretero S, Martinez JA. Current nutritional status assessment tools for metabolic care and clinical nutrition. *Curr Opin Clin Nutr Metab Care.* (2019) 2:323–8. doi: 10.1097/MCO.0000000000000581
21. Juan W, Zhen H, Yan-Ying F, Hui-Xian Y, Tao Z, Pei-Fen G, et al. A comparative study of two tube feeding methods in patients with dysphagia after stroke: a randomized controlled trial. *J Stroke Cerebrovasc Dis.* (2020) 29:104602. doi: 10.1016/j.jstrokecerebrovasdis.2019.104602
22. Wan B, Fu H, Yin J. Early jejunal feeding by bedside placement of a nasointestinal tube significantly improves nutritional status and reduces complications in critically ill patients versus enteral nutrition by a nasogastric tube. *Asia Pac J Clin Nutr.* (2015) 24:51–7. doi: 10.6133/apjcn.2015.24.1.03

23. Meinert E, Bell MJ, Buttram S, Kochanek PM, Balasubramani GK, Wisniewski SR, et al. Initiating nutritional support before 72 hours is associated with favorable outcome after severe traumatic brain injury in children: a secondary analysis of a randomized, controlled trial of therapeutic hypothermia. *Pediatr Crit Care Med*. (2018) 19:345–52. doi: 10.1097/PCC.0000000000001471

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer LZ declared a shared affiliation with the authors to handling editor at time of review.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Jiao, Chen, Yang, Li, Zhou, Li, Xiao, Zhao, Li and Xia. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

SYSTEMATIC REVIEW
published: 22 March 2022
doi: 10.3389/fsurg.2022.841275

The Best Evidence for the Prevention and Management of Lower Extremity Deep Venous Thrombosis After Gynecological Malignant Tumor Surgery: A Systematic Review and Network Meta-Analysis

Jiaqi Hu[1], *Yidan Geng*[1], *Jingyi Ma*[1], *Xuefan Dong*[1], *Shuqin Fang*[2] *and Jianli Tian*[1]*

[1] College of Nursing, Chengde Medical University, Chengde, China, [2] Department of Gynecology, Affiliated Hospital of Chengde Medical University, Chengde, China

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Ying He,
First Affiliated Hospital of Hebei North University, China
Shenghui Yang,
Hainan Provincial People's Hospital, China

***Correspondence:**
Jianli Tian
cytianjianli@126.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *22 December 2021*
Accepted: *22 February 2022*
Published: *22 March 2022*

Citation:
Hu J, Geng Y, Ma J, Dong X, Fang S and Tian J (2022) The Best Evidence for the Prevention and Management of Lower Extremity Deep Venous Thrombosis After Gynecological Malignant Tumor Surgery: A Systematic Review and Network Meta-Analysis. Front. Surg. 9:841275. doi: 10.3389/fsurg.2022.841275

Background: To search and obtain the relevant evidence of prevention and management of lower extremity deep venous thrombosis (DVT) after gynecological malignant tumor operation and to summarize the relevant evidence.

Methods: We searched the JBI evidence summary, up to date, the national comprehensive cancer network of the United States, the guide library of the National Institute of clinical medicine of the United Kingdom, PubMed, the Chinese biomedical literature database, CNKI, Wanfang, and other relevant evidence on the prevention and management of DVT in patients with gynecological malignant tumors. It includes clinical practice guidelines, best practice information book, expert consensus, evidence summary, original research, etc. The retrieval time limit is from database establishment till August 20, 2021. Two researchers independently evaluated the literature quality, combined with professional judgment, and extracted the literature that met the standards.

Results: Finally, 18 literatures were included, including eight guidelines, three evidence summaries, four systematic evaluations, two expert consensuses, and one best practice information volume. A total of 26 pieces of the best evidence on the prevention and management of postoperative venous thrombosis in gynecological malignant tumors were summarized. It includes risk assessment, drug prevention, mechanical prevention, management strategy, and health education.

Conclusion: This study summarized the best evidence of risk, prevention, and health management of DVT in postoperative patients with gynecological malignant tumors to provide evidence-based basis for clinical nurses and to improve the nursing level.

Keywords: deep venous thrombosis, after tumor operation, gynecological malignant, prevention, meta-analysis

INTRODUCTION

According to the latest data released by the international agency for research on cancer (IARC) (1), the global cancer burden has risen to 19.3 million new cases and 10 million deaths in 2020. The second leading cause of death in cancer patients is deep venous thromboembolism (DVT) (2). The incidence of postoperative DVT in gynecological malignant tumors is as high as 19.6–38% (3). DVT refers to abnormal coagulation of blood in the deep vein, which blocks venous lumen and leads to abnormal venous reflux (4). If it is not found and effectively controlled in time, it can cause pulmonary embolism and even disability and death (5). Therefore, the importance of prevention and management of postoperative deep venous thrombosis (DVT) in gynecological malignant tumors cannot be ignored. There are many studies on DVT prevention at home and abroad, mainly in the form of literature review, and the research method is relatively single. Although China has published guidelines for the prevention of thrombotic diseases, there is a lack of guidelines or best practice manuals for the prevention and management of postoperative DVT of gynecological malignant tumors. This study systematically searched the relevant literature on the prevention and management of postoperative DVT of gynecological malignant tumors at home and abroad, evaluated, classified, and summarized the evidence by using the method of evidence-based nursing, and finally formed the best evidence to provide references for the prevention and management of postoperative DVT of gynecological malignant tumors.

MATERIALS AND METHODS

Search Strategy and Selection Criteria

The problem development tool of evidence-based nursing center of Fudan University was adopted to form evidence-based nursing problems based on pipost (6). They included the following: (1) evidence application target population (P): patients with gynecological malignant tumors after operation; (2) intervention (I): evaluation, prevention, drug and physical intervention methods of DVT; (3) professional (P): clinicians and nurses; (4) outcome (o): incidence of DVT, patients' cognition of DVT prevention, and compliance with prevention and management measures. Acceptance, cognition, and implementation of evidence by medical staff; (5) setting (s): gynecological ward and operating room; (6) type of evidence (T): guide, expert consensus, best practice information book, system evaluation, and evidence summary.

The evidence retrieval is carried out according to the "6S" evidence model (7). The databases searched are: computer search up to date (Chinese version), JBI evidence summary, National Comprehensive Cancer Network (NCCN), National Institute for health and care excellence (NICE), PubMed, Chinese biomedical literature database, CNKI, Wanfang. The English search subject words are: "deep vein thrombosis/deep venous thrombosis/venous thrombosis/deep venous thrombosis/thrombemembolism/" cancer/ gynecological cancers/gynecological malignant tumors "risk assessment/assessment/risk factors."

Inclusion criteria are as follows: the subjects were patients after radical operation of gynecological malignant tumors, and the evidence applicable to patients after operation of gynecological malignant tumors were also included; research involving evaluation and intervention of DVT; outcome measures included complications caused by DVT; research types include evidence summary, best clinical practice information book, guidelines (2016–2021), expert consensus, systematic evaluation, etc. The research language is English. Exclusion criteria include the following: incomplete literature and information that cannot obtain the full text, where the literature includes abstract, plan, report, and draft; and studies that did not pass literature evaluation.

Data Collection

Two researchers with an evidence-based medicine background independently completed the quality evaluation of the included literature to determine the inclusion and exclusion criteria of the literature. In case of disagreement, the evidence-based nursing team composed of nursing management and gynecological nursing experts in our hospital shall decide to include or eliminate the research. After the evidence was extracted, another researcher carefully checked it again to ensure the accuracy of the data. When the evidence conclusions from different sources conflict, the inclusion principle followed in this study is evidence-based evidence first, high-quality evidence first, and the latest published guidelines and authoritative literature first (8).

Literature quality evaluation criteria: (1) the guideline adopts the British clinical guidelines research and evaluation system (9) (the approval of guidelines for research and evaluation instrument, agree II) updated in 2012, including 6 independent fields and 23 items. Grade seven scoring method is adopted (one means highly disagree and seven means highly agree). The score of each field is the sum of the scores of each item in the field and is normalized to the percentage of the highest possible score in the field. Standardized percentage of each field = (actual score–minimum possible score)/(maximum possible score–minimum possible score) × 100%. The higher the score, the higher the quality of the guide. It is divided into three recommendation levels: Grade A, and 6 areas with scores ≥ 60%, which is strongly recommended; Grade B, with scores of 30–60% in at least three fields, which is recommended; Grade C, with scores ≤ 30 in at least three fields, which is not recommended temporarily (9). (2) Expert consensus, systematic evaluation, case-control, and randomized control were used to evaluate the literature according to the evaluation criteria of JBI evidence-based health care center in Australia (2016) (10). The evaluation items of the evaluation tools of different research types are different, but the unified evaluation criteria adopted by each item are "yes, no and unclear"; (3) the quality evaluation of evidence summary is directly based on the original research literature to classify the evidence level and the recommendation level, and the quality evaluation tools for various original studies of the JBI evidence-based health care center in Australia are used for evaluation (11); (4) the quality evaluation of clinical decision-making and best practice can be traced back to the original literature on which the

evidence is based, and the relevant evaluation criteria are selected for evaluation according to the literature type.

Statistical Analysis

A network meta-analysis was conducted on the occurrence of lower extremity deep venous embolism in the perioperative period of gynecological malignant tumors. We use an extension of the frequency random-effects model for multiple comparisons. The network meta-analysis was performed using Stata's mvmeta command. We used the raw data in the 2 × 2 table in the analysis. The odds ratio, risk ratio or ratio, and appropriate variance are calculated and combined in the analysis to obtain the overall relative risk. An interaction term is added to the model to estimate the difference between direct and indirect evidence results. All potential interactions were tested in an overall test to determine whether there were any inconsistencies in our network meta-analysis. The following sensitivity analyses are planned: each study design, each funding source (whether industry-sponsored or not), within the first user, and based on the risk of bias. All statistical analyses were performed using Stata version 22.0.

RESULTS

Characteristics of Included Studies

A total of 345 relevant literatures were initially retrieved and 18 were finally included, including eight guidelines, three evidence summaries, four systematic evaluations, two expert consensuses, and 1 best practice information volume. The PRISMA flow diagram is shown in **Figure 1**. The relevant information of the included literature is shown in **Table 1** (1, 6, 12–29). A total of 8 guidelines (12–18, 30) were included in this study, including two from the national comprehensive cancer network of the United States, two from the guide library of the National Institute of clinical medicine of the United Kingdom, two from PubMed, and two from HowNet. The quality evaluation results of the guidelines are shown in **Table 2** (1, 3, 5, 6, 12–15).

Four systematic reviews (19–21, 28) were included in this study, including one (19) from PubMed, two (20, 28) from the Cochrane Library, and one (21) from MEDLINE. Among the systematic evaluation quality evaluation results by Insin et al. (19), only the evaluation result of item seven "whether the proposed further research direction is appropriate" is "unclear," and the evaluation results of other items are "yes". In the systematic evaluation quality evaluation results by Hajibandeh et al. (20), only the evaluation result of Item nine "whether to evaluate the possibility of publication bias" is "no," and other items are "yes" (Kahn et al. and Pavon et al.). Only in Item four "is the retrieved database or resources sufficient?" the evaluation result is "no," and the evaluation result of other items is "yes." The overall quality evaluation is high. Two expert consensuses articles (1, 25) were included in this study and derived from HowNet (1) and Wanfang medical database (25), and their quality was evaluated according to the standards of the JBI evidence-based practice center in Australia. All the item options of the two items were "yes." One best practice manual from JBI and three evidence summaries from JBI are traced back to the original literature, including one guide and two systematic reviews. One guideline (13) coincides with the literature included in this study, and the evaluation result of item four of the remaining systematic evaluation is "no" and the rest is "yes"; one item nine evaluation result of the article is "no," and the rest is "yes".

By summarizing the evidence of prevention and management of venous thromboembolism after gynecological malignant tumor operation, 26 pieces of evidence were formed from five aspects: risk assessment, drug prevention, mechanical prevention, management strategy, and health education. In this study, the evidence classification and evidence recommendation level system of JBI evidence-based health care center in Australia (2014) (26) was used to divide the evidence level included in this study into five levels 1–5. According to the preciseness and scientificity of the research design, the recommendation level was divided into A-level recommendation (strong recommendation) and B-level recommendation (weak recommendation).

Risk Assessment

Evidence 1–3 summarizes the methods, contents, and high-risk factors of postoperative DVT evaluation of gynecological malignant tumors. The commonly used VTE risk evaluation tool caprini (1) scoring scale is used to calculate the total score through risk factors and assignment. The risk is divided into low risk (0–1), medium risk (2), high risk (3–4), and very high risk ($\geq$5). Caprini thrombus risk assessment scale is used to assess high-risk groups, and its sensitivity and specificity should be improved. At present, most risk assessment tools are based on retrospective analysis, and a large sample prospective research is needed in the future.

Evidence 4–6 summarizes the evaluation methods of DVT, including imaging evaluation, test evaluation, and clinical performance evaluation. The typical clinical manifestations of DVT are swelling and pain of the affected limb, and then changes in limb skin color and temperature (not all patients have the above symptoms). The preferred imaging method for the preliminary diagnosis of DVT is Doppler ultrasound. The routine laboratory examination indexes are D-dimer and protein C/s activity. If the patient has no clinical manifestations related to DVT and if the D-dimer test is negative, unstable, or active DVT can be excluded (22). Mastering the methods and contents of evaluation is of great significance to effectively prevent and manage the occurrence of postoperative DVT of gynecological malignant tumors.

Evidence 7–10 summarizes the methods of DVT drug prevention for gynecological malignant tumors. Drug prevention should be considered when the risk of thrombosis is greater than the risk of bleeding (17). About 2–12 h before operation, the highest dose of low molecular weight heparin (13) was used to prevent postoperative venous thromboembolism in patients with gynecological malignant cancer without relevant treatment contraindications (12).

The use of low molecular weight heparin for gynecologic malignancies after laparotomy and laparoscopy was extended to 4 weeks (for patients with a high risk of venous thromboembolism and a low risk of bleeding) (13). The high incidence period of DVT is the first 6 months after cancer diagnosis. Once

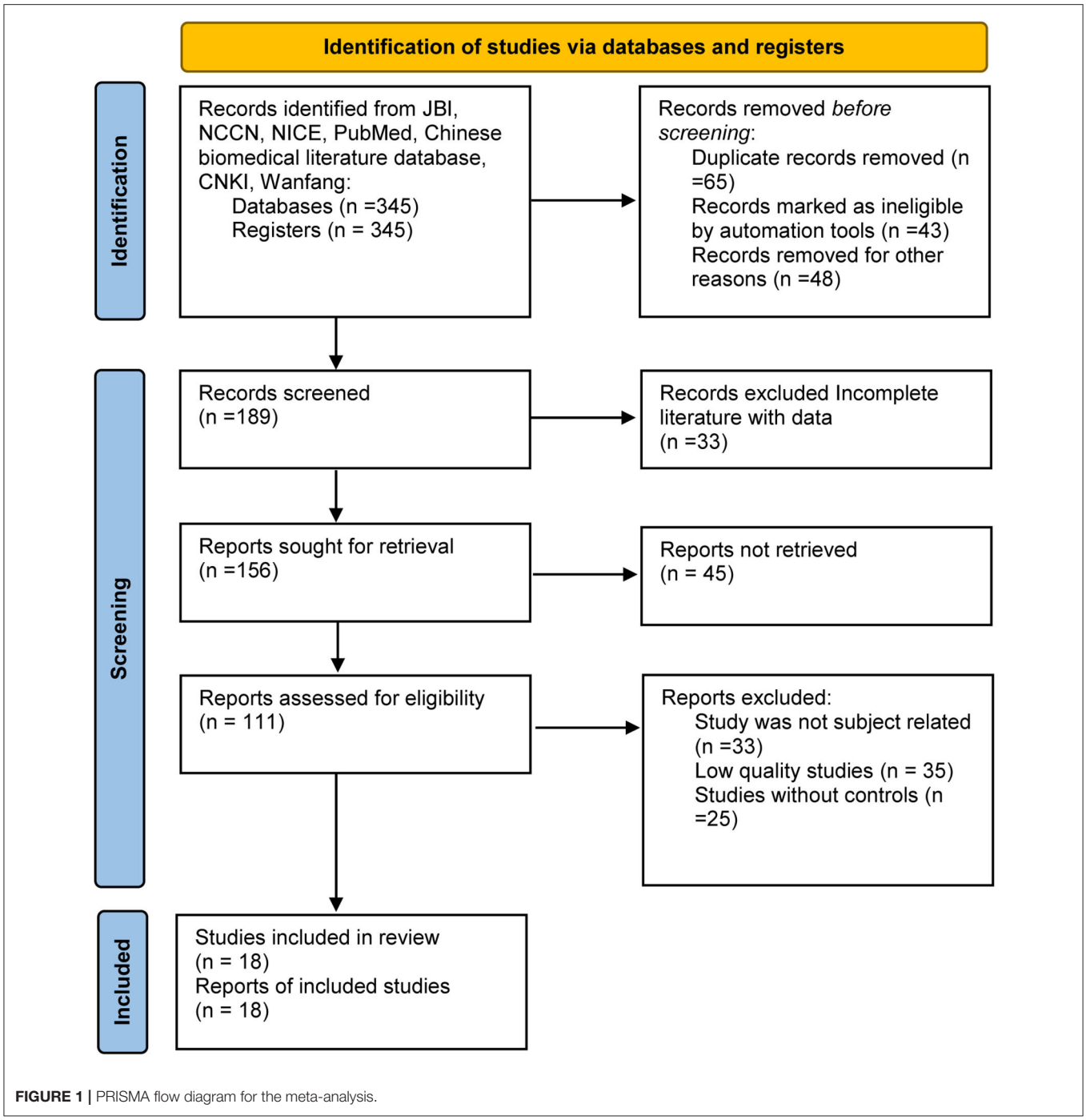


FIGURE 1 | PRISMA flow diagram for the meta-analysis.

patients with gynecological malignant tumors are diagnosed with DVT, anticoagulant therapy should be started immediately (25). Therefore, early assessment and detection of risk factors of DVT and timely adoption of effective drug prevention can effectively reduce the incidence of DVT.

Evidence 11–15 summarizes the methods of mechanical prevention of DVT in gynecological malignant tumors, including intermittent pneumatic compression (IPC), plantar venous pump (VFP), neuromuscular electrical stimulation (20), and graded compression stockings (GCS). If there is no contraindication, it is recommended that the patient can use the portable intermittent pneumatic compression (IPC) on both legs until the end of the operation. IPC is preferred to patients with high bleeding risk. GCS is preferred and worn all day. Different models are selected according to the diameter of lower limbs, and grade I pressure is preferred. During the GCS period, the temperature, blood supply, dorsalis pedis artery pulsation, limb sensation, and leg circumference of patients' lower limb skin

TABLE 1 | General information included in the literature.

Number	Included literature	Research topics	Nature of evidence	Database source	Publication time
1	NCCN (1)	GLOBOCAN Estimates of Incidence	Guide	NCCN	2021
2	Farge et al. (12)	Treatment and prophylaxis of venous thromboembolism	System evaluation	Pubmed	2019
3	Liew et al. (13)	Asian venous thromboembolism guidelines	System evaluation	Pubmed	2017
4	Wade et al. (14)	Graduated compression stockings for the prevention of deep-vein thrombosis	System evaluation	JBI	2015
5	NICE (15)	Reducing the risk of hospital-acquired deep vein thrombosis	Guide	NICE	2019
6	Streiff et al. (16)	Cancer-associated venous thromboembolic disease	System evaluation	Pubmed	2018
7	Wu and Cheng (17)	Analysis of perioperative risk factors	System evaluation	Pubmed	2020
8	Guo et al. (18)	Coagulation alteration and deep vein thrombosis	System evaluation	Medline	2018
9	Insin et al. (19)	Prevention of venous thromboembolism	System evaluation	Cochrane Library	2021
10	Hajibandeh et al. (20)	Prevention of venous thromboembolism	System evaluation	Pubmed	2017
11	Pavon et al. (21)	Effectiveness of intermittent pneumatic compression devices	System evaluation	Cochrane Library	2016
12	Buesing et al. (22)	Deep venous thrombosis and venous thromboembolism prophylaxis	System evaluation	MedLine	2015
13	Lieberman (23)	Deep vein thrombosis prophylaxis	System evaluation	JBI	2018
14	Fan et al. (24)	Perioperative prevalence of deep vein thrombosis	System evaluation	JBI	2020
15	Li et al. (25)	Incidence and locations of deep venous thrombosis	System evaluation	Pubmed	2020
16	Matsusaki et al. (26)	Central venous thrombosis and perioperative vascular access	System evaluation	Cochrane Library	2012
17	NCCN (6)	Deep vein thrombosis and serum D-dimer	Guide	NCCN	2020
18	Gantz et al. (27)	Incidence and cost in emergency general surgery	System evaluation	Pubmed	2020

were evaluated every day, and the integrity and flatness of GCs were regularly checked to ensure the effectiveness of pressure (1). Inferior vena cava (IVC) can be prevented in patients with acute proximal lower extremity DVT who are absolutely contraindicated by anticoagulant treatment. The temporary or recyclable filter is preferred, and the filter shall be taken out in time after the risk of PE is relieved (13). The use of inferior vena cava filters is not recommended for routine prevention (29).

Although the latest version of the guidelines for the diagnosis and treatment of DVT (Third edition) in China affirms the role of mechanical and drug prevention, according to the investigation on the implementation status of DVT risk assessment and prevention in general surgery conducted by Shanghai DVT prevention and control alliance in 2019, the risk assessment rate of DVT in general surgery is only 61.9%, It can be reflected from the side that the risk assessment and prevention implementation of DVT in China need to be further improved (27).

Evidence 16 indicates that when patients with malignant tumors are diagnosed with DVT, the initial treatment is to use low molecular weight heparin (LMWH) (24) when the creatinine clearance rate is $\geq$30 ml/min. When treating venous

TABLE 2 | Quality evaluation results included in the guidelines.

Inclusion guidelines	Scope and purpose	Participants	Rigor of production	Clarity and clarity	Applicability	Editorial independence	Number of fields ≥60% (PCs.)	≥30% fields	Recommendation level
NCCN (1)	98.32	88.74	90.43	93.34	91.65	100	6	6	A
Farge et al. (12)	100	89.67	100	98.78	97.91	100	6	6	A
Liew et al. (13)	87.51	56.38	86.28	78.41	86.52	48.82	4	6	B
Wade et al. (14)	97.22	88.89	58.31	67.87	42.16	68.52	3	6	B
NICE (15)	78.48	89.64	46.78	84.23	58.33	43.15	3	6	B
NCCN (6)	76.91	61.91	68.38	77.62	73.72	89.23	6	6	A
Nicklas et al. (3)	87.81	58.72	95.42	74.12	82.47	88.48	5	6	B
Aufwerber et al. (5)	93.32	78.72	87.28	67.43	73.34	56.52	5	6	B

thromboembolism in cancer patients, low molecular weight heparin or direct oral anticoagulant drugs should be used for at least 6 months (28).

Evidence 18–19 summarize the need to manage the risk of bleeding when deciding to use anticoagulants for thromboprophylaxis. When the patient's condition worsens, different anticoagulant drugs are replaced, and surgery is performed, the bleeding risk needs to be reassessed and corresponding management measures should be taken (19). Patients with gynecological malignant tumor DVT should receive anticoagulant therapy for at least 3–6 months, and patients with DVT combined with PE should receive anticoagulant therapy for at least 6–12 months. For patients with persistent DVT risk factors, indefinite anticoagulation should be considered (16).

Evidence 17 summarizes the bleeding management. When the patient has bleeding during anticoagulation, it is necessary to immediately ask the time of the last use of anticoagulant drugs, test the blood creatinine clearance and hemoglobin to quickly evaluate the coagulation function, and take corresponding treatment measures according to the severity of bleeding and the individual situation of the patient (18).

Evidence 20–21 summarize the health education on DVT prevention and management of gynecological malignant tumors, explain the relevant knowledge of thrombosis prevention to patients, and guide patients to develop scientific and reasonable eating habits and healthy lifestyle, such as quitting smoking and alcohol, controlling blood glucose and blood lipid (14). These evidence encourage patients to move and get out of bed early after operation, guide patients to exercise ankle pump to promote lower limb blood circulation, and remind patients to pay attention to the use of bed bars to prevent falling off the bed (19).

Evidence 22–23 summarizes the appropriate rehydration of postoperative patients, educating patients to drink 1,500–2,500 ml/day to avoid blood concentration (14). The upper limb with PICC catheterization side can relax and clench to promote the blood circulation of the upper limb (13).

Evidence 24–26 summarize the health education related to mechanical prevention, inform patients and family members of the risks and consequences of DVT and the necessity of taking mechanical preventive measures, and guide the correct application of mechanical pre-treatment methods, precautions, possible adverse reactions, and response plans. If GCS is used, it is recommended to wear it both during the day and at night. GCS has to be taken off every day for limb evaluation, such as skin cleanliness, temperature, dorsalis pedis artery pulsation, limb sensation, and leg circumference (23). The flatness and integrity of GCs surface to ensure the effectiveness of pressure has to be regularly checked. Even if relevant preventive measures are implemented, the risk of DVT will be greatly reduced, but it cannot be completely avoided. Therefore, clinical doctors need to take individualized health education according to the different conditions of patients with gynecological malignant tumors to improve their quality of life

and treatment compliance, and also to reduce the incidence of venous thrombosis.

DISCUSSION

Deep venous thrombosis is a frequently occurring disease with multiple factors and polygenic defects. It is a disease with high mortality. This study analyzed the risk factors of perioperative DVT patients with gynecological malignant tumors in China. It plays an important role in determining high-risk groups of DVT, implementing individualized prevention strategies, and reducing incidence rate and mortality. The clinical manifestations of DVT patients are non-specific, and this makes clinicians ignore the severity of their condition. This study shows that the most common clinical manifestations of DVT are swelling and pain of affected limbs, up to 68.23%. It is pointed out in the literature at home and abroad that the peripheral diameter of the lower leg should be measured when diagnosing DVT. Nicklas et al. (3) even proposed that the difference in the circumference of both legs I $>$ 2 cm can be used as a clinical sign of DVT, which has high diagnostic sensitivity. Therefore, it is suggested that measuring the leg circumference in clinical work is also an inspection method that cannot be ignored.

In addition, the results of this study showed that when DVT had pulmonary symptoms, the main manifestations were dyspnea, chest pain, cough, and rapid heart rate. However, patients with pulmonary embolism are often complicated with some respiratory and cardiovascular diseases, and the symptoms and signs are lack of specificity. So it is difficult to distinguish the real cause of the patient and easy to miss diagnosis or misdiagnose. At present, clinical practice has confirmed that only 20% of patients with the traditional triple syndrome of pulmonary embolism (dyspnea, chest pain, and hemoptysis) exist at the same time. In addition, more patients with DVT and PE are asymptomatic, or their clinical symptoms and signs lack specificity, which makes the diagnosis difficult. Therefore, we should pay attention to risk factors and combine correct auxiliary examinations to diagnose DVT.

Risk Factors of DVT

Previous studies have found that the three elements of the pathogenesis of DVT are slow blood flow, abnormal blood composition, and venous endothelial injury. Therefore, in the perioperative period of gynecological malignant tumors, any etiology causing these three factors can lead to DVT, including primary and secondary. In addition to age, which has been proved to be an independent and important risk factor for DVT, there are also many risk factors. This study found that among the risk factors of DVT, age $>$40 years old ranked first, suggesting that the incidence of DVT after 40 years old increased. This may be associated with increasing age. Rough vascular intima, increased chance of endothelial damage, increased production of procoagulant substances, and hypercoagulability are also closely related to the occurrence of DVT. Especially in patients with hypertension, hyperlipidemia, diabetes, coronary heart disease, cancer, etc. In addition, it may also be related to the increase of blood viscosity and the change of gonadotropin sex hormone. The results of this study show that the clear risk factors that can be found in patients with DVT also include surgery, smoking, heart disease, malignant tumor, hypertension, trauma, bed rest, previous DVT history, etc., and some patients have more than two risk factors, suggesting that multiple risk factors are synergistic and superimposed, which is more likely to lead to thrombosis.

The results of this study showed that the DVT related to surgery accounted for 27.51%. Preoperative fasting, anesthesia, long-term postoperative braking, and surgical trauma can affect limb movement, resulting in slow venous blood flow, and the damage of vascular wall can promote the adhesion and aggregation of platelets. Trauma, blood loss, and hypoxia can activate the coagulation system as stressors, which is conducive to thrombosis. Smoking was also a common risk factor in this study (18.56%). A large number of studies have shown that smoking is related to a variety of thrombotic diseases. Smoking can increase platelet activity and enhance platelet aggregation, where the level of fibrinogen in smokers increases. At the same time, carbon monoxide and nicotine produced by smoking can directly damage vascular endothelium and affect the antithrombotic effect of endothelium. The risk factors of heart disease include congenital heart disease, angina pectoris, and myocardial infarction, and can promote the occurrence of DVT. Studies have shown that the activation of platelet and coagulation system and fibrin renewal are significantly accelerated, coagulation factors are increased, and anticoagulants are reduced. Patients with cardiac insufficiency are blocked by venous reflux, causing blood stasis and DVT.

The relationship between malignant tumor and thrombosis is close and complex. DVT is not only a common complication of tumor patients, but also a sign and signal of occult tumor, which can provide opportunities for early diagnosis and treatment of tumor patients. Tumor can not only secrete procoagulant substances to promote platelet aggregation and release, but also secrete fibrinolytic activity inhibitors, resulting in hypercoagulable state. Some chemotherapeutic drugs can cause the deficiency of protein C and protein S and the decrease of antithrombin. In addition, tumor compression on blood vessels, long-term bed rest, and other factors can promote the formation of DVT. A high proportion of patients included in this study were found to have tumors, which once again confirmed the obvious correlation between tumors and DVT.

Long-term bed rest is the most important risk factor for DVT. Some studies have pointed out that the detection rate of DVT is only 15% in those who stay in bed for $<$1 week, and higher than 80% in those who stay in bed for more than 1 week. Due to the loss of the function of muscle pump, local blood flow stagnates in bedridden patients, causing venous dilatation, vascular endothelial injury, and coagulation factor accumulation activating the coagulation system and promoting the formation of thrombosis. The results of this study showed that 6.59% of DVT patients had bedridden factors. The previous history of DVT is one of the common risk factors for DVT recurrence, especially when these patients are in the period of major surgery or serious medical diseases requiring hospitalization. According to literature reports, the risk of DVT in hospitalized patients

with a previous history of PTE or DVT was 7.9 times that of general hospitalized patients. In the 6-month course of DVT anticoagulation, the recurrence rate of DVT was twice that of patients without previous history of DVT. Diabetes and hypertension can lead to vascular endothelial cell injury, platelet activation, coagulation, fibrinolytic system imbalance, hypercoagulability state, thereby inducing the formation of DVT. Infection and rheumatic diseases can cause vascular endothelial injury, which creates favorable conditions for thrombosis. Polycythemia vera and primary thrombocytosis in hematological diseases can cause the blood to be in a state of high viscosity, resulting in slow blood flow and thrombosis.

In addition to the acquired risk factors, DVT also has genetic risk factors, including antithrombin deficiency, protein C, and protein S genetic deficiency. In recent years, it has been reported that the genetic risk factors of DVT are mainly coagulation factor V mutation and activated protein C resistance. Wang's study shows that FV Leiden mutation exists in the normal population of China. The relationship between FV Leiden, anti-APC, and venous thrombosis in China needs further study in the future. This study summarizes the characteristics of DVT patients in China, which is of great significance to understand and control venous thrombosis. It is an important strategy to be alert to risk factors, recognize the characteristics of clinical signs, and use accurate examination methods to diagnose DVT. Early correction of risk factors and early intervention and treatment are key factors to prevent DVT and reduce the mortality of patients.

Clinical Implications of the Study

This article summarizes the current prevention and management of DVT in postoperative patients with gynecological malignant tumors, which provides evidence basis for clinical nurses and nursing managers. In the process of evidence application, we need to fully consider the specific situation of departments and the intention of patients. Most of the literatures included in this study are in foreign languages. Due to different regions, values, and medical levels, clinical nurses must be able to use the same principle according to the feasibility, suitability, clinical significance, and effectiveness of the evidence (26).

CONCLUSION

Before the application of evidence, it is verified in practice according to the applicability and popularization of evidence. We should comprehensively evaluate patients' self-care ability, understanding ability, and coagulation function and then formulate personalized DVT prevention and management measures to improve patients' compliance, and finally effectively apply the best evidence to clinical practice.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

JH and JT designed the study and prepared the manuscript. YG and JM collected the data. XD and SF analyzed the data. All authors read and approved the final manuscript.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* (2021) 71:209–49. doi: 10.3322/caac.21660
2. Mohammed BM, Cheng Q, Ivanov IS, Gailani D. Murine models in the evaluation of heparan sulfate-based anticoagulants. *Methods Mol Biol.* (2022) 2303:789–805. doi: 10.1007/978-1-0716-1398-6_59
3. Nicklas JM, Gordon AE, Henke PK. Resolution of deep venous thrombosis: proposed immune paradigms. *Int J Mol Sci.* (2020) 21:2080. doi: 10.3390/ijms21062080
4. Aydin E, Bademci MS, Kocaaslan C, Oztekin A, Denli YE. Iliofemoral deep venous thrombosis treatment modalities. *J Vasc Surg Venous Lymphat Disord.* (2020) 8:906. doi: 10.1016/j.jvsv.2019.10.027
5. Aufwerber S, Heijne A, Edman G, Gravare SK, Ackermann PW. Early mobilization does not reduce the risk of deep venous thrombosis after Achilles tendon rupture: a randomized controlled trial. *Knee Surg Sports Traumatol Arthrosc.* (2020) 28:312–9. doi: 10.1007/s00167-019-05767-x
6. Komatsu H, Shimada M, Osaku D, Deura I, Sato S, Oishi T, et al. Deep vein thrombosis and serum D-dimer after pelvic lymphadenectomy in gynecological cancer. *Int J Gynecol Cancer.* (2020) 30:860–4. doi: 10.1136/ijgc-2019-000914
7. Dicenso A, Bayley L, Haynes RB. Accessing pre-appraised evidence: fine-tuning the 5S model into a 6S model. *Evid Based Nurs.* (2009) 12:99–101. doi: 10.1136/ebn.12.4.99-b
8. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med.* (2015) 8:2–10. doi: 10.1111/jebm.12141
9. Aromataris E, Fernandez R, Godfrey CM, Holly C, Khalil H, Tungpunkom P. Summarizing systematic reviews: methodological development, conduct and reporting of an umbrella review approach. *Int J Evid Based Healthc.* (2015) 13:132–40. doi: 10.1097/XEB.0000000000000055
10. Borges MC, Stein C, Colpani V, Barker TH, Munn Z, Falavigna M. How are systematic reviews of prevalence conducted? A methodological study. *BMC Med Res Methodol.* (2020) 20:96. doi: 10.1186/s12874-020-00975-3
11. Buccheri RK, Sharifi C. Critical appraisal tools and reporting guidelines for evidence-based practice. *Worldviews Evid Based Nurs.* (2017) 14:463–72. doi: 10.1111/wvn.12258
12. Farge D, Frere C, Connors JM, Ay C, Khorana AA, Munoz A, et al. 2019 International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol.* (2019) 20:e566–81. doi: 10.1016/S1470-2045(19)30336-5
13. Liew NC, Alemany GV, Angchaisuksiri P, Bang SM, Choi G, DE Silva DA, et al. Asian venous thromboembolism guidelines: updated recommendations for the prevention of venous thromboembolism. *Int Angiol.* (2017) 36:1–20. doi: 10.23736/S0392-9590.16.03765-2
14. Wade R, Sideris E, Paton F, Rice S, Palmer S, Fox D, et al. Graduated compression stockings for the prevention of deep-vein thrombosis in postoperative surgical patients: a systematic review and economic model with a value of information analysis. *Health Technol Assess.* (2015) 19:1–220. doi: 10.3310/hta19980

15. *Venous Thromboembolism in Over 16s: Reducing the Risk of Hospital-Acquired Deep Vein Thrombosis or Pulmonary Embolism*. London, National Institute for Health and Care Excellence (NICE) (2019).
16. Streiff MB, Holmstrom B, Angelini D, Ashrani A, Bockenstedt PL, Chesney C, et al. NCCN guidelines insights: cancer-associated venous thromboembolic disease, version 2.2018. *J Natl Compr Canc Netw.* (2018) 16:1289–303. doi: 10.6004/jnccn.2018.0084
17. Wu L, Cheng B. Analysis of perioperative risk factors for deep vein thrombosis in patients with femoral and pelvic fractures. *J Orthop Surg Res.* (2020) 15:597. doi: 10.1186/s13018-020-02131-5
18. Guo X, Zhang F, Wu Y, Gao L, Wang Q, Wang Z, et al. Coagulation alteration and deep vein thrombosis in brain tumor patients during the perioperative period. *World Neurosurg.* (2018) 114:e982–91. doi: 10.1016/j.wneu.2018.03.128
19. Insin P, Vitoopinyoparb K, Thadanipon K, Charakorn C, Attia J, McKay GJ, et al. Prevention of venous thromboembolism in gynecological cancer patients undergoing major abdominopelvic surgery: a systematic review and network meta-analysis. *Gynecol Oncol.* (2021) 161:304–13. doi: 10.1016/j.ygyno.2021.01.027
20. Hajibandeh S, Hajibandeh S, Antoniou GA, Scurr JR, Torella F. Neuromuscular electrical stimulation for the prevention of venous thromboembolism. *Cochrane Database Syst Rev.* (2017) 11:D11764. doi: 10.1002/14651858.CD011764.pub2
21. Pavon JM, Adam SS, Razouki ZA, McDuffie JR, Lachiewicz PF, Kosinski AS, et al. Effectiveness of intermittent pneumatic compression devices for venous thromboembolism prophylaxis in high-risk surgical patients: a systematic review. *J Arthroplasty.* (2016) 31:524–32. doi: 10.1016/j.arth.2015.09.043
22. Buesing KL, Mullapudi B, Flowers KA. Deep venous thrombosis and venous thromboembolism prophylaxis. *Surg Clin North Am.* (2015) 95:285–300. doi: 10.1016/j.suc.2014.11.005
23. Lieberman JR. Deep vein thrombosis prophylaxis: state of the art. *J Arthroplasty.* (2018) 33:3107–8. doi: 10.1016/j.arth.2018.01.051
24. Fan W, Qiao T, You Y, Zhang J, Gao J. Perioperative prevalence of deep vein thrombosis in patients with percutaneous kyphoplasty: a retrospective study with routine ultrasonography. *Medicine.* (2020) 99:e19402. doi: 10.1097/MD.0000000000019402
25. Li J, Zhu Y, Chen W, Zhao K, Zhang J, Meng H, et al. Incidence and locations of deep venous thrombosis of the lower extremity following surgeries of tibial plateau fractures: a prospective cohort study. *J Orthop Surg Res.* (2020) 15:605. doi: 10.1186/s13018-020-02136-0
26. Matsusaki T, Sakai T, Boucek CD, Abu-Elmagd K, Martin LM, Amesur N, et al. Central venous thrombosis and perioperative vascular access in adult intestinal transplantation. *Br J Anaesth.* (2012) 108:776–83. doi: 10.1093/bja/aes016
27. Gantz O, Mulles S, Zagadailov P, Merchant AM. Incidence and cost of deep vein thrombosis in emergency general surgery over 15 years. *J Surg Res.* (2020) 252:125–32. doi: 10.1016/j.jss.2020.03.022
28. Kahn SR, Morrison DR, Diendere G, Piche A, Filion KB, Klil-Drori AJ, et al. Interventions for implementation of thromboprophylaxis in hospitalized patients at risk for venous thromboembolism. *Cochrane Database Syst Rev.* (2018) 4:D8201. doi: 10.1002/14651858.CD008201.pub3
29. Zhao W, McArthur A, Yu Z, Hu Y, Luo J. Prevention of venous thromboembolism in postoperative abdominal patients: a best practice implementation project. *JBI Database System Rev Implement Rep.* (2018) 16:1887–901. doi: 10.11124/JBISRIR-2017-003665
30. Sheth T, Natarajan MK, Hsieh V, Valettas N, Rokoss M, Mehta S, et al. Incidence of thrombosis in perioperative and non-operative myocardial infarction. *Br J Anaesth.* (2018) 120:725–33. doi: 10.1016/j.bja.2017.11.063

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Hu, Geng, Ma, Dong, Fang and Tian. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 22 March 2022
doi: 10.3389/fsurg.2022.862655

Clinical Analysis of Factors Influencing the Development of Placenta Praevia and Perinatal Outcomes in First-Time Pregnant Patients

Chunhua Zhou†, *Yang Zhao*† *and Yongmei Li**

Department of Obstetrics, Renmin Hospital, Hubei University of Medicine, Shiyan, China

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Fang Wei,
Central South University, China
Qiang Wang,
Guizhou University, China

***Correspondence:**
Yongmei Li
Li1232022@163.com

†*These authors share first authorship*

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *26 January 2022*
Accepted: *21 February 2022*
Published: *22 March 2022*

Citation:
Zhou C, Zhao Y and Li Y (2022) Clinical Analysis of Factors Influencing the Development of Placenta Praevia and Perinatal Outcomes in First-Time Pregnant Patients. Front. Surg. 9:862655. doi: 10.3389/fsurg.2022.862655

Objective: To analyze the risk factors associated with the development of placenta praevia (PP) in first-time pregnant patients and to observe the perinatal clinical outcomes of patients.

Methods: The clinical data of 112 pregnant women with PP (PP group) and 224 pregnant women with normal placental position (general group) who delivered in our hospital from August 2016 to August 2021 were retrospectively analyzed. Baseline demographic data such as age, gestational week, uterine history, assisted reproductive technology use, pregnancy comorbidities, pre-pregnancy body mass index (BMI), smoking, alcohol consumption, placental position, educational level, work were collected from both groups, and logistic regression models were used to analyze the factors influencing the occurrence of PP in patients with first pregnancy. Perinatal outcomes such as implementation of hemostatic treatment (uterine balloon compression, arterial ligation, and B-Lynch suture), maternal postpartum related indicators (amount of postpartum bleeding, incidence of postpartum hemorrhage, blood transfusion rate, blood transfusion volume, and length of hospital stay), and neonatal condition (birth weight, Apgar score at 1 and 5 min after birth) were counted and compared between the two groups.

Results: Histories of endometriosis, use of assisted reproductive technology, and smoking or secondhand smoke inhalation were all high risk factors for PP in patients with first pregnancies, and the proportion of maternal and neonatal adverse outcomes was significantly higher in the PP group than in the general group ($P < 0.05$).

Conclusion: Histories of endometriosis, smoking (secondhand smoke), and use of assisted reproductive technologies are independent risk factors for PP in patients with first pregnancies, which can increase the risk of labor and death of the newborn.

Keywords: first pregnancy, placenta praevia, risk factors, perinatal period, clinical outcome

PREFACE

Placenta praevia (PP) is one of the most common conditions causing vaginal bleeding during pregnancy and usually occurring after 28 weeks of gestation. It means that the lower edge of the placenta is attached to the lower part of the uterus or reaches (covers) the inner cervical os and the edge of the placenta is lower than the fetal presentation (1). According to the literature, the incidence of PP shows an increasing trend year by year with the increase of cesarean section rate, abortion rate, and uterine operations (2–4). The presence of PP can increase the risk of maternal hemorrhage in late pregnancy, during labor, and in the postpartum period, and in severe cases can lead to hemodynamic instability, reduced oxygen supply, and organ damage causing emergency unscheduled surgery requiring massive blood transfusion; it can also produce serious symptoms such as disseminated intravascular coagulation and multiple organ dysfunction syndrome, which are the main causes of maternal and perinatal death (5, 6).

The exact pathogenesis of PP has not yet been elucidated. Some studies (7–9) suggest that it may be related to damage to the endometrial layer of the uterus due to multiple cesarean sections, multiple abortions, multiple curettage and other uterine operations, and poor blood supply to the placenta during pregnancy; it may also be related to abnormalities in the placenta itself in pregnant patients; it may also be related to the advanced age of the pregnant woman, history of multiple pregnancies and multiple deliveries. In addition, as the frequency of assisted reproductive techniques such as *in vitro* fertilization-embryo transfer increases in infertile patients, the use of ovulation-promoting drugs may also cause the placenta to develop asynchronously with the endometrium, leading to the development of PP. In recent years, the incidence of PP has increased, so it is significant to explore the risk factors associated with the occurrence of PP to reduce the occurrence of adverse maternal and perinatal outcomes (10). However, most of the current studies are on the risk factors associated with the development of PP in patients with a history of prior pregnancy and delivery (11, 12), and there are few reports on the factors

TABLE 2 | Assignments.

Influencing factors	Assignment
History of uterine fibroids	Yes = 0, no = 1
History of endometriosis	Yes = 0, no = 1
Application of assisted reproductive technology	Yes = 0, no = 1
Posterior placenta	Yes = 0, no = 1
Smoking (secondhand smoke)	Yes = 0, no = 1
Alcohol consumption	Yes = 0, no = 1

TABLE 1 | Univariate analysis of PP in first-time pregnant patients [mean, SD (*n*, %)].

Indicators		PP group ($n = 112$)	General group ($n = 224$)	t/χ^2-value	*P*-value
Age (years old)		29.46 ± 6.43	30.21 ± 5.22	1.147	0.252
Week of gestation (weeks)		36.26 ± 3.23	35.48 ± 4.51	1.632	0.104
History of uterine fibroids	Yes	7 (6.25)	4 (1.79)	4.699	0.030
	No	105 (93.75)	220 (98.21)		
History of endometriosis	Yes	13 (11.61)	8 (3.57)	8.229	0.004
	No	99 (88.39)	216 (96.43)		
Application of assisted reproductive technology	Yes	10 (8.93)	7 (3.13)	5.236	0.022
	No	102 (91.07)	217 (96.87)		
Combined gestational hypertension	Yes	8 (7.14)	17 (7.59)	0.022	0.883
	No	104 (92.86)	207 (92.41)		
Combined gestational diabetes	Yes	7 (6.25)	15 (6.70)	0.024	0.876
	No	105 (93.75)	209 (93.30)		
Pre-pregnancy BMI (kg/m^2)		23.37 ± 4.33	24.21 ± 3.58	1.888	0.060
Drinking	Yes	35 (31.25)	43 (19.20)	6.086	0.014
	No	77 (68.75)	181 (80.80)		
Smoking (second-hand smoke)	Yes	63 (56.25)	82 (36.61)	11.744	0.001
	No	49 (43.75)	142 (63.39)		
Placental position	Anterior	45 (40.18)	116 (51.79)	4.031	0.045
	Posterior	67 (59.82)	108 (48.21)		
Educational level	Primary and below	16 (14.29)	29 (12.95)	0.762	0.683
	Junior - Senior	40 (35.71)	91 (40.63)		
	University and above	56 (50.00)	104 (46.43)		
Work	Practitioners	69 (61.61)	130 (58.04)	0.394	0.530
	None	43 (38.39)	94 (41.96)		

influencing the development of PP in first-time pregnant women and the perinatal clinical outcomes. Clinical data show (13) that the incidence of PP in first-time pregnant patients is also increasing year by year, and the etiology is unclear. Based on this, this study analyzed the influencing factors related to the occurrence of PP in first-time pregnant patients and observed the perinatal outcomes such as the implementation of hemostatic treatment, maternal related indicators, and neonatal conditions in both groups. The aim was to identify high-risk factors early so that close monitoring during pregnancy, and active prevention of related complications intraoperatively and postpartum.

DATA AND METHODS

Study Population and Grouping

Retrospective analysis of the clinical data of patients who delivered by cesarean section in our hospital from August 2016 to August 2021. Diagnostic criteria (14) for PP: placenta attached to the lower uterine segment reaching or covering the internal cervical os after 28 weeks of gestation and positioned below the previa; also intraoperative diagnosis based on the position of the placenta. **Inclusion criteria:** (1) 28 weeks < pregnancy time < 41 weeks; (2) first pregnancy; (3) singleton with normal fetal position; (4) cesarean section to termination pregnancy; (5) complete case information; (6) meets the diagnostic criteria for PP. **Exclusion criteria:** (1) patients with previous history of miscarriage, cesarean section, or pregnancy; (2) patients with hematologic disorders, malignant tumors, or infectious diseases; (3) previous or existing mental disorders. A total of 336 cases were included in the study, of which 112 pregnant women with PP were counted in the PP group and 224 pregnant women with normal placenta position were counted in the general group.

Clinical Data Collection

Age, gestational week, uterine history (fibroids, endometriosis), assisted reproductive technology use (yes, no), pregnancy comorbidities (gestational hypertension, gestational diabetes), pre-pregnancy body mass index (BMI), smoking (including secondhand smoke, yes, no), alcohol consumption (yes, no), placental position (anterior, posterior), educational level (Primary and below, Junior–Senior, University and above), work (practitioners, none), and other information. Perinatal outcomes

TABLE 3 | Multifactorial analysis of PP in first-time pregnant patients.

Indicators	*B*	SE	Walds	*P*	OR (95% CI)
History of uterine fibroids	0.316	0.213	3.058	0.160	1.372 (0.903∼2.082)
History of endometriosis	1.324	0.622	32.247	<0.001	3.758 (1.111∼12.719)
Application of assisted reproductive technology	1.225	0.438	35.158	<0.001	3.404 (1.443∼8.032)
Posterior placenta	0.717	0.634	2.331	0.324	2.048 (0.591∼7.097)
Smoking (secondhand smoke)	1.052	0.413	16.138	<0.001	2.866 (1.276∼6.440)
Alcohol consumption	0.531	0.463	3.423	0.152	1.701 (0.686∼4.214)

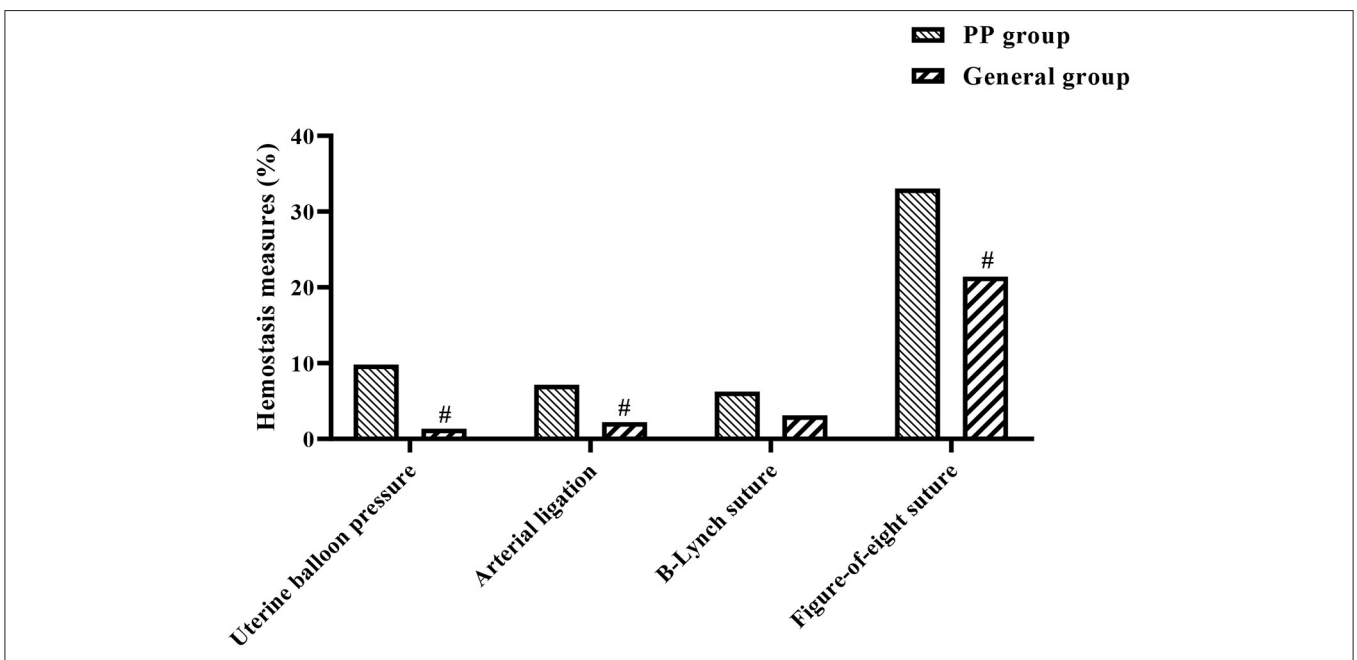


FIGURE 1 | Histogram of the implementation of hemostatic measures in both groups. #indicates comparison between two groups, $P < 0.05$.

such as implementation of hemostatic treatment (uterine balloon compression, arterial ligation, and B-Lynch suture), maternal postpartum related indicators (amount of postpartum bleeding, incidence of postpartum hemorrhage, blood transfusion rate, blood transfusion volume, and length of hospital stay), and neonatal condition (birth weight, Apgar score at 1 and 5 min after birth) were also counted in both groups.

Statistical Methods

SPSS 20.0 was used for data processing and analysis, and patients' past medical history, comorbidities, and other count data were described by descriptive statistics such as frequency and percentage (n, %), and the χ^2 test was used for comparison between two groups. Patients' age, BMI and other measurement data were described by statistical indicators such as mean and standard deviation (meam, SD), and t-test was used for comparison between two groups. A multifactorial logistic regression model was used to analyse the risk factors associated with the development of PP in first-time pregnant patients. The difference was considered statistically significant at $P < 0.05$.

RESULTS

Univariate Analysis of PP in First-Time Pregnant Patients

A comparison of the clinical data of pregnant women in the PP group with those in the general group showed that

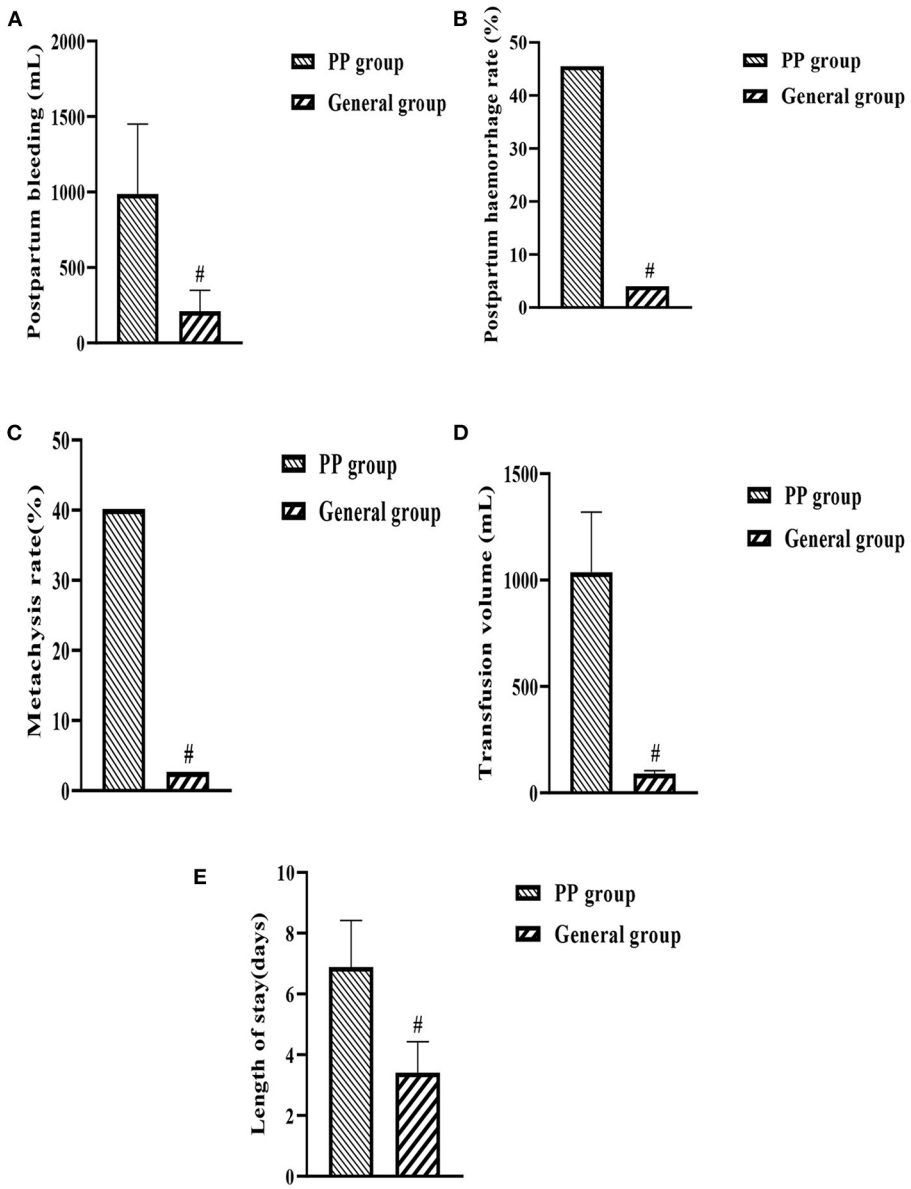


FIGURE 2 | (A–E) Histogram of maternal postpartum conditions in both groups. # indicates comparison between two groups, $P < 0.05$.

the proportions of history of uterine fibroids, history of endometriosis, application of assisted reproductive technology, posterior placenta, smoking (secondhand smoke), and alcohol consumption were significantly higher in the PP group compared with the general group ($P < 0.05$). In contrast, there were no statistically significant differences between the two groups in terms of age, gestational week, combined gestational hypertension, combined gestational diabetes, pre-pregnancy BMI, education level, and whether or not they worked ($P > 0.05$), as shown in **Table 1**.

Multifactorial Analysis of PP in First-Time Pregnant Patients

The presence or absence of PP in patients with first pregnancy was used as the dependent variable (Assignment: yes = 0, no = 1), and the indicators that differed in the univariate analysis, such as history of uterine fibroids, history of endometriosis, application of assisted reproductive technology, posterior placenta, smoking (secondhand smoke), and alcohol consumption were used as independent variables (see **Table 2** for assignments) into a multifactorial logistic regression model. The results showed that history of endometriosis, application of assisted reproductive technology, and smoking (secondhand smoke) were independent risk factors for the development of PP in patients with first pregnancy ($P < 0.05$, **Table 3**).

Comparison of the Implementation of Intraoperative Hemostatic Treatment in the Two Groups

The probability of patients in the PP group having intraoperative haemostatic treatments such as intrauterine balloon compression, arterial ligation, B-Lynch suture and local figure-of-eight suture was 9.82% (11 cases), 7.14% (8 cases), 6.25% (7 cases), and 33.04% (37 cases), respectively. In the general group, the probabilities were 1.34% (3 cases), 2.23% (5 cases), 3.13% (7 cases), and 21.43% (48 cases), respectively. This shows that the proportion of hemostatic measures such as uterine balloon compression, arterial ligation, and local figure-of-eight sutures performed was significantly higher in the PP group than in the general group ($P < 0.05$; see **Figure 1**).

Comparison of Postpartum Conditions Between the Two Groups

Postpartum hemorrhage (a), postpartum hemorrhage rate (b), blood transfusion rate (c), blood transfusion volume (d), and hospital stay (e) were significantly at higher levels in the PP group when compared with the general group ($P < 0.05$, **Figures 2A–E**).

Comparison of Neonatal Conditions Between the Two Groups

Neonatal birth weight (a), 1-min Apgar score (b), and 5-min Apgar score (c) were significantly lower in the PP group when compared with the general group ($P < 0.05$, **Figures 3A–C**).

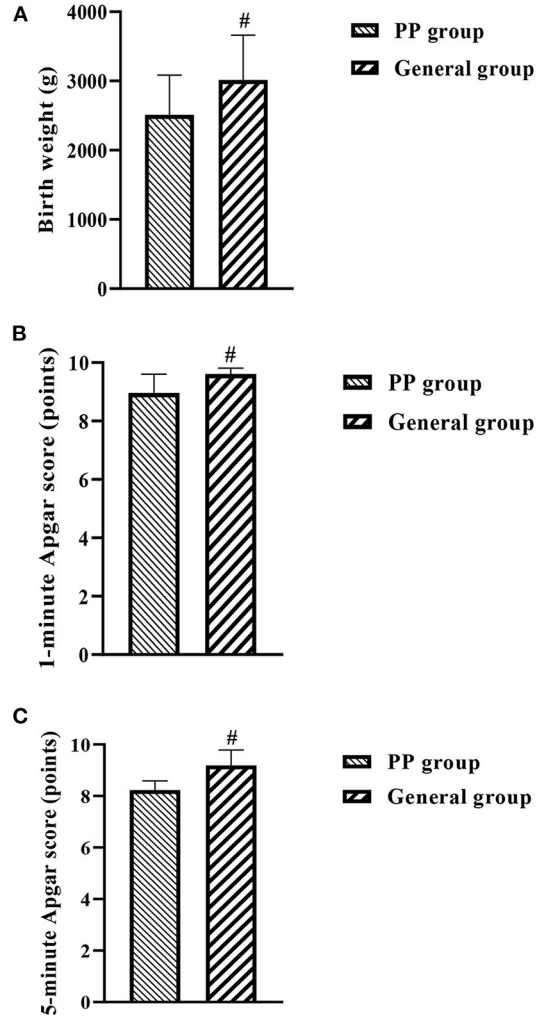


FIGURE 3 | (A–C) Histogram of neonatal conditions in both groups. #indicates comparison between two groups, $P < 0.05$.

DISCUSSION

PP is a common and serious complication of pregnancy and is one of the main causes of maternal hemorrhage in the second trimester, and can also cause maternal postpartum hemorrhage, amniotic fluid embolism, and other adverse events (15, 16). In addition, studies (17, 18) have shown that the incidence of preterm fetal delivery and low birth weight fetuses is significantly higher in women with PP than in those with normal placental position, which shows that the occurrence of PP can also increase the risk of adverse neonatal outcomes, bring serious adverse effects to the family and society. Therefore, it is particularly important to investigate the risk factors associated with the occurrence of PP to reduce the occurrence of adverse maternal and infant outcomes. The current literature (19, 20) mostly examines risk factors for the occurrence of PP in transmaternal women with childbirth history, such as history of miscarriage,

history of cesarean delivery, and age. However, reports on the risk factors associated with the development of placenta previa in first-time pregnant patients are rare. Based on the purpose of clarifying the etiology of placenta previa in first-time pregnant women, this study was conducted to observe 336 pregnant women admitted to our hospital as follows.

History of Endometriosis

This study found that first-time pregnant patients with a history of endometriosis were 3.25 times more likely to develop PP than pregnant women without a history of endometriosis. The results of logistic multivariate analysis indicated that history of endometriosis was an independent risk factor for the development of PP in first-time pregnant patients. Analysis of the reasons for this may be the presence of pelvic adhesions in patients with endometriosis, an abnormally fixed position of the uterus, restricted mobility of the uterus or abnormal contraction of the uterine musculature, which in turn leads to the downward displacement of the placenta to form PP (21). It has been suggested (22) that endometriosis can alter endometrial properties and affect the expression of various factors, especially during the period of placental implantation. It has also been shown (23) that proper progesterone levels play an important role in regulating the endometrium and that endometriosis can cause progesterone resistance, which can lead to the development of PP.

Application of Assisted Reproductive Technology

The results of this study found that the use of assisted reproductive technology was an independent risk factor for PP in first-time pregnant patients (OR: 3.404, 95% CI: 1.443–8.032). With the widespread application of assisted reproductive technology in clinical practice, the risk of pregnancy related to it has gradually attracted people's attention, and most of the people who use assisted reproductive technology are older, have a history of endometriosis, and have a history of chronic salpingitis (24). In addition to related confounding factors, the application of assisted reproductive technology often requires the use of ovulation-stimulating drugs to change the level of sex hormones in the patients, which may lead to dysregulated or uncontrolled expression of genes related to endometrial turnover, making the asynchrony between endometrial and embryonic development more pronounced and resulting in the formation of PP (25, 26). It has also been suggested (27) that during implantation of the embryo through the mid-uterine cavity using mechanical methods, the transfer tube causes prostaglandin release during passage through the cervical os, leading to uterine contraction, which may result in implantation of the placenta in the lower uterine segment, significantly increasing the probability of PP.

Smoking or Inhalation of Second-Hand Smoke

Whether smoking or inhalation of secondhand smoke is a risk factor for PP has been controversial in previous national and international studies. A study by Hung et al. (28) confirmed that the risk of PP due to smoking or passive smoking is 2.2 times higher than that of non-smoking or passive smoking. The results of this study showed that smoking or secondhand smoke inhalation was an independent risk factor for PP in first-time pregnant patients (OR: 2.866, 95% CI: 1.276–6.440). Analyzing the reasons for this, exposure to nicotine and carbon monoxide when pregnant women smoke or inhale secondhand smoke can cause chronic placental hypoxia, and placental hypoxia can lead to necrosis in the decidua of the uterus and microthrombus formation in the placenta, presumably extending and expanding to cover the endocervix in order to obtain more nutrients leading to PP (29, 30).

In addition, the study also looked at maternal and neonatal conditions in both groups and showed that intraoperative haemostatic measures such as intrauterine balloon compression, arterial ligation and local figure-of-eight sutures were used significantly more frequently in the PP group than in the general group of pregnant women. Postpartum hemorrhage, postpartum hemorrhage, blood transfusion rate, transfusion volume, and length of stay were significantly higher in the PP group compared to the general group, while the PP group had lower birth weight, 1 and 5 min Apgar scores. This suggests that the occurrence of PP has a more detrimental effect on both the mother and the neonate, increasing the risk of labor, as well as causing respiratory distress in the neonate and increasing the risk of neonatal death.

In summary, histories of endometriosis, use of assisted reproductive technology, and smoking or secondhand smoke inhalation are all high-risk factors for PP in first-time pregnant patients. Therefore, we should strengthen the promotion of reproductive health information, avoid smoking or secondhand smoke inhalation in pregnant women, and pay close attention to patients with these risk factors in clinical practice, and take appropriate measures to improve the outcome of patients and newborns.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Medical Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors contributed to this experiment, including experimental design, case collection, data analysis, and paper writing. All authors read and agreed to the final version.

REFERENCES

1. Jain V, Bos H, Bujold E. Guideline No. 402: diagnosis and management of placenta previa. *J Obstet Gynaecol Can.* (2020) 42:906–17.e1. doi: 10.1016/j.jogc.2019.07.019
2. Park HS, Cho HS. Management of massive hemorrhage in pregnant women with placenta previa. *Anesth Pain Med (Seoul).* (2020) 15:409–16. doi: 10.17085/apm.20076
3. Kingdom JC, Hobson SR, Murji A, Allen L, Windrim RC, Lockhart E, et al. Minimizing surgical blood loss at cesarean hysterectomy for placenta previa with evidence of placenta increta or placenta percreta: the state of play in 2020. *Am J Obstet Gynecol.* (2020) 223:322–9. doi: 10.1016/j.ajog.2020.01.044
4. Liu B, Deng S, Lin M, Chen Y, Cai J, Yang J, et al. Prediction of cesarean hysterectomy in placenta previa complicated with prior cesarean: a retrospective study. *BMC Pregnancy Childbirth.* (2020) 20:81. doi: 10.1186/s12884-020-2790-9
5. Carusi DA, Fox KA, Lyell DJ, Perlman NC, Aalipour S, Einerson BD, et al. Placenta accreta spectrum without placenta previa. *Obstet Gynecol.* (2020) 136:458–65. doi: 10.1097/AOG.0000000000003970
6. Wasim T, Bushra N, Riaz S, Iqbal HI. Fetomaternal outcome in patients with placenta previa. *Pak J Med Sci.* (2020) 36:952–7. doi: 10.12669/pjms.36.5.1647
7. Shainker SA, Coleman B, Timor-Tritsch IE, Bhide A, Bromley B, Cahill AG, et al. Society for maternal-fetal medicine. Electronic address: pubs@smfm.org. Special Report of the Society for Maternal-Fetal Medicine Placenta Accreta Spectrum Ultrasound Marker Task Force: Consensus on definition of markers and approach to the ultrasound examination in pregnancies at risk for placenta accreta spectrum. *Am J Obstet Gynecol.* (2021) 224:B2–B14. doi: 10.1016/j.ajog.2020.09.001
8. Balachandar K, Melov SJ, Nayyar R. The risk of adverse maternal outcomes in cases of placenta praevia in an Australian population between 2007 and 2017. *Aust N Z J Obstet Gynaecol.* (2020) 60:890–5. doi: 10.1111/ajo.13172
9. Adere A, Mulu A, Temesgen F. Neonatal and maternal complications of placenta praevia and its risk factors in Tikur Anbessa specialized and gandhi memorial hospitals: unmatched case-control study. *J Pregnancy.* (2020) 2020:5630296. doi: 10.1155/2020/5630296
10. Takeda S, Takeda J, Makino S. Cesarean section for placenta previa and placenta previa accreta spectrum. *Surg J (N Y).* (2020) 6:S110–S21. doi: 10.1055/s-0039-3402036
11. King LJ, Dhanya Mackeen A, Nordberg C, Paglia MJ. Maternal risk factors associated with persistent placenta previa. *Placenta.* (2020) 99:189–92. doi: 10.1016/j.placenta.2020.08.004
12. Jansen CHJR, Kleinrouweler CE, van Leeuwen L, Ruiter L, Mol BW, Pajkrt E. Which second trimester placenta previa remains a placenta previa in the third trimester: a prospective cohort study. *Eur J Obstet Gynecol Reprod Biol.* (2020) 254:119–23. doi: 10.1016/j.ejogrb.2020.08.038
13. Matsuzaki S, Nagase Y, Ueda Y, Kakuda M, Maeda M, Matsuzaki S, et al. Placenta previa complicated with endometriosis: contemporary clinical management, molecular mechanisms, and future research opportunities. *Biomedicines.* (2021) 9:1536. doi: 10.3390/biomedicines9111536
14. Ueno Y, Kitajima K, Kawakami F, Maeda T, Suenaga Y, Takahashi S, et al. Novel MRI finding for diagnosis of invasive placenta praevia: evaluation of findings for 65 patients using clinical and histopathological correlations. *Eur Radiol.* (2014) 24:881–8. doi: 10.1007/s00330-013-3076-7
15. Ma Y, You Y, Jiang X, Lin X. Use of nitroglycerin for parallel transverse uterine cesarean section in patients with pernicious placenta previa and placenta accrete and predicted difficult airway: a case report and review of literature. *Medicine (Baltimore).* (2020) 99:e18943. doi: 10.1097/MD.0000000000018943
16. Wan Adnan WF, Shamsudin F, Mohamad Zon E. Uterine torsion in patient with major placenta previa. *Eur J Obstet Gynecol Reprod Biol.* (2021) 258:467–469. doi: 10.1016/j.ejogrb.2020.12.007
17. Ishibashi H, Miyamoto M, Shinmoto H, Soga S, Matsuura H, Kakimoto S, et al. The use of magnetic resonance imaging to predict placenta previa with placenta accreta spectrum. *Acta Obstet Gynecol Scand.* (2020) 99:1657–65. doi: 10.1111/aogs.13937
18. Balayla J, Desilets J, Shrem G. Placenta previa and the risk of intrauterine growth restriction (IUGR): a systematic review and meta-analysis. *J Perinat Med.* (2019) 47:577–84. doi: 10.1515/jpm-2019-0116
19. Feng Y, Li XY, Xiao J, Li W, Liu J, Zeng X, et al. Risk factors and pregnancy outcomes: complete versus incomplete placenta previa in mid-pregnancy. *Curr Med Sci.* (2018) 38:597–601. doi: 10.1007/s11596-018-1919-9
20. Kancherla V, Räisänen S, Gissler M, Kramer MR, Heinonen S. Placenta previa and risk of major congenital malformations among singleton births in Finland. *Birth Defects Res A Clin Mol Teratol.* (2015) 103:527–35. doi: 10.1002/bdra.23371
21. Matsuzaki S, Nagase Y, Ueda Y, Lee M, Matsuzaki S, Maeda M, et al. The association of endometriosis with placenta previa and postpartum hemorrhage: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM.* (2021) 3:100417. doi: 10.1016/j.ajogmf.2021.100417
22. Gasparri ML, Nirgianakis K, Taghavi K, Papadia A, Mueller MD. Placenta previa and placental abruption after assisted reproductive technology in patients with endometriosis: a systematic review and meta-analysis. *Arch Gynecol Obstet.* (2018) 298:27–34. doi: 10.1007/s00404-018-4765-x
23. Takemura Y, Osuga Y, Fujimoto A, Oi N, Tsutsumi R, Koizumi M, et al. Increased risk of placenta previa is associated with endometriosis and tubal factor infertility in assisted reproductive technology pregnancy. *Gynecol Endocrinol.* (2013) 29:113–5. doi: 10.3109/09513590.2012.706669
24. Petersen SH, Bergh C, Gissler M, Åsvold BO, Romundstad LB, Tiitinen A, et al. Time trends in placenta-mediated pregnancy complications after assisted reproductive technology in the Nordic countries. *Am J Obstet Gynecol.* (2020) 223:226.e1–e19. doi: 10.1016/j.ajog.2020.02.030
25. Jeon H, Min J, Kim DK, Seo H, Kim S, Kim YS. Women with endometriosis, especially those who conceived with assisted reproductive technology, have increased risk of placenta previa: meta-analyses. *J Korean Med Sci.* (2018) 33:e234. doi: 10.3346/jkms.2018.33.e234
26. Sakai Y, Ono M, Iizuka T, Kagami K, Masumoto S, Nakayama M, et al. Embryo transfer associated with hormone replacement therapy cycles using assisted reproductive technology increases placenta accreta spectrum. *J Obstet Gynaecol Res.* (2019) 45:2394–9. doi: 10.1111/jog.14111
27. Qin JB, Wang H, Sheng X, Xie Q, Gao S. Assisted reproductive technology and risk of adverse obstetric outcomes in dichorionic twin pregnancies: a systematic review and meta-analysis. *Fertil Steril.* (2016) 105:1180–92. doi: 10.1016/j.fertnstert.2015.12.131
28. Hung TH, Hsieh CC, Hsu JJ, Chiu TH, Lo LM, Hsieh TT. Risk factors for placenta previa in an Asian population. *Int J Gynaecol Obstet.* (2007) 97:26–30. doi: 10.1016/j.ijgo.2006.12.006
29. Shobeiri F, Jenabi E. Smoking and placenta previa: a meta-analysis. *J Matern Fetal Neonatal Med.* (2017) 30:2985–90. doi: 10.1080/14767058.2016.1271405
30. Tsuji M, Shibata E, Askew DJ, Morokuma S, Aiko Y, Senju A, et al. Associations between metal concentrations in whole blood and placenta previa and placenta accreta: the Japan Environment and Children's Study (JECS). *Environ Health Prev Med.* (2019) 24:40. doi: 10.1186/s12199-019-0795-7

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Zhou, Zhao and Li. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 24 March 2022
doi: 10.3389/fsurg.2022.865238

Effect of Psychological Support Therapy on Psychological State, Pain, and Quality of Life of Elderly Patients With Femoral Neck Fracture

*Qun Li, Yin Wang and Xiang Shen**

Department of Orthopedics, The Fourth Hospital of Changsha, Affiliated Changsha Hospital of Hunan Normal University, Changsha, China

Purpose: To explore the intervention effect of psychological support therapy (PST) on elderly patients with femoral neck fracture.

Methods: A total of 82 elderly patients with femoral neck fractures admitted to our hospital from July 2020 to June 2021 were selected. Patients were randomly divided into conventional group ($n = 41$) and intervention group ($n = 41$). The conventional group received routine nursing care. The intervention group was given PST on the basis of the conventional group. The joint function, psychological state, pain, quality of life, and nursing satisfaction of both groups were observed.

Results: Compared with before intervention, the Harris hip joint score and the General Quality-of-Life Inventory-74 scores of both groups increased after the intervention, and the increase was more obvious in the intervention group ($p < 0.05$). Compared with before intervention, the self-rating anxiety scale, the self-rating depression scale scores, and the visual analog scales score in both groups decreased after the intervention, and the decrease was more obvious in the intervention group ($p < 0.05$). The total satisfaction of the intervention group (92.68%) was higher than that of the conventional group (75.61%) ($p < 0.05$).

Conclusion: Psychological support therapy has a certain intervention effect on elderly patients with femoral neck fracture, which can improve psychological state, reduce pain, improve quality of life, and improve nursing satisfaction.

Keywords: femoral neck fracture, psychological support therapy, psychological state, pain, quality of life

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Li Zhang,
University of South China, China
Fenglong Sun,
Capital University of Medical Sciences, China

****Correspondence:***
Xiang Shen
shenxiang19750901@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *29 January 2022*
Accepted: *22 February 2022*
Published: *24 March 2022*

Citation:
Li Q, Wang Y and Shen X (2022) Effect of Psychological Support Therapy on Psychological State, Pain, and Quality of Life of Elderly Patients With Femoral Neck Fracture. Front. Surg. 9:865238. doi: 10.3389/fsurg.2022.865238

INTRODUCTION

With the aging of the population and the development of transportation in China, the incidence of fractures among the elderly is increasing year by year, and most patients with fractures suffer from sudden accidental injuries, which are mainly manifested by the change from mobility to bedridden, leading to the inability of patients to take care of themselves (1). Femoral neck fracture is a fracture from the femoral head to the base of femoral neck, which is a common hip fracture type in orthopedics, and its incidence rate accounts for 46.39% of all fractures in the elderly (2). Because of the particularity of anatomical structure and physiology of femoral neck in the elderly, hip joint function recovery of patients after fracture is often poor, and even avascular

necrosis of femoral head and joint stiffness may occur. Some elderly patients with a fracture are prone to complications such as pneumonia, cardiovascular and cerebrovascular diseases, deep vein thrombosis, skin pressure injury, urinary system infection, etc., which can lead to death in severe cases (3, 4). Femoral neck fracture has become a type of disease that seriously affects the quality of life of the elderly. With the continuous improvement of medical technology and the continuous development of orthopedic internal fixation materials in China, total hip arthroplasty has become the main method to treat femoral neck fracture, it can effectively correct joint deformity, maintain joint stability, and promote joint function recovery (5). However, patients with femoral neck fracture have limited activities, decreased self-care ability, and are prone to negative emotions such as anxiety and depression. At the same time, fracture pain, surgical trauma, changes of hospitalization role, and so on have caused different degrees of psychological stress to patients. Poor psychological state will restrict the functions of patients' various organs and systems through related endocrine and immune mechanisms, thus affecting the therapeutic effect and disease rehabilitation of patients (6, 7). How to improve the physical and psychological health of patients with femoral neck fracture has become the focus of clinical attention.

For elderly patients with femoral neck fracture, although the surgical technique is important, good post-operative recovery cannot be separated from scientific and effective nursing measures. At present, with the increasing demand of people for medical services, nursing work has been innovated and reformed. Some psychological studies have proved that people are often irrational under stress, and psychological support therapy (PST) is a key point that needs clinical attention at present, including emotion, mentality, personality, and other aspects (8). During the implementation of PST, it is beneficial to the treatment and rehabilitation of patients by helping them understand problems, improve their emotions, and enhance their confidence. Psychological intervention for patients in various ways can improve the central nervous system, affect the immune mechanism, and then alleviate the psychological disorder of patients (9, 10). We aim to explore the intervention effect of PST on elderly patients with femoral neck fracture and its influence on psychological state, pain, and quality of life.

MATERIALS AND METHODS

Research Object

In total, 82 elderly patients with femoral neck fractures admitted to our hospital from July 2020 to June 2021 were selected. Inclusion criteria: the femoral neck fracture was diagnosed when: (1) the patient had tripped and fell; (2) there were clear signs, swelling, pain, limited movement of the affected side of the medullary joint, shortening of the lower limb, external rotation deformity, and there was shock pain when tapping lengthwise; and (3) radiographs of the medullary joint showed femoral neck fracture; all patients who had a definite history of trauma; patients who had normal weight-bearing and walking ability before fracture, and the activity level was good; and patients who had received surgical treatment, age $\geq$60 years old, primary school education or above, able to communicate independently, and complete questionnaire independently. Exclusion criteria: multiple fractures; pathological femoral neck fracture due to osteomyelitis; past history of long-term use of analgesics; cognitive disorder and consciousness disorder; poor compliance; complicated with other serious organic diseases; vital signs are unstable; and patients who have participated in other clinical studies. Elimination criteria: follow-up patients who have fallen off; patients with recurrent femoral neck fracture during follow-up; in the course of the study, other diseases occurred in patients, which affected the results of the study; and transferred to hospital for other reasons during treatment. Patients were randomly divided into conventional group ($n = 41$) and intervention group ($n = 41$). The general data of the two groups were balanced and comparable ($p > 0.05$), as shown in **Table 1**.

Methods

The conventional group received routine nursing care, which included: (1) health education, information about the causes and preventive measures of fracture complications and other related knowledge, and implementation of psychological intervention and dietary guidance; (2) oral analgesic drugs or analgesic pump to relieve pain; and (3) guided functional exercise, priority to rest, passive massage of the affected limb and ankle dorsiflexion after the operation, and instructions to patients to take regular care and follow-up by telephone.

The intervention group was given PST on the basis of the conventional group. (1) The department sets up a psychological support group, whose members were composed of nurses with solid nursing skills and doctors with rich clinical experience. Psychological counselors should train the group members in psychological intervention skills, including how to understand patients' bad psychological emotions, how to effectively improve patients' bad psychological emotions, and communication skills with patients. (2) Elderly patients with fracture often have a poor understanding of the content of psychological intervention due to the decline of cognitive function and reaction. Therefore, in the implementation of PST, team members should patiently answer patients' questions, understand patients' needs, and take targeted intervention measures. The group evaluated the psychological status of the elderly patients with fracture, interviewed the patients, observed the changes in the patients' behaviors, obtained a comprehensive understanding of the patients' psychological emotions after fracture, and gave targeted psychological guidance according to the patients' psychological status. (3) According to the patient's education level and knowledge acceptance ability, an appropriate way was chosen to explain the fracture-related knowledge to the patient. In the process of the functional exercise, the importance of functional exercise was explained for the physical rehabilitation of patients. For patients and their families who have problems, explained them in time to eliminate the patients' confusion and relieve their anxiety. (4) Nursing staff need to strengthen communication with patients, gave psychological counseling according to their personality characteristics, explained the correlation between emotions and post-operative recovery and the negative influence of bad emotions on the treatment effect, and told patients

TABLE 1 | Comparison of general data between the two groups (n, %, $\bar{x} \pm s$).

Group	Gender		Average age (years)	Complicated disease		
	Male	Female		Hypertension	Diabetes	Coronary heart disease
Conventional group ($n = 41$)	26 (63.41%)	15 (36.59%)	72.16 ± 2.58	15 (36.58%)	13 (31.71%)	12 (29.27%)
Intervention group ($n = 41$)	24 (58.54%)	17 (41.46%)	72.39 ± 2.47	16 (39.02%)	11 (26.83%)	10 (24.39%)
χ^2/t value	0.205		0.412		0.264	
p-value	0.651		0.681		0.876	

to keep a good attitude and build up treatment confidence. (5) Encouraged patients to maintain communication with the outside world, strive for the support of family members, and instructed patients' families to spend more time with patients, communicate with patients, and listen patiently to help patients adjust themselves and reduce negative emotions. (6) Patients' favorite and soothing light music or TV series to be played to divert patients' attention, make them have fun, raise their pain threshold, and relieve their nervousness and pessimism. (7) Patients who successfully recovered after fracture were invited to share their experience on-site, so as to encourage patients to establish a good attitude and strengthen their confidence in rehabilitation.

Observation Index

Before and 1 month after intervention, the Harris hip joint score was used to evaluate the joint function of patients. The main contents were hip deformity (4 points), pain (44 points), range of motion (5 points), and function (47 points), with a total score of 100 points. The higher the score, the better the hip function.

Before and 1-month after intervention, the self-rating anxiety scale (SAS) and the self-rating depression scale (SDS) were used to evaluate the psychological state of patients. SAS and SDS have a total of 20 entries, using the four-level scoring method. The higher the score, the worse the psychological state.

Before and 1-month after intervention, the patients' pain was evaluated by the visual analog scale (VAS). According to the pain, the horizontal line of 10 cm was marked, which was divided into 0–10 points. The higher the score, the stronger the pain.

Before and 1 month after intervention, the patients' quality of life was evaluated by the General Quality-of-Life Inventory-74 (GQOL-74). There were 74 items in the questionnaire, and the main contents were physical function (5 factors), psychological function (5 factors), social function (5 factors), and living state (4 factors), with a total score of 100 points. The higher the score, the better the quality of life.

One month after intervention, the self-made satisfaction questionnaire of our hospital was used to evaluate patients' nursing satisfaction. The main contents were daily guidance, precautions, civilized medical practice, nursing quality, health education and comprehensive management, etc., with a total score of 100 points: >85: very satisfied, 70–85: satisfied, 60–70: generally satisfied, <60: dissatisfied, total satisfaction = (very satisfied + satisfied)/total number of cases × 100%. The content validity index of the self-made satisfaction questionnaire was 0.79, and the reliability coefficient of Cronbach's α was 0.83.

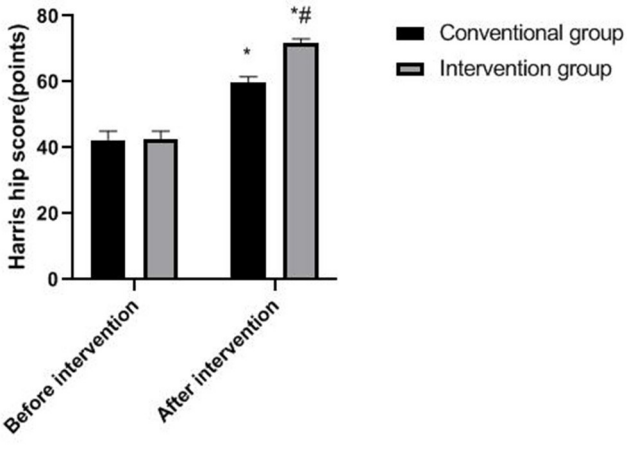


FIGURE 1 | Joint function of two groups. Compared with before intervention, $^*p < 0.05$; compared with the conventional group, $^{\#}p < 0.05$.

Statistical Methods

The SPSS 22.0 software was used for analysis, measurement data were expressed as $\bar{x} \pm s$, and the t-test was used to analyze the comparison. Count data were expressed as a ratio, the χ^2-test was used to analyze the comparison, and $p < 0.05$ was statistically significant.

RESULTS

Joint Function of Two Groups

Compared with before intervention, the Harris hip joint score of both groups increased after the intervention, and the increase was more obvious in the intervention group ($p < 0.05$), as shown in **Figure 1**.

Psychological State of Two Groups

Compared with before intervention, SAS and SDS scores in both groups decreased after the intervention, and the decrease was more obvious in the intervention group ($p < 0.05$), as shown in **Figure 2**.

Pain in Two Groups

Compared with before intervention, the VAS score of both groups decreased after the intervention, and the decrease was more obvious in the intervention group ($p < 0.05$), as shown in **Figure 3**.

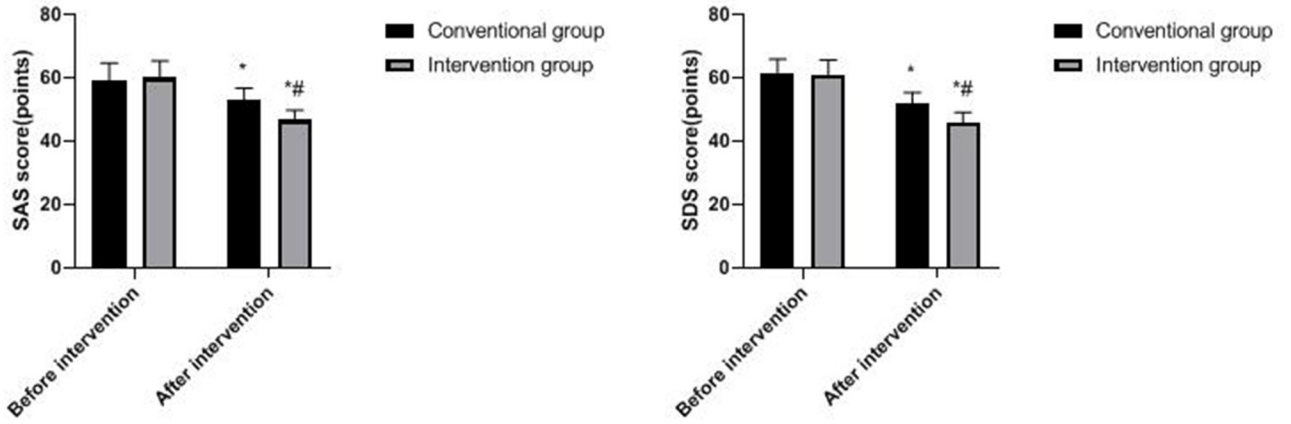


FIGURE 2 | Psychological state of two groups. Compared with before intervention, $^{*}p < 0.05$; compared with the conventional group, $^{\#}p < 0.05$.

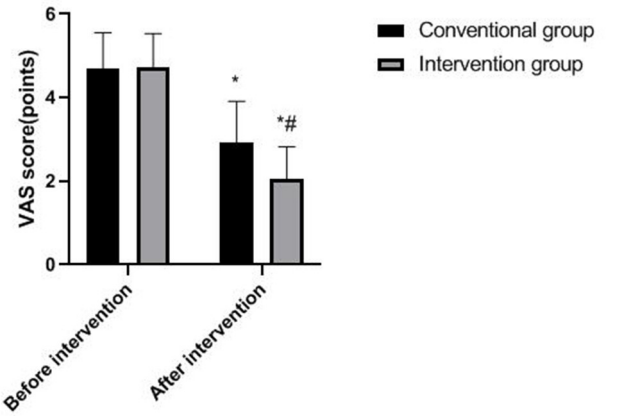


FIGURE 3 | Pain in two groups. Compared with before intervention, $^{*}p < 0.05$; compared with the conventional group, $^{\#}p < 0.05$.

Quality of Life of Two Groups

Compared with before intervention, the GQOL-74 scores of both groups increased after the intervention, and the increase was more obvious in the intervention group ($p < 0.05$), as shown in **Figure 4**.

Nursing Satisfaction of Two Groups

The total satisfaction of the intervention group (92.68%) was higher than that of the conventional group (75.61%; $p < 0.05$), as shown in **Table 2**.

DISCUSSION

Femoral neck fractures often occur in the elderly, and the reason is that the physical function of the elderly is declining, and most of them are often complicated with chronic diseases such as hypertension and diabetes, with limited absorption of nutrients and obvious osteoporosis (11). At present, surgical treatment is widely used for hip fracture clinically, which can reduce the incidence and mortality of complications and has a good improvement effect (12). However, because most of the patients are elderly people, they have poor psychological endurance, lack knowledge about diseases and operations, and worry too much about whether the fracture site can return to normal after operation, which will lead to a certain degree of psychological disorder. As patients with fractures need to stay in bed for a long time after operation, and the post-operative mobility disorder and pain will further aggravate the patient's anxiety, insecurity, depression, and other negative psychology (13, 14). When the patient is in a bad psychological state for a long time, excessive stress will lead to a series of neuroendocrine reactions in the body, and the levels of catecholamine transmitters and adrenocortical hormones in blood will increase, which will increase the oxygen consumption of the body and aggravate the heart load, which is not conducive to the recovery of patients with femoral neck fracture (15, 16). Therefore, it is of great significance to take effective nursing intervention for elderly patients with femoral neck fracture after operation, and the psychological nursing of patients with fracture has aroused great concern in medical circles.

Traditional nursing methods for elderly patients with femoral neck fracture can shorten the time of stay in bed and improve the physical disorder, but this nursing measure is easy to ignore the psychological state and functional rehabilitation of patients after operation (17). Psychologically unhealthy patients often have neuroendocrine disorders, in which substance P and serotonin are not only strong pain-causing substances but also participate in the occurrence of anxiety and bad emotions (18). With the transformation of modern medical model from biological model to biological–psychological–social model, PST is increasingly favored by clinical nursing. PST can improve the psychological homeostasis, maintain normal stress ability, and eliminate adverse emotional reactions by adjusting patients' psychological health (19). In recent years, many scholars' studies have shown that it is very important to take positive psychological assessment and corresponding

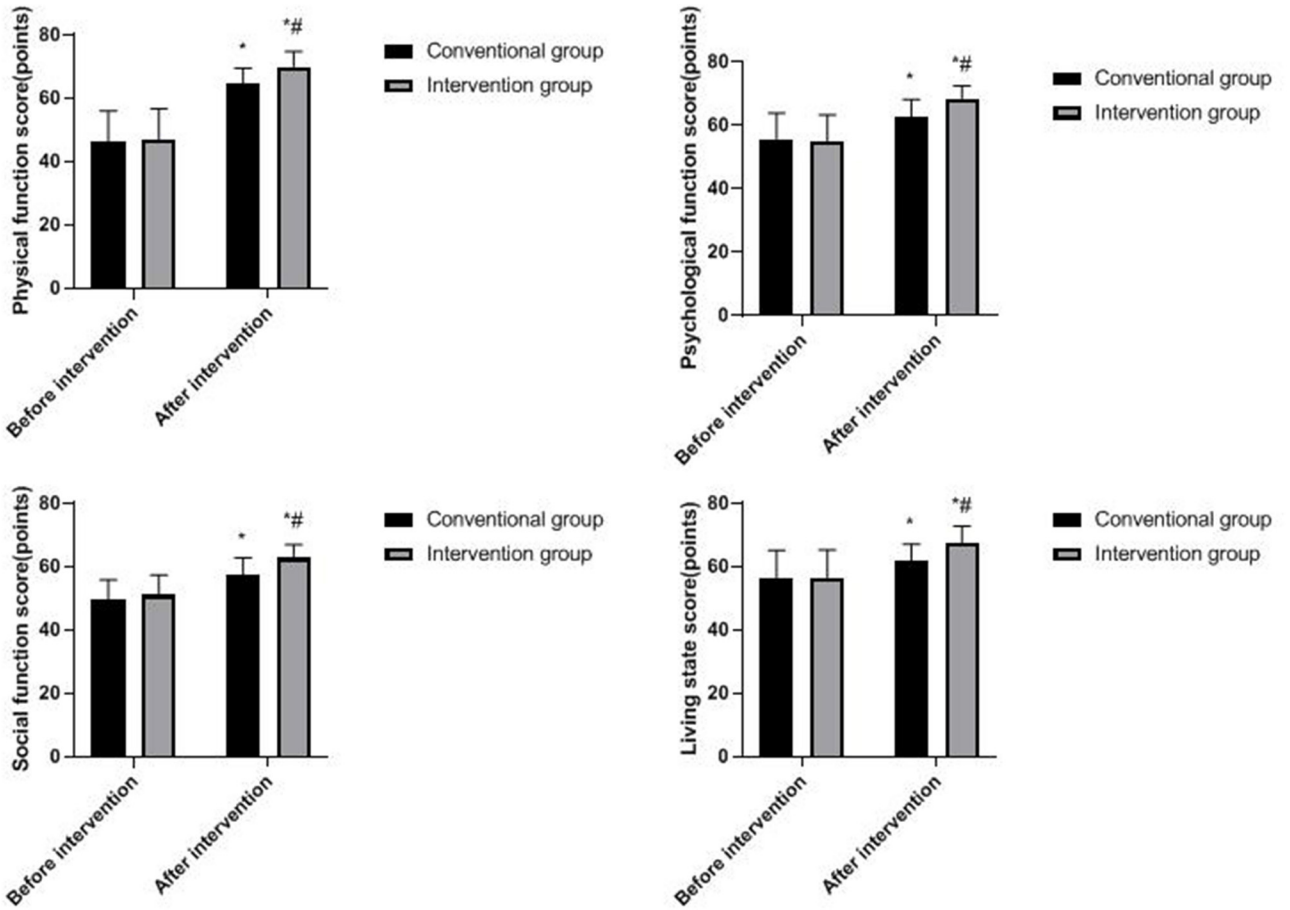


FIGURE 4 | Quality-of-life of two groups. Compared with before intervention, $^{*}p < 0.05$; compared with the conventional group, $^{\#}p < 0.05$.

TABLE 2 | Nursing satisfaction of two groups (*n*, %).

Group	Very satisfied	Satisfied	Generally satisfaction	Dissatisfied	Total satisfaction
Conventional group ($n = 41$)	17 (41.46%)	14 (34.15%)	6 (14.63%)	4 (9.76%)	31 (75.61%)
Intervention group ($n = 41$)	22 (53.66%)	16 (39.02%)	2 (4.88%)	1 (2.44%)	38 (92.68%)
χ^2 value					4.479
p-value					0.034

nursing care for patients with fractures while recovering their post-operative function, which is conducive to improving their quality of life. Johnson's team found that long-term non-union after fracture would cause great psychological pressure on patients, which often leads to psychological disorder. It is necessary to identify patients' psychological problems early and give targeted psychological treatment (20). Yadav's team research shows that the nursing mode of health education for patients with fractures by using digital education platform can prevent fractures caused by falling again, limit the psychology of "fear of falling," and improve the confidence of patients (21).

In this study, the Harris hip joint score and the GQOL-74 score in the PST group were significantly increased, the SAS, SDS score, and VAS score were significantly decreased, and the total nursing satisfaction was 92.68% in the PST group. The results showed that PST has a positive effect on the psychological state, pain, and quality of life of elderly patients with femoral neck fracture. We think that in the implementation of PST, through the evaluation of the psychological status of elderly patients with fracture, we can understand the psychological mood of patients after fracture, analyze the causes of the formation of negative psychology, conduct psychological counseling for patients, increase the communication between

nurses and patients, and gain the trust of patients, which play an important role in accelerating the rehabilitation of fractures. Medical staff encourage patients to set up a healthy state of mind, explain the harm of negative psychology to them, encourage patients to take the initiative to express, patiently answer their doubts, eliminate patients' misconceptions about diseases, alleviate patients' concerns, make patients have a correct view on diseases, and relieve psychological pressure, thus encouraging patients to develop the habit of self-regulating emotions (22). PST can improve patients' ability to deal with pain, reduce their psychological burden, and enhance confidence in recovery, thereby strengthening the psychological and physiological adaptation mechanism, enhancing patients' tolerance to stimulation and adaptive response, and further reducing pain (23). In addition, after the implementation of PST, nurses encourage patients with fracture to keep in communication with the outside world and instruct their relatives and friends to take care for them as much as possible, so that patients could get high-quality social support, relieve their anxiety and depression, and improve their unhealthy psychology from all aspects. By playing their favorite light music or TV drama for patients, PST can guide patients to imagine the beautiful things in life and divert patient's attention, so as to reduce the bad beliefs brought by diseases, delight their body and mind, raise the pain threshold, help patients form a positive psychological state, and improve the satisfaction evaluation of patients and their families on medical care.

CONCLUSION

To sum up, PST has a certain intervention effect on elderly patients with femoral neck fracture, which can improve psychological state, reduce pain, improve quality of life, and improve nursing satisfaction.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Fourth Hospital of Changsha. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XS served as a supervisor to guide the entire study. All authors of this study made equal contributions, including the design of the study, conduct of the experiments, evaluation of the results, statistics of the data, and writing of the paper. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Jones CB, Walker JB. Diagnosis and management of ipsilateral femoral neck and shaft fractures. *J Am Acad Orthop Surg*. (2018) 26:e448–54. doi: 10.5435/JAAOS-D-17-00497
2. Augat P, Bliven E, Hackl S. Biomechanics of femoral neck fractures and implications for fixation. *J Orthop Trauma*. (2019) 33:S27–32. doi: 10.1097/BOT.0000000000001365
3. Xu DF, Bi FG, Ma CY, Wen ZF, Cai XZ. A systematic review of undisplaced femoral neck fracture treatments for patients over 65 years of age, with a focus on union rates and avascular necrosis. *J Orthop Surg Res*. (2017) 12:28. doi: 10.1186/s13018-017-0528-9
4. Wang Y, Ma JX, Yin T, Han Z, Cui SS, Liu ZP, et al. Correlation between reduction quality of femoral neck fracture and femoral head necrosis based on biomechanics. *Orthop Surg*. (2019) 11:318–24. doi: 10.1111/os.12458
5. Guyen O. Hemiarthroplasty or total hip arthroplasty in recent femoral neck fractures? *Orthop Traumatol Surg Res*. (2019) 105:S95–101. doi: 10.1016/j.otsr.2018.04.034
6. Jung KH, Park JH, Song JY, Han JW, Park KB. State-anxiety in geriatric patients undergoing surgical treatment for femoral neck or intertrochanteric fractures. *Geriatr Orthop Surg Rehabil*. (2021) 20:21514593211063320. doi: 10.1177/21514593211063320
7. Alexiou KI, Roushias A, Varitimidis SE, Malizos KN. Quality of life and psychological consequences in elderly patients after a hip fracture: a review. *Clin Interv Aging*. (2018) 13:143–50. doi: 10.2147/CIA.S150067
8. Robinson H, Norton S, Jarrett P, Broadbent E. The effects of psychological interventions on wound healing: a systematic review of randomized trials. *Br J Health Psychol*. (2017) 22:805–35. doi: 10.1111/bjhp.12257
9. Cuijpers P, Quero S, Dowrick C, Arroll B. Psychological treatment of depression in primary care: recent developments. *Curr Psychiatry Rep*. (2019) 21:129. doi: 10.1007/s11920-019-1117-x
10. Svensson HK, Olsson LE, Hansson T, Karlsson J, Hansson-Olofsson E. The effects of person-centered or other supportive interventions in older women with osteoporotic vertebral compression fractures-a systematic review of the literature. *Osteoporos Int*. (2017) 28:2521–40. doi: 10.1007/s00198-017-4099-8
11. Liu P, Zhang Y, Sun B, Chen H, Dai J, Yan L. Risk factors for femoral neck fracture in elderly population. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. (2021) 46:272–7. doi: 10.11817/j.issn.1672-7347.2021.190378
12. Ekhtiari S, Gormley J, Axelrod DE, Devji T, Bhandari M, Guyatt GH. Total hip arthroplasty versus hemiarthroplasty for displaced femoral neck fracture: a systematic review and meta-analysis of randomized controlled trials. *J Bone Joint Surg Am*. (2020) 102:1638–45. doi: 10.2106/JBJS.20.00226
13. Zachwieja E, Butler AJ, Grau LC, Summers S, Massel D, Orozco F, et al. The association of mental health disease with perioperative outcomes following femoral neck fractures. *J Clin Orthop Trauma*. (2019) 10:S77–83. doi: 10.1016/j.jcot.2019.01.002
14. Zhong M, Liu D, Tang H, Zheng Y, Bai Y, Liang Q, et al. Impacts of the perioperative fast track surgery concept on the physical and psychological rehabilitation of total hip arthroplasty: a prospective cohort study of 348 patients. *Medicine*. (2021) 100:e26869. doi: 10.1097/MD.0000000000026869
15. Kitayama A, Hida M, Takami H, Hirata N, Deguchi Y, Miyaguchi K, et al. Factors associated with psycho-cognitive functions in patients with persistent pain after surgery for femoral neck fracture. *J Clin Med Res*. (2017) 9:771–5. doi: 10.14740/jocmr3104w
16. Kristoffersen MH, Dybvik E, Steihaug OM, Kristensen TB, Engesaeter LB, Ranhoff AH, et al. Cognitive impairment influences the risk of reoperation after hip fracture surgery: results of 87,573 operations reported to the Norwegian Hip Fracture Register. *Acta Orthop*. (2020) 91:146–51. doi: 10.1080/17453674.2019.1709712
17. Ping H, Ling X, Xue Y, Dong F. Effect of ERAS combined with comfortable nursing on quality of life and complications in femoral neck fractures of the aged people. *Evid Based Complement Alternat Med*. (2021) 2021:8753076. doi: 10.1155/2021/8753076

18. Ortega A, Gauna F, Munoz D, Oberreuter G, Breinbauer HA, Carrasco L. Music therapy for pain and anxiety management in nasal bone fracture reduction: randomized controlled clinical trial. *Otolaryngol Head Neck Surg*. (2019) 161:613–9. doi: 10.1177/0194599819856604
19. van Laake-Geelen CCM, Smeets RJEM, Quadflieg SPAB, Kleijnen J, Verbunt JA. The effect of exercise therapy combined with psychological therapy on physical activity and quality of life in patients with painful diabetic neuropathy: a systematic review. *Scand J Pain*. (2019) 19:433–9. doi: 10.1515/sjpain-2019-0001
20. Johnson L, Igoe E, Kleftouris G, Papachristos IV, Papakostidis C, Giannoudis PV. Physical health and psychological outcomes in adult patients with long-bone fracture non-unions: evidence today. *J Clin Med*. (2019) 8:1998. doi: 10.3390/jcm8111998
21. Yadav L, Gill TK, Taylor A, Jasper U, De Young J, Visvanathan R, et al. Cocreation of a digital patient health hub to enhance education and person-centred integrated care post hip fracture: a mixed-methods study protocol. *BMJ Open*. (2019) 9:e033128. doi: 10.1136/bmjopen-2019-033128
22. Huang L, Zhang C, Xu J, Wang W, Yu M, Jiang F, et al. Function of a psychological nursing intervention on depression, anxiety, and quality of life in older adult patients with osteoporotic fracture. *Worldviews Evid Based Nurs*. (2021) 18:290–8. doi: 10.1111/wvn.12518
23. Bishnoi S, Huda N, Islam S, Pant A, Agarwal S, Dholariya R. Association between psychological status and functional outcome in surgically managed fractures around hip in geriatric patients - a prospective study. *Malays Orthop J*. (2021) 15:18–25. doi: 10.5704/MOJ.2107.004

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Li, Wang and Shen. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 24 March 2022
doi: 10.3389/fsurg.2022.859269

Improvement of Negative Psychological Stress Response in Elderly Patients With Femoral Neck Fracture by Integrated High-Quality Nursing Model of Medical Care

*Qun Li, Yin Wang and Xiang Shen**

Orthopaedics Department, The Fourth Hospital of Changsha (Affiliated Changsha Hospital of Hunan Normal University), Changsha, China

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Yan Zou,
University of South China, China
Jing Xu,
Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, China

****Correspondence:***
Xiang Shen
Shenxiang19750901@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *21 January 2022*
Accepted: *16 February 2022*
Published: *24 March 2022*

Citation:
Li Q, Wang Y and Shen X (2022) Improvement of Negative Psychological Stress Response in Elderly Patients With Femoral Neck Fracture by Integrated High-Quality Nursing Model of Medical Care. Front. Surg. 9:859269. doi: 10.3389/fsurg.2022.859269

Objective: The objective of this study was to explore the nursing effect and negative psychological stress response of elderly patients with femoral neck fracture by applying the high-quality nursing mode of medical care.

Methods: A total of 130 elderly patients with femoral neck fractures hospitalized in our hospital from January 2020 to June 2021 were randomly divided into the control group and observation group, with 65 patients in each group. The control group adopted the conventional nursing mode, while the observation group adopted the high-quality nursing mode of medical care. The observation indexes selected in this study are nursing satisfaction, hip flexion activity on the 1, 15, and 30 days after the operation, the time when the affected limb was lifted off the bed actively, and the anxiety and depression of patients.

Results: On the 1, 15, and 30 days after the operation, there were statistically significant differences between the two groups in hip flexion activity and the time when the affected limb was lifted off the bed ($P < 0.05$). The nursing satisfaction of the observation group was 95.38%, which was statistically significant compared with the 80.00% of the control group ($P < 0.05$). After treatment, the self rating depression scale (SDS) and self rating anxiety scale (SAS) scores in the observation group were lower than those in the control group ($P < 0.05$).

Conclusion: The high-quality nursing model of medical care can effectively promote the rehabilitation of elderly patients with femoral neck fracture, reduce the negative psychological stress reaction of patients, and improve nursing satisfaction, which has important application value and guiding significance for the nursing of patients with femoral neck fracture.

Keywords: femoral neck fracture, integration of medical care, quality care, medical care, elderly patients

INTRODUCTION

Femoral neck fracture is a common and frequently-occurring disease in clinics, with the highest incidence rate among middle-aged and elderly patients, accounting for 3.58% of all fractures. Femoral neck fracture is a serious type of fracture and it takes a long time to reconstruct or recover the fracture site after an operation, which has brought serious adverse effects to the patients' normal work and life (1, 2). Elderly patients with femoral neck fractures will feel obvious pain at the broken end of the fracture, especially when moving the injured limbs. Pain has a variety of adverse effects on the body, which not only form complex physiological reactions and affect the rehabilitation exercise of patients but also lead to negative emotions of patients (3).

At present, the treatment of femoral neck fracture mainly uses artificial hip joint replacement, which can relieve the pain of patients as soon as possible, reduce the damage to patients' bodies, and restore normal life. However, the curative effect of the operation is closely related to good nursing care, so it is necessary to strengthen nursing management during the perioperative period to promote the early recovery of patients. Medical integration refers to the process in which doctors and nurses provide medical care services to patients with certain professional knowledge and ability through open coordination and communication on the premise of equality, independence, mutual respect, and trust (4, 5). The integrated high-quality nursing model of medical care is a new type of whole-course management model, which is widely used in clinical nursing. However, there are few in-depth reports on the application of the integrated high-quality nursing model of medical care in the perioperative period of elderly patients with femoral neck fractures. At present, the nursing work for elderly patients is still based on the traditional medical model of "independent evaluation of medical care, doctors' orders, and nurses' orders," which lacks the cooperation and communication between doctors and nurses. This study focuses on the in-depth analysis of the high-quality nursing model of medical care for elderly patients with femoral neck fracture, which is reported as follows.

DATA AND METHODS

General Information

A total of 130 elderly patients with femoral neck fractures hospitalized in our hospital from January 2020 to June 2021 were selected and divided into the control group and the observation group with 65 patients in each group according to the random number table method. Inclusion criteria: age $\geq$60 years old; imaging diagnosis is femoral neck fracture; postoperative hospital stay $>$ 5 days; awareness, communication skills, and no surgical contraindications. Exclusion criteria: accompanied by serious heart, lung, liver, kidney, and other diseases; Complicated with neurological, immune, and endocrine system diseases; Severe preoperative malnutrition; Poor foundation, unable to tolerate surgery. This study was approved by the Ethics Committee of our hospital and the patients' and their families informed consent.

Research Methods

Nursing Method of the Control Group: The Patients Were Nursed by Conventional Nursing Mode

Doctors and nurses made ward rounds every day to make treatment and care plans, respectively, and implement the plans, respectively, such as fasting and water deprivation for 6 h after operation, general diet for 6 h, absolutely lying in bed after the operation, with the affected limb higher or slightly higher than the heart level, maintaining knee joint flexion of 20–30 degrees, performing metatarsophalangeal joint and toe joint movement of the affected limb after anesthesia recovery after the operation, and performing doctor-permitted movement after except fixation 6–8 weeks after the operation.

Nursing Method of Observation Group: Adopt the High-Quality Nursing Mode of Medical Care

1. Establish a medical and nursing integrated diagnosis and treatment team: its members include doctors and nurses at all levels, and the department heads and head nurses are responsible for it. In the observation group, the medical staff in the group jointly completed the medical history collection, physical examination, and condition evaluation. The doctors wrote inpatient medical records and nurses set up nursing logs.
2. Integrated medical ward rounds: doctors and nurses make ward rounds every morning and evening to learn about the patient's condition and the implementation of treatment. The degree of limb swelling, self-care ability of patients in daily life, implementation of doctor's advice, adverse drug reactions reported by doctors, etc. design the record of joint medical rounds, convey the opinions of doctors to all nurses in this group, and adjust the functional exercise and nursing plan.
3. Painless handling. Doctors and nurses cooperate with each other in transportation. The doctors are responsible for pulling the affected limb and choosing different numbers of nurses according to the patient's weight. Nurses respectively support the patient's torso and the contralateral lower limbs so that the patient can maintain the abduction neutral position. The doctor gave the orders, and at the same time, the doctor lifted the patient. Under the doctor's traction, the affected limb is always on the same horizontal line as the patient's longitudinal axis. After the operation, the doctors and nurses put the patient together in a comfortable position.
4. Quality environmental care. For patients hospitalized for a long time, the ward environment should be kept clean to prevent hospital infection. Ventilation keeps the air in the ward fresh every day. A total of 84 kinds of disinfectants are used to wipe the table and floor every day.
5. Integration of medical care and functional exercise: Individualized functional exercise programs for patients should be developed based on the general situation of patients, osteoporosis, and self-care ability in daily life. Under the guidance of the doctor and the assistance of nurses, the patients' families were instructed to do the decompression exercise to reduce the pressure of the calf and thigh muscle from the patient's heel 6 h after the operation, three times a day, each time for 15 min, and 48 h after the operation, the patients were treated with double lower limb pneumatic

TABLE 1 | Comparison of general information of two groups of patients.

Group	Number	Gender		Age (years)	Cause of injury			Fracture site		
		Male	Woman		Traffic accident	Wrestling	Fall down	Other	Left side	Right side
Control group	65	34	31	71.02 ± 3.27	15	34	6	10	39	26
Observation group	65	35	30	70.94 ± 3.11	19	32	8	6	37	28
t/χ^2 value	0.031	0.143	1.817	0.127						
P value	0.860	0.887	0.611	0.722						

pump. Exercise should be carried out step by step under the guidance of a doctor, and should not be too hasty to avoid injury again.

6. Psychological care. According to the patient's education level and knowledge receiving ability, choose a suitable way to explain the disease and the correlation between postoperative rehabilitation-related knowledge, emotion, and postoperative recovery, so that patients can do a good job in ideological work Tell the patients to keep a good attitude and insist on rehabilitation training, which will help to improve the rehabilitation effect. Doctors and nurses must actively answer the problems existing in the patients' treatment and rehabilitation. Encourage the patients to maintain communication with the outside world and win the support of family members, especially children or spouses of patients. Help the patients to establish reasonable cognition, reduce negative emotions, and build their confidence to cooperate with the treatment and rehabilitation exercises. During the implementation of psychological nursing, the nurses implemented the corresponding functional exercise measures for the patients and signed them to ensure that the nursing measures were in place.

Observation Indicators

The observation indexes selected in this study are nursing satisfaction, hip flexion activity on the 1, 15, and 30 days after the operation, the time when the affected limb is lifted off the bed actively, and the anxiety and depression of patients. Among them, nursing satisfaction was measured by the self-made questionnaire of clinical nursing satisfaction of patients in our hospital. Out of 100, >85 is very satisfactory, 70–85 is satisfactory, 60–70 is fair, <60 is unsatisfactory, and satisfaction = very satisfactory rate+satisfactory rate. The content validity index of the self-made questionnaire in our hospital was 0.83, and the α coefficient of Kehlenbach was 0.816, with good reliability and validity. The self-rating anxiety scale (SAS) and self-rating depression scale (SDS) were used to evaluate the anxiety and depression of patients before nursing (when entering the group) and after nursing (30 days after the operation). The cut-off value of the SAS scale is 50 points, 50–59 points for mild anxiety, 60–69 points for moderate anxiety, and 69 points or more for severe anxiety. The demarcation value of the SDS scale is 53 points, 53–62 points for mild depression, 63–72 points for moderate depression, and 72 points or more for severe depression.

TABLE 2 | Comparison of flexion range of hip joint between two groups.

Group	Number	Hip joint flexion range of motion (°)		
		1d	15d	30d
Control group	65	46.59 ± 7.39	61.83 ± 6.03	81.21 ± 5.29
Observation group	65	55.80 ± 6.27	74.25 ± 7.24	105.28 ± 9.13
t value		7.662	10.627	18.391
P value		<0.001	<0.001	<0.001

Statistical Methods

The SPSS22.0 software (IBM Corp., Armonk, NY, USA) was used to process the experimental data. The experimental data were in accordance with the normal distribution. The measurement data were expressed by the mean SD ($\bar{x} \pm s$), and the counting data was expressed by (%). The *t*-test analysis was used for pairwise comparison of measurement data between groups, and the χ^2 test was used for counting data. The test level is $\alpha = 0.05$, and the difference is statistically significant when $P < 0.05$.

RESULTS

Comparison of General Data of Two Groups of Patients

There was no significant difference in general data such as gender and age between the two groups ($P > 0.05$). As shown in **Table 1**.

Comparison of Hip Joint Flexion Range of Motion Between Two Groups

There was a statistically significant difference in the hip joint flexion range of motion of the patients in the observation group is higher than that of the patients in the control group on the 1, 15, and 30 days after the operation ($P < 0.05$). As shown in **Table 2**.

Comparison of Active Lifting Time of Affected Limb From Bed Between Two Groups of Patients

There was a statistically significant difference in the time when the affected limb was lifted off the bed surface between the two groups ($P < 0.05$). As shown in **Figure 1**.

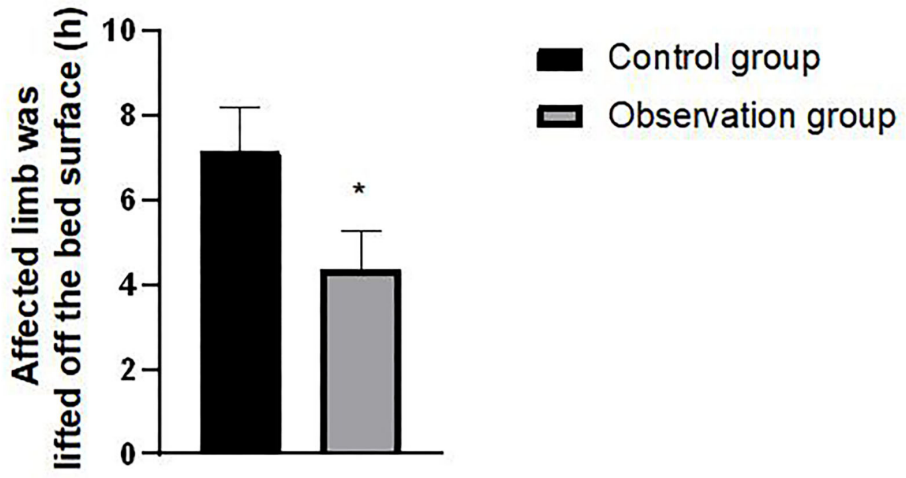


FIGURE 1 | Comparison of active lifting time of affected limb from bed between two groups of patients. Compared with the control group, $^{*}t = 16.465$, $P < 0.001$.

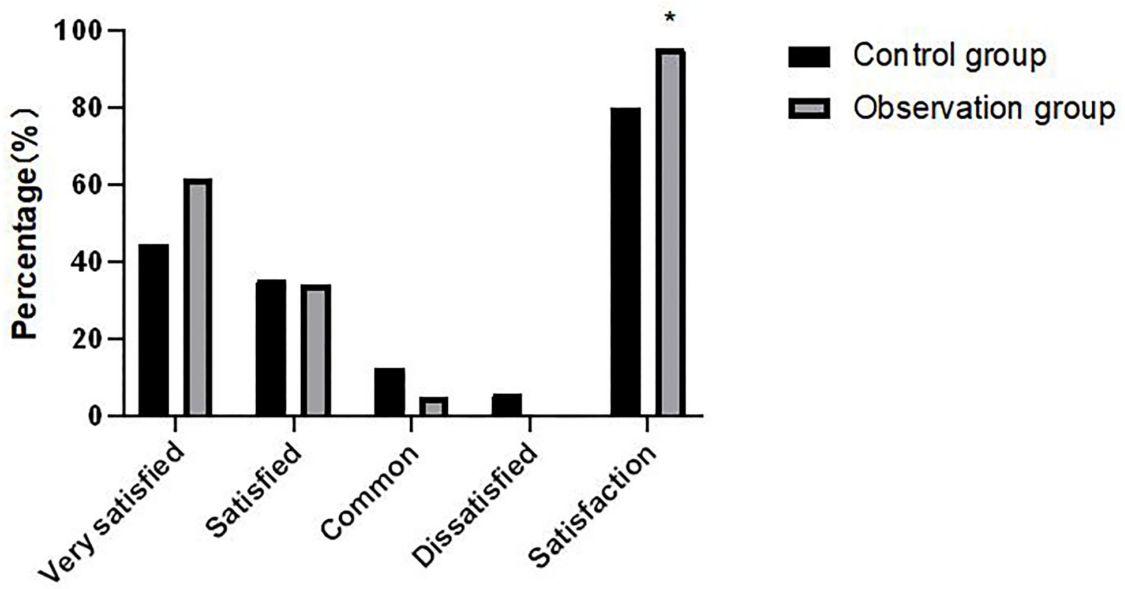


FIGURE 2 | Comparison of nursing satisfaction between two groups of patients. Compared with the control group, $^{*}\chi^2 = 9.049$, $P = 0.029$.

Comparison of Nursing Satisfaction Between Two Groups of Patients

The nursing satisfaction of the observation group was 95.38%, which was statistically significant compared with the 80.00% of the control group ($P < 0.05$). As shown in **Figure 2**.

Comparison of the SDS and SAS Scores Between the Two Groups Before and After Treatment

After treatment, the SDS and SAS scores of the patients in the observation group were lower than those in the control group, and the difference was statistically significant ($P < 0.05$). As shown in **Table 3**.

DISCUSSION

With the arrival of China's aging society, the incidence of osteoporosis is getting higher and higher, and the incidence of femoral neck fracture is on the rise, which has aroused great concern in medical circles. For the treatment of this disease, surgery is widely favored by patients and doctors for its definite curative effect and low incidence of complications (6). A large number

TABLE 3 | Comparison of the SDS and SAS scores between the two groups before and after treatment.

Group	Number	SDS score		SAS score	
		Before treatment	After treatment	Before treatment	After treatment
Control group	65	60.15 ± 7.03	49.37 ± 6.19	57.92 ± 6.31	47.29 ± 5.02
Observation group	65	59.23 ± 6.71	32.85 ± 5.93	59.12 ± 6.69	31.94 ± 6.18
t value		0.763	15.537	1.052	15.543
P value		0.447	<0.001	0.295	<0.001

of clinical studies have proved that good nursing intervention to patients with femoral neck fracture can promote postoperative rehabilitation of elderly patients (7, 8).

The high-quality nursing mode of medical care integrates the etiology, manifestation, prevention, rehabilitation, and nursing of elderly patients with femoral neck fracture, finds out the changes of patients' condition in time, and breaks the original pattern of the doctor-patient nurse-patient parallel (9). The high-quality nursing mode of medical and nursing integration has set up a brand-new three-dimensional integrated working pattern of doctors, nurses, and patients, implements the joint ward rounds of doctors and nurses, and made targeted planning of perioperative nursing measures of patients, making the cooperation between doctors and nurses more systematic (10).

The high-quality nursing mode of medical integration can help nurses understand the key points of the patients' functional exercise. Doctors and nurses can jointly guide patients to carry out individualized functional exercises to ensure the safety and effectiveness of functional exercise. At the same time, targeted education should be taken to improve the quality of functional exercise and patient compliance according to the patient's mastery (11, 12). The observation group implemented the high-quality nursing mode of integrated nursing of medical staff and worked out the early functional exercise plan of the affected limb to help patients recover. The observation indexes were all better than those of the control group. Especially on the 1, 15, and 30 days after the operation, the improvement effect of hip flexion activity, the time for the affected limb to lift off the bed surface, and other indexes are better than that of the control group, which provides powerful help for achieving the ideal rehabilitation effect. It can be seen that the high-quality nursing model of integration of medical care and nursing adopted in this study has achieved an ideal nursing effect, shortened the recovery time of patients, and laid a solid foundation for them to resume a normal life.

In the process of implementing the high-quality nursing model of medical integration, patients are also involved, and the relationship between doctors and patients is transformed into a new cooperative relationship (13). This study shows that the nursing satisfaction of the observation group is significantly higher than that of the control group. In the process of patient treatment, the medical staff really take the patients as their own responsibilities and obligations and do their duty to the patients in charge, so that patients can enjoy high-quality and satisfactory care, meet the knowledge needs of patients and their families, further deepen and highlight the connotation of high-quality medical services, and improve patient satisfaction (14). It has important application value and guiding significance for the treatment of patients with femoral neck fractures or fractures in other parts of lower limbs.

Although the operation has a good effect on femoral neck fracture, because most of the patients are elderly, they have poor psychological endurance, slow reaction, unclear language expression, lack of understanding of diseases and operations knowledge, and worry too much that the fracture site will return to normal after the operation, which will easily lead to negative psychology such as anxiety and depression, etc. If they are not dealt with in time and effectively, it will affect the postoperative recovery of patients (15, 16). This study showed that after treatment, the SDS and SAS scores of the patients in the observation group were significantly lower than those in the control group after treatment. It shows that the high-quality nursing mode of integrating medical care with nursing care has a certain effect on improving patients' negative emotions. From the patient's point of view, the integrated high-quality nursing model, clear division of labor between doctors and nurses, and personalized high-quality nursing service greatly improve the nursing quality. Compared with simple clinical treatment and routine nursing, it can relieve patients' negative psychological stress and promote their rehabilitation (17, 18).

To sum up, the high-quality nursing model of medical and nursing integration can effectively promote the rehabilitation of elderly patients with femoral neck fracture, reduce the negative psychological stress reaction of patients and improve nursing satisfaction, which has important application value and guiding significance for the nursing of patients with femoral neck fracture.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the Fourth Hospital of Changsha. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QL, YW, and XS made equal contributions to this study, including study design, inclusion of cases, evaluation of results, data statistics, and article writing. XS was the supervisor of the entire study. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Bastard C. Fracture du col du fémur [Femoral neck fracture]. *Rev Prat.* (2019) 69:1124–8.
2. Xu DF Bi FG, Ma CY, Wen ZF, Cai XZ. A systematic review of undisplaced femoral neck fracture treatments for patients over 65 years of age, with a focus on union rates and avascular necrosis. *J Orthop Surg Res.* (2017) 12:28. doi: 10.1186/s13018-017-0528-9
3. Alexiou KI, Roushias A, Varitimidis SE, Malizos KN. Quality of life and psychological consequences in elderly patients after a hip fracture: a review. *Clin Interv Aging.* (2018) 13:143–50. doi: 10.2147/CIA.S150067
4. Heinen M, van Oostveen C, Peters J, Vermeulen H, Huis A. An integrative review of leadership competencies and attributes in advanced nursing practice. *J Adv Nurs.* (2019) 75:2378–92. doi: 10.1111/jan.14092
5. Li H, Liu Y, Li Q, Fan J, Gan L, Wang Y. Effects of a fast track surgery nursing program in perioperative care of older patients with a hip fracture. *Eur Geriatr Med.* (2020) 11:519–25. doi: 10.1007/s41999-020-00298-y
6. Tian ZZ, Pang D, Liu HN, Zhou L, Zheng YY. Effect of enhanced recovery after surgery for elderly patients with hemiarthroplasty for the treatment of femoral neck fracture. *Zhonghua Yi Xue Za Zhi.* (2020) 100:2903–7. doi: 10.3760/cma.j.cn112137-20200308-00647
7. Ping H, Ling X, Xue Y, Dong F. Effect of ERAS Combined with Comfortable Nursing on Quality of Life and Complications in Femoral Neck Fractures of the Aged People. *Evid Based Complement Alternat Med.* (2021) 3:8753076. doi: 10.1155/2021/8753076
8. Liu J, Zhao Q, Wang J, Zhang J, Jiang J, Wang H. The effect of continuing care on postoperative life quality and long-term functional recovery in elderly patients with hip fracture. *Am J Transl Res.* (2021) 13:5512–8.
9. Chen YR, Chen YL, Chen WY, Lin YC, Jane SW. Evidence-Based Nursing Care of Older Adult Patient With Postoperative Delirium and Hip Fracture. *Hu Li Za Zhi.* (2021) 68:90–6. doi: 10.6224/JN.202102_68(1)0.12
10. Wang Y, Wang F, Lu C. Pain-free nursing care improves therapeutic outcome for patients with acute bone fracture after orthopedics surgery. *Asian J Surg.* (2020) 43:1086–7. doi: 10.1016/j.asjsur.2020.07.003
11. Shen Y, Xu L, Xu X, Shi L, Xu J, Shen Q, et al. Effect of predictive trauma nursing on emergency traumatic fracture patients. *Minerva Surg.* (2021) 76:606–8. doi: 10.23736/S2724-5691.21.08893-6
12. Jiang M, Liu S, Deng H, Liang X, Bo Z. The efficacy and safety of fast track surgery (FTS) in patients after hip fracture surgery: a meta-analysis. *J Orthop Surg Res.* (2021) 16:162. doi: 10.1186/s13018-021-02277-w
13. Zhong M, Liu D, Tang H, Zheng Y, Bai Y, Liang Q, et al. Impacts of the perioperative fast track surgery concept on the physical and psychological rehabilitation of total hip arthroplasty: A prospective cohort study of 348 patients. *Medicine (Baltimore).* (2021) 100:26869. doi: 10.1097/MD.0000000000026869
14. Deng YH, Yang YM, Ruan J, Mu L, Wang SQ. Effects of nursing care in fast-track surgery on postoperative pain, psychological state, and patient satisfaction with nursing for glioma. *World J Clin Cases.* (2021) 9:5435–41. doi: 10.12998/wjcc.v9.i20.5435
15. Zhang HM, Wang QH, Xu ST, Hu MM, Xin XT, Song JF, et al. Psychological care combined with enhanced recovery after surgery management in perioperative nursing care of andrological patients: A randomi zed controlled study. *Zhonghua Nan Ke Xue*. (2020) 26:917–21.
16. Füssenich W, Gerhardt DM, Pauly T, Lorenz F, Olieslagers M, Braun C, et al. A comparative health care inventory for primary hip arthroplasty between Germany versus the Netherlands. Is there a downside effect to fast-track surgery with regard to patient satisfaction and functional outcome?. *Hip Int.* (2020) 30:423–30. doi: 10.1177/1120700019876881
17. Zhang C, Xiao J. Application of fast-track surgery combined with a clinical nursing pathway in the rehabilitation of patients undergoing total hip arthroplasty. *J Int Med Res.* (2020) 48:718. doi: 10.1177/0300060519889718
18. Berg U, Berg M, Rolfson O, Erichsen-Andersson A. Fast-track program of elective joint replacement in hip and knee-patients' experiences of the clinical pathway and care process. *J Orthop Surg Res.* (2019) 14:186. doi: 10.1186/s13018-019-1232-8

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Li, Wang and Shen. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 25 March 2022
doi: 10.3389/fsurg.2022.860968

Comparison of Application Value of Different Radiation Dose Evaluation Methods in Evaluating Radiation Dose of Adult Thoracic and Abdominal CT Scan

Jimin He[1], *Guanwei Dong*[1], *Yi Deng*[2], *Jun He*[1], *ZhiGang Xiu*[1] *and Fanzi Feng*[1]*

[1] *Department of Radiology, The First People's Hospital of Longquanyi District, Chengdu, China,* [2] *Department of Rehabilitation, The First People's Hospital of Longquanyi District, Chengdu, China*

Objective: To explore the differences among volumetric CT dose index ($CTDI_{vol}$), body-specific dose assessment ($SSDE_{ED}$) based on effective diameter (ED), and $SSDE_{WED}$ based on water equivalent diameter (WED) in evaluating the radiation dose of adult thoracic and abdominal CT scanning.

Methods: From January 2021 to October 2021, enhanced chest CT scans of 100 patients and enhanced abdomen CT scans of another 100 patients were collected. According to the body mass index (BMI), they can be divided into groups A and D (BMI $<$ 20 kg/m^2), groups B and E (20 kg/m^2 $\leq$ BMI $\leq$ 24.9 kg/m^2), and groups C and F (BMI $>$ 24.9 kg/m^2). The CTDIvol, anteroposterior diameter (AP), and the left and rght diameter (LAT) of all the patients were recorded, and the ED, water equivalent diameter (WED), the conversion factor ($f_{size,ED}$), ($f_{size,WED}$), $SSDE_{ED}$, and $SSDE_{WED}$ were calculated. The differences were compared between the different groups.

Results: The AP, LAT, ED, and WED of groups B, E, C, and F were higher than those of groups A and D, and those of groups C and F were higher than those of groups B and E ($P < 0.05$). The $f_{size,ED}$ and $f_{size,WED}$ of groups B, E, C, and F are lower than those of groups A and D, and those of groups C and F are lower than those of groups B and E ($P < 0.05$). $CTDI_{vol}$, $SSDE_{ED}$, and $SSDE_{WED}$ in groups B, E, C, and F are higher than those in groups A and D, and those in groups C and F are higher than those in groups B and E ($p < 0.05$). In the same group, patients with chest- and abdomen-enhanced have higher $SSDE_{WED}$ and $SSDE_{ED}$ than $CTDI_{vol}$, patients with chest-enhanced CT scans have higher $SSDE_{WED}$ than $SSDE_{ED}$, and patients with abdomen-enhanced CT scans have higher $SSDE_{ED}$ than $SSDE_{WED}$ ($P < 0.05$).

Conclusion: CTDIvol and ED-based SSDEED underestimated the radiation dose of the subject exposed, where the patient was actually exposed to a greater dose. However, $SSDE_{WED}$ based on WED considers better the difference in patient size and attenuation characteristics, and can more accurately evaluate the radiation dose received by patients of different sizes during the chest and abdomen CT scan.

Keywords: volume CT dose index, effective diameter, equivalent diameter of water, body specific dose assessment, CT scanning

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Wenjie Song,
Fourth Military Medical University, China
Feng Qin,
Shanghai Jiao Tong University School of Medicine, China

***Correspondence:**
Fanzi Feng
47991493@qq.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *24 January 2022*
Accepted: *22 February 2022*
Published: *25 March 2022*

Citation:
He J, Dong G, Deng Y, He J, Xiu Z and Feng F (2022) Comparison of Application Value of Different Radiation Dose Evaluation Methods in Evaluating Radiation Dose of Adult Thoracic and Abdominal CT Scan. Front. Surg. 9:860968. doi: 10.3389/fsurg.2022.860968

INTRODUCTION

With the rapid development of clinical diagnosis and treatment and radiology technology, the application and popularity of CT examination are constantly improving, and the ionizing radiation received by patients is also constantly increasing, which has aroused widespread concern about the potential cancer risk (1). The radiation diagnosed by CT is usually higher than that reported, so it is necessary to accurately evaluate and strictly control the radiation dose of CT. At present, the CT radiation dose index ($CTDI_{vol}$) under the reference standard phantom is usually used to characterize the CT radiation dose clinically, and its value reflects the radiation dose output by the CT equipment but does not consider the patient's body shape factor. In the actual scanning process, different objects have different scanning diameters and attenuation coefficients (2). Therefore, it is inaccurate to evaluate the effective dose of CT in patients with $CTDI_{vol}$ index. The research of Kidoh et al. (3) shows that there is a strong correlation between the specific body dose assessment (SSDE) of patients and the average skin dose, which can more accurately estimate the error of radiation dose reduction. Based on the factors of the patient's body shape, American Medical Physics Association proposed to use effective diameter (ED) and water equivalent diameter (WED) to estimate the specific dose assessment (SSDE) based on the patient's body shape to make up and correct the influence of body shape on $CTDI_{vol}$ and other indicators (4). In this study, we compare the differences among $CTDI_{vol}$, ED-based $SSDE_{ED}$, and WED-based $SSDE_{WED}$ in evaluating the radiation dose of CT scan in the chest and the abdomen of adults with different body mass index (BMI) and discuss the further application of different radiation dose evaluation methods in clinic to provide a reference for clinical research.

DATA AND METHODS

General Information

Enhanced chest CT scans of 100 patients and enhanced abdomen CT scans of another 100 patients were collected from January 2021 to October 2021 in our hospital. Inclusion criteria: patients and families members' informed consent; complete clinical image data; clear image, which can meet the research requirements; no metal artifact affecting the radiation dose. Among 200 patients, there were 118 men and 82 women, 21–72 years of age with an average of (48.92 ± 7.24) years, and a body mass index (BMI) of (24.02±3.19) kg/m^2. This study was approved by the Ethics Committee of our hospital, and the patients and their families provided informed consent.

Research Methods

GE 128-slice spiral CT scanner was used. The patient was placed in the supine position, feet moved forward, hands raised. The chest scanning was from the top of the lung to the bottom of the lung and abdominal scanning was from the top of the liver to the lower pole of both the kidneys. During the scan, the patient was told to hold his/her breath. The scanning parameters are: adopting automatic tube current modulation technology, the tube current is 80–370 mAs, the tube voltage is 120 kV, the detector collimation is 64 lli.625 mm, the screw pitch is 0.993, and the X-ray tube rotation time is 0.75 s. All scanned images were transmitted to the image storage and transmission system for measurement, and CTDIvol of all patients was recorded. The anteroposterior diameter (AP) and left-right diameter (LAT) of all the patients were measured (at the level of left renal vein trunk and nipple) using workstation measurement software, and $ED = \sqrt{AP \times ALT}$, conversion factor $(f_{size,ED}) = a \times e^{-b \times ED}$, and $SSDE_{ED} = ff_{size,ED} \times CTDI_{vol}$ were calculated at the same time (5).

An elliptical ROI was selected, including the whole section (except the bed board), the average CT value and area (A) of ROI was recorded, and the $WED = \sqrt{(2)}\left(\frac{CT}{1000} + 1\right) \times \frac{A}{}$, the conversion factor $(f_{size,WED}) = a \times e^{-b \times WED}$, and $SSDE_{WED} = f_{size,WED} \times CTDI_{vol}$ for each patient was calculated. In this examination, all subjects used a 16-cm phantom in the scanning except the scout, and the other four enhanced scans used a 32-cm standard phantom to obtain $CTDI_{vol}$ values (6).

A total of 100 patients with enhanced chest CT scanning and 100 patients with enhanced abdomen CT scanning were divided into groups according to BMI. Patients with enhanced chest CT scan were divided into 30 patients in group A (BMI < 20 kg/m^2), 36 patients in group B (20 $kg/m^2 \leq$ BMI $\leq$ 24.9 kg/m^2), and 34 patients in group C (BMI > 24.9 kg/m^2). Patients with abdominal enhanced CT scan were divided into 31 patients in group D (BMI < 20 kg/m^2), 35 patients in group E (20 $kg/m^2 \leq$ BMI $\leq$ 24.9 kg/m^2), and 34 patients in group F (BMI > 24.9 kg/m^2).

Statistical Methods

SPSS22.0 software was used for processing, experimental data were measured using mean standard deviation (±s), and one-way analysis of variance was used to compare the differences between the groups in AP, LAT, ED, $f\,size_{ED}$, WED, and $f\,size_{WED}$, respectively. The differences of CTDIvol, $SSDE_{ED}$, and $SSDE_{WED}$ among different BMI groups were compared using the *t*-test. The test level is $\alpha = 0.05$, and the difference is statistically significant when $P < 0.05$.

RESULTS

Comparison of AP, LAT, ED, $f_{size,ED}$, WED, and $f_{size,WED}$ in Patients With Enhanced Chest CT Scan

The AP, LAT, ED, and WED of groups B and C are all higher than those of group A, and that of group C is higher than that of group B, with statistical significance ($P < 0.05$). The $f_{size,ED}$ and $f_{size,WED}$ of group B and C are lower than that of group A, and that of group C is lower than that of group B ($P < 0.05$), as shown in **Table 1**.

Comparison of $CTDI_{vol}$, $SSDE_{ED}$, and $SSDE_{WED}$ in Patients With Enhanced Chest CT Scan

The values of $CTDI_{vol}$, $SSDE_{ED}$, and $SSDE_{WED}$ in groups B and C are higher than those in group A, and those in group C are higher

TABLE 1 | Comparison of AP, LAT, ED, $f_{size,ED}$, WED and $f_{size,WED}$ in patients with enhanced chest CT scan (n,±s).

Group	AP (cm)	LAT (cm)	ED (cm)	$f_{size,ED}$	WED (cm)	$f_{size,WED}$
Group A ($n = 30$)	21.63 ± 62.14	30.19 ± 12.51	25.55 ± 51.71	1.44 450.07	20.91 ± 91.45	1.71 790.13
Group B ($n = 36$)	22.65 ± 62.67[a]	32.17 ± 12.73[a]	26.99 ± 91.92[a]	1.37 390.06[a]	22.81 ± 81.52[a]	1.59 580.09[a]
Group C ($n = 34$)	24.99 ± 92.81[ab]	35.04 ± 03.05[ab]	29.59 ± 52.27[ab]	1.25 250.04[ab]	26.17 ± 11.96[ab]	1.41 410.08[ab]
F-value	14.496	24.847	34.461	98.750	82.678	72.400
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Compared with group A, [a]P < 0.05. Compared with group B, [b]P < 0.05.

TABLE 2 | Comparison of $CTDI_{vol}$, $SSDE_{ED}$, and $SSDE_{WED}$ in patients with enhanced chest CT scan (*n*, ±s).

Group	$CTDI_{vol}$ (mGy)	$SSDE_{ED}$ (mGy)	$SSDE_{WED}$ (mGy)
Group A ($n = 30$)	3.74 7 0.61	5.32 3 0.73[c]	6.34 3 1.04[cd]
Group B ($n = 36$)	4.36 3 0.67[a]	5.89 8 0.89[ac]	6.90 9 1.02[acd]
Group C ($n = 34$)	6.53 5 0.75[ab]	8.03 0 1.16[abc]	9.12 1 1.48[abcd]
F-value	151.948	74.670	50.612
P-value	<0.001	<0.001	<0.001

Compared with group A, [a]P < 0.05. Compared with group B, [b]P < 0.05. Compared with CTDIvol in the same group, [c]P < 0.05. Compared with $SSDE_{ED}$ in the same group, [d]P < 0.05.

than those in group B, with statistical significance ($P < 0.05$). In the same group, $SSDE_{ED}$ and $SSDE_{WED}$ were higher than $CTDI_{vol}$; $SSDE_{WED}$ was higher than $SSDE_{ED}$; and the difference was statistically significant ($p < 0.05$), as shown in **Table 2**.

Comparison of AP, LAT, ED, $f_{size,ED}$, WED, and $f_{size,WED}$ in Patients With Abdominal CT Enhanced Scanning

The AP, LAT, ED, and WED of groups E and F are all higher than those of group D, and those of group F are higher than those of group E, with statistical significance ($P < 0.05$). The $f_{size,ED}$ and $f_{size,WED}$ of group E and F are lower than those of group D, and that of group F is lower than that of group E, with statistical significance ($P < 0.05$), as shown in **Table 3**.

Comparison of $CTDI_{vol}$, $SSDE_{ED}$, and $SSDE_{WED}$ in Patients With Abdominal CT Enhanced Scanning

The values of $CTDI_{vol}$, $SSDE_{ED}$, and $SSDE_{WED}$ in groups E and F are higher than those in group D, and those in group F are higher than those in group E, with statistical significance ($p < 0.05$). In the same group, $SSDE_{ED}$ and $SSDE_{WED}$ were higher than $CTDI_{vol}$, $SSDE_{ED}$ was higher than $SSDE_{WED}$, and the difference was statistically significant ($P < 0.05$), as shown in **Table 4**.

DISCUSSION

The area on the parallel lines along the axis (z) under the single-layer scanning dose distribution curve is denoted by CDTI. Due to some limitations in its measurement, $CDTI_{100}$, $CDTI_W$, and $CTDI_{vol}$ were subsequently exported. $CTDI_{vol}$ can be used to compare the radiation doses from different CT scanners. $CTDI_{vol}$ represents the radiation dose value of one-layer images along the rotation axis, which is the radiation dose output level calculated based on the standard phantom. However, it has nothing to do with the scanning length. It reflects the radiation dose level output of the equipment, rather than the radiation dose received by patients, and can not truly reflect the radiation dose assessment received by patients with different body types (7, 8). Therefore, when $CTDI_{vol}$ is used to evaluate the radiation dose received by patients, the problem of underestimating the radiation dose received by patients with low body weight will appear (9). $CTDI_{vol}$ is very sensitive to the changes of scanning parameters, such as tube voltage, tube current, X-ray tube rotation time, etc. For different human bodies, its scanning diameter is different and the radiation dose is different. The emergence of SSDE parameter solves this problem.

Body-specific dose estimation is a CT dose estimation value corrected by the patient's body shape. It is obtained by standardizing $CTDI_{vol}$ with f on the basis of $CTDI_{vol}$. Considering f, a factor related to the patient's body shape, it can more accurately evaluate the actual radiation dose received by the patient (10). Australia, New Zealand, and other countries have suggested using SSDE in chest examination to establish the dose reference (11, 12). The results show that with the increase of BMI, AP, LAT, ED, and WED of different types of patients' chest and abdomen enhanced CT scans all increased to varying degrees, while $f_{size,ED}$, $f_{size,WED}$ showed a downward trend. In this study, the standard phantom with a diameter of 32 cm was used, but the ED of abdominal CT scan in most patients was <30 cm, and only 6 patients had an ED that fluctuated in the range of 30–32 cm, which was obviously different from that of the standard phantom. This study also shows that $CTDI_{vol}$ is used to evaluate the radiation dose in enhanced CT scans of the chest and abdomen, which is obviously lower than that of $SSDE_{ED}$ and $SSDE_{WED}$, and there is a problem of underestimating the actual radiation dose.

The SSDE effectively makes up for the deficiency of $CTDI_{vol}$ in body shape difference and tissue attenuation. Based on the method of ED evaluation, it is assumed that the patient's body cross-section is elliptical, and the internal components are all water, and then the circle diameter F equal to the elliptical area is used to correct. However, it is not suitable for this changeable and irregular geometric shape of the human body, and the radiation

TABLE 3 | Comparison of AP, LAT, ED, $f_{size,ED}$, WED, and $f_{size,WED}$ in patients with abdominal CT enhanced scanning (n, ±s).

Group	AP (cm)	LAT (cm)	ED (cm)	$f_{size,ED}$	WED (cm)	$f_{size,WED}$
Group D ($n = 31$)	18.92 ± 91.84	27.84 ± 82.01	22.95 ± 91.24	1.59 590.17	23.82 ± 82.06	1.54 580.18
Group E ($n = 35$)	20.16 ± 11.97[a]	29.23 ± 2.27[a]	24.28 ± 21.37[a]	1.51 520.15[a]	25.68 ± 62.21[a]	1.44 460.16[a]
Group F ($n = 34$)	21.75 ± 72.03[ab]	31.49 ± 42.64[ab]	26.17 ± 11.52[ab]	1.41 410.13[ab]	28.94 ± 92.74[ab]	1.27 290.13[ab]
F-value	17.223	20.469	211.461	64.629	39.462	22.746
P-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Compared with group D, [a]P < 0.05. Compared with group E, [b]P < 0.05.

TABLE 4 | Comparison of $CTDI_{vol}$, $SSDE_{ED}$ and $SSDE_{WED}$ in patients with abdominal CT enhanced scan (*n*, ±s).

Group	$CTDI_{vol}$ (mGy)	$SSDE_{ED}$ (mGy)	$SSDE_{WED}$ (mGy)
Group D ($n = 31$)	3.52 5 0.55	5.52 5 0.91[c]	5.35 3 0.84[cd]
Group E ($n = 35$)	4.19 1 0.58[a]	6.28 2 0.96[ac]	5.96 9 0.89[acd]
Group F ($n = 34$)	6.09 0 0.69[ab]	8.50 5 1.17[abc]	7.67 6 1.02[abcd]
F-value	155.919	39.510	56.389
P-value	<0.001	<0.001	<0.001

Compared with group D, [a]P < 0.05. Compared with group E, [b]P < 0.05. Compared with CTDIvol in the same group, [c]P < 0.05. Compared with $SSDE_{ED}$ in the same group, [d]P < 0.05.

dose will be underestimated when the tissue density of the CT scan is quite different from that of water (13, 14). The method of calculating radiation dose based on WED can consider the size and X-ray attenuation factors of different parts of the patient's chest and abdomen. It is closely related to X-ray imaging and is suitable for irregular and uneven tissues of the human body (15, 16). However, there are few SSDE based on WED. This study discusses the application of SSDE based on WED calculation in the adult thorax and abdomen by comparing the differences of three different body-specific dose assessments in the body.

The results show that with the increase of BMI, the values of $SSDE_{ED}$ and $SSDE_{WED}$ gradually increase. The $SSDE_{WED}$ of patients with enhanced CT scan in the chest is higher than that of $SSDE_{ED}$, while that of patients with enhanced CT scan in the abdomen is lower than that of $SSDE_{ED}$. Since the air content in the chest is obviously lower than that in the water model and the overall attenuation in the chest area is obviously lower than that in the water model, the average CT value corresponding to X-ray attenuation *in vivo* is negative, while the density of abdomen tissues is roughly the same as that in the water model, the overall attenuation is consistent with that in the water model, and the average CT value corresponding to X-ray attenuation is positive. With the increase of BMI, the difference between $SSDE_{ED}$ and $SSDE_{WED}$ also gradually increases (17).

There are still some limitations in this research. This study involves only adult patients. Some studies based on ED $SSDE_{ED}$ show that it is meaningful for infants and young children (18). At the same time, the number of cases distributed in different BMI ranges is relatively small, which needs to be further discussed in the follow-up study.

To sum up, CTDIvol and ED-based SSDEED underestimated the radiation dose to which the subject was exposed, and the patient was actually exposed to a greater dose. However, $SSDE_{WED}$ based on WED better considers the difference in patient size and attenuation characteristics, and can more accurately evaluate the radiation dose received by patients of different sizes during the chest and abdomen CT scan.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was approved by the Medical Ethics Committee of the First People's Hospital of Longquanyi District. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JiH is responsible for the writing of the paper. GD is responsible for the design of the study. YD is responsible for the inclusion of cases. JuH is responsible for the evaluation of the results. ZX is responsible for the statistics of the data. FF is responsible for the guidance of the entire study. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Garba I, Zarb F, McEntee MF, Fabri SG. Computed tomography diagnostic reference levels for adult brain, chest and abdominal examinations: a systematic review. *Radiography (Lond).* (2021) 27:673–81. doi: 10.1016/j.radi.2020.08.011
2. Sun J, Li H, Li J, Yu T, Li M, Zhou Z, et al. Improving the image quality of pediatric chest CT angiography with low radiation dose and contrast volume

using deep learning image reconstruction. *Quant Imaging Med Surg.* (2021) 11:3051–8. doi: 10.21037/qims-20-1158
3. Kidoh M, Utsunomiya D, Oda S, Funama Y, Yuki H, Nakaura T, et al. Validity of the size-specific dose estimate in adults undergoing coronary CT angiography: comparison with the volume CT dose index. *Int J Cardiovasc Imaging.* (2015) 2:205–11. doi: 10.1007/s10554-015-0782-z
4. Haba T, Koyama S, Kinomura Y, Ida Y, Kobayashi M. Influence of 320-detector-row volume scanning and AAPM report 111 CT dosimetry metrics on size-specific dose estimate: a Monte Carlo study. *Australas Phys Eng Sci Med.* (2016) 39:697–703. doi: 10.1007/s13246-016-0465-7
5. Li B, Behrman RH. Comment on the "report of AAPM TG 204: size-specific dose estimates (SSDE) in pediatric and adult body CT examinations" [report of AAPM TG 204, 2011]. *Med Phys.* (2012) 39:4613–4. doi: 10.1118/1.4725756
6. Gabusi M, Riccardi L, Aliberti C, Vio S, Paiusco M. Radiation dose in chest CT: assessment of size-specific dose estimates based on water-equivalent correction. *Phys Med.* (2016) 32:393–7. doi: 10.1016/j.ejmp.2015.12.008
7. Demb J, Chu P, Yu S, Whitebird R, Solberg L, Miglioretti DL, et al. Analysis of computed tomography radiation doses used for lung cancer screening scans. *JAMA Intern Med.* (2019) 179:1650–7. doi: 10.1001/jamainternmed.2019.3893
8. Konishi T, Shibutani T, Okuda K, Yoneyama H, Moribe R, Onoguchi M, et al. Metal artifact reduction for improving quantitative SPECT/CT imaging. *Ann Nucl Med.* (2021) 35:291–8. doi: 10.1007/s12149-020-01560-w
9. Özsoykal I, Yurt A, Akgüngör K. Size-specific dose estimates in chest, abdomen, and pelvis CT examinations of pediatric patients. *Diagn Interv Radiol.* (2018) 24:243–8. doi: 10.5152/dir.2018.17450
10. Anam C, Haryanto F, Widita R, Arif I, Dougherty G, McLean D. The impact of patient table on size-specific dose estimate (SSDE). *Australas Phys Eng Sci Med.* (2017) 40:153–8. doi: 10.1007/s13246-016-0497-z
11. Jackson D, Atkin K, Bettenay F, Clark J, Ditchfield MR, Grimm JE, et al. Paediatric CT dose: a multicentre audit of subspecialty practice in Australia and New Zealand. *Eur Radiol.* (2015) 25:3109–22. doi: 10.1007/s00330-015-3727-y
12. Hwang JY, Choi YH, Yoon HM Ryu YJ, Shin HJ, Kim HG, et al. Establishment of local diagnostic reference levels of pediatric abdominopelvic and chest CT examinations based on the body weight and size in Korea. *Korean J Radiol.* (2021) 22:1172–84. doi: 10.3348/kjr.2020.0890
13. Bashier EH, Suliman II. Multi-slice CT examinations of adult patients at Sudanese hospitals: radiation exposure based on size-specific dose estimates (SSDE). *Radiol Med.* (2018) 123:424–310. doi: 10.1007/s11547-018-0859-6
14. Kidoh M, Utsunomiya D, Oda S, Nakaura T, Funama Y, Yuki H, et al. Breast dose reduction for chest CT by modifying the scanning parameters based on the pre-scan size-specific dose estimate (SSDE). *Eur Radiol.* (2017) 27:2267–74. doi: 10.1007/s00330-016-4618-6
15. Xu J, He X, Xiao H, Xu J. Comparative study of volume computed tomography dose index and size-specific dose estimate head in computed tomography examination for adult patients based on the mode of automatic tube current modulation. *Med Sci Monit.* (2019) 25:71–6. doi: 10.12659/MSM.913927
16. Bostani M, McMillan K, Lu P, Kim GH, Cody D, Arbique G, et al. Estimating organ doses from tube current modulated CT examinations using a generalized linear model. *Med Phys.* (2017) 44:1500–13. doi: 10.1002/mp.12119
17. Fujii K, Nomura K, Muramatsu Y, Goto T, Obara S, Ota H, et al. Correlation analysis of organ doses determined by Monte Carlo simulation with dose metrics for patients undergoing chest-abdomen-pelvis CT examinations. *Phys Med.* (2020) 77:1–9. doi: 10.1016/j.ejmp.2020.07.016
18. Imai R, Miyazaki O, Horiuchi T, Kurosawa H, Nosaka S. Local diagnostic reference level based on size-specific dose estimates: assessment of pediatric abdominal/pelvic computed tomography at a Japanese national children's hospital. *Pediatr Radiol.* (2015) 45:345–53. doi: 10.1007/s00247-014-3189-4

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 He, Dong, Deng, He, Xiu and Feng. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 28 March 2022
doi: 10.3389/fsurg.2022.862676

Effects of Nifedipine Tablets Combined With Magnesium Sulfate on Blood Coagulation Index, Oxidative Stress, NO and ET-1 Levels in Patients With Pregnancy Hypertension

*Xiaomei Yu and Qiang Zhou**

Department of Obstetrics, Weifang People's Hospital, Weifang, China

Objective: To explore the effects of nifedipine tablets combined with magnesium sulfate on blood coagulation indexes, oxidative stress and levels of NO and ET-1 in patients with Pregnancy-induced hypertension syndrome (PIH).

Methods: A total of 110 patients with hypertension during pregnancy were admitted to our hospital from January 2020 to January 2021. According to the random number table method, 110 patients were divided into the control group and the therapy group, with 55 cases in each group. The blood pressure levels (systolic and diastolic blood pressure), coagulation indexes (TT, PT, APTT, Fib), oxidative stress indexes (LPO, MDA, SOD), vascular endothelial function (ET-1, NO), clinical efficacy and adverse reactions of the two groups were compared.

Results: After therapy, the systolic blood pressure and diastolic blood pressure of the two groups were significantly decreased, and the therapy group was significantly lower than the control group ($P < 0.05$). After therapy, PT, TT, and APTT in two groups were significantly increased, and Fib was significantly decreased, and PT, TT, APTT in the therapy group were higher than those in the control group, and Fib was lower than that in the control group ($P < 0.05$). After therapy, LPO and MDA in two groups were significantly decreased, and SOD was significantly increased, and LPO and MDA in the therapy group were lower than those in the control group, and SOD was higher than that in the control group ($P < 0.05$). After therapy, ET-1 in two groups were significantly increased, and NO and ET-1/NO was significantly decreased, and ET-1 in the therapy group was higher than that in the control group, and NO and ET-1/NO were lower those in the control group ($P < 0.05$). The total clinical effective rate of patients in the therapy group was 94.5%, and in the control group was 81.8%, the therapy group was significantly better than the control group ($P < 0.05$). The total incidence of adverse reactions in the therapy group was 7.3%, and in the control group was 21.8%, the therapy group was significantly lower than the control group ($P < 0.05$).

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Li Zhu,
Central South University, China
Jing Xu,
Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, China

****Correspondence:***
Qiang Zhou
zhouqiang198312210@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *26 January 2022*
Accepted: *22 February 2022*
Published: *28 March 2022*

Citation:
Yu X and Zhou Q (2022) Effects of Nifedipine Tablets Combined With Magnesium Sulfate on Blood Coagulation Index, Oxidative Stress, NO and ET-1 Levels in Patients With Pregnancy Hypertension. Front. Surg. 9:862676. doi: 10.3389/fsurg.2022.862676

Conclusion: Nifedipine tablets combined with magnesium sulfate in the treatment of PIH can improve the blood coagulation function of patients, reduce oxidative stress damage, adjust the serum levels of ET-1 and NO, and improve the clinical efficacy.

Keywords: nifedipine tablets, magnesium sulfate, pregnancy-induced hypertension, coagulation indicators, oxidative stress, NO, ET-1

INTRODUCTION

Pregnancy-induced hypertension syndrome (PIH) is also known as pregnancy-induced hypertension. It usually occurs at 20 weeks of gestation or 2 weeks after delivery. In addition to high blood pressure, it can also be accompanied by edema, proteinuria, thrombocytopenia, and liver Clinical manifestations such as functional impairment (1, 2). PIH is more harmful to mothers and babies. It can cause high-risk complications such as miscarriage and postpartum hemorrhage. It greatly increases the risk of maternal delivery and affects the outcome of pregnancy. It is one of the main factors leading to maternal and perinatal death. Studies have shown that PIH is not treated in time, it will cause systemic dysfunction, secondary coma, convulsions, etc., and the main lesion of PIH is the spasm of arterioles in the whole body, which leads to the vasospasm of important organs in the whole body. Therefore, it is necessary not only to effectively control blood pressure during treatment, the key is to relieve the spasm (3). At present, the clinical treatment of hypertension in pregnancy is mainly based on drug therapy, which to a certain extent can help relieve patients' spasms, reduce patients' blood pressure, and reduce and improve cardiac load at the same time. However, in the course of drug treatment, certain drugs will inevitably cause a certain degree of damage to the fetus. Therefore, care must be taken in the choice of drugs during the treatment process. At present, the main drugs used in the treatment of pregnancy-induced hypertension are magnesium sulfate and nifedipine tablets. Nifedipine tablets can inhibit the influx of calcium ions into the cells by obstructing the membrane transport of calcium ions in the myocardium and vascular smooth muscle, which increases the coronary blood flow and improves the tolerance of the myocardium to ischemia, thereby achieving the effect of lowering blood pressure (4, 5). Magnesium sulfate can inhibit the central nervous system, relax skeletal muscles, have the effects of sedation, antispasm, and reduce intracranial pressure. It is often used to treat convulsions, eclampsia, uremia, tetanus and hypertensive encephalopathy (6). Nitric oxide (NO) is the most representative endogenous relaxing factor, and Endothelin-1 (ET-1) is a strong vasoconstrictor found so far, which is related to inflammatory reactions In the process, monocyte infiltration is related, and it is a type of inflammatory cytokines with chemotactic function (7, 8), but the expression of the two in the serum of gestational diabetes patients is currently unclear. Therefore, the purpose of this study is to treat patients with pregnancy-induced hypertension through the clinical efficacy of nifedipine tablets combined with magnesium sulfate intervention, as well as the effects of patients' blood coagulation, oxidative stress indicators, and NO and ET-1 levels.

MATERIALS AND METHODS

General Information and Grouping

A total of 110 patients with hypertension during pregnancy were admitted to our hospital from January 2020 to January 2021. According to the random number table method, 110 patients were divided into the control group and the therapy group, with 55 cases in each group. The patients in the therapy group were 21–36 years old, with an average age of (29.64 ± 2.13) years; 40 cases of primiparas and 15 cases of postpartum women; gestational age was 32–40 weeks, with an average of (36.02 ± 2.13) weeks; systolic blood pressure was 141–165 mmHg, average systolic blood pressure (153.64 ± 2.13) mmHg; diastolic blood pressure 93–109 mmHg, average diastolic blood pressure (96.15 ± 2.58) mmHg. The control group was 22–35 years old, with an average age of (28.95 ± 2.06) years; 38 cases of primiparous women and 17 cases of postpartum women; gestational age was 33–39 weeks, with an average of (35.67 ± 2.01) weeks; systolic blood pressure was 140–161 mmHg, The average systolic blood pressure was (151.38 ± 2.06) mmHg; the diastolic blood pressure was 91–105 mmHg, and the average diastolic blood pressure was (93.06 ± 2.11) mmHg. All patients met the relevant diagnostic criteria of our hospital for pregnancy-induced hypertension. There was no statistically significant difference between the two groups of patients in general information such as age, gestational age, and birth experience ($P > 0.05$).

Inclusion Criteria

All patients were diagnosed with pregnancy-induced hypertension, systolic blood pressure ≧140 mmHg and diastolic blood pressure ≧90 mmHg, accompanied by proteinuria 0.3 g/24 h, or random urine protein (+). All patients underwent routine fundus examination, blood coagulation function examination, biochemical index examinations such as heart, liver, kidney function, blood electrolytes, fetal growth and development index examination, cardiac ultrasonography, liver, gallbladder, spleen and kidney ultrasound examination to rule out important organ diseases. This subject was approved by the hospital ethics committee, and the patients and their families voluntarily participated in this experiment and signed an informed consent form.

Exclusion Criteria

Patients with history of hypertension, history of diabetes, abnormal blood biochemistry and urine tests before pregnancy. Patients with liver, kidney and other organ diseases. Those who were allergic to the drugs used in this study. Complicated

with hematological diseases. Combined with malignant tumor. Cognitive impairment. Incomplete clinical data.

Treatment Methods

Patients in the control group were given magnesium sulfate intervention treatment. The total dosage of magnesium sulfate was 20 g for 24 h on the 1st day; the loading dose was 25% magnesium sulfate injection (Hangzhou Minsheng Medical Liquid Co., Ltd., product batch number 1409281, National Medicine Standard H33021961) 20 ml (5 g) Dilute with 20 ml of 5% glucose injection, and slowly inject intravenously within 15–20 min; then used a maintenance meter, that was, 60 ml (15 g) of 25% magnesium sulfate and dilute with 500 ml of 5% glucose injection for intravenous infusion, 1–2 g/h intravenous drip for maintenance. After that, 60 ml (5 g) of magnesium sulfate was used daily. Knee tendon reflex examinations should be done regularly before and during medication to measure the patient's breathing frequency and urine output. If the knee tendon reflex was found to be significantly weakened or disappeared, or the number of breaths was <16 times/min, the patient's urine output was <25 ml/h, the medication should be stopped immediately, 7 days as a course of treatment. On the basis of the control group, the therapy group was given nifedipine (CSPC Ouyi Pharmaceutical Co., Ltd., approval number: H13021315), 3 times a day, 10 mg each time, orally with warm water, 7 days as a course of treatment.

The principle of medication is to be treated in strict accordance with the treatment standards for hypertension in pregnancy in the Guidelines for the Diagnosis and Treatment of Hypertension in Pregnancy. During the administration and treatment of the two groups of patients, the relevant medical staff should pay close attention to the patients' usual urine output, fetal heart rate, respiration, and magnesium ion levels to prevent the patients from experiencing poisoning symptoms. And during the treatment, the patient's blood pressure, heart rate, and breathing changes are recorded in detail, and adverse reactions and changes in symptoms such as dizziness and headache are observed. Record the occurrence of pregnancy complications.

Observation Indicators

Blood Pressure Detection

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the two groups of patients before and after therapy were measured and compared.

Coagulation Index

Before and after therapy, 5 ml of fasting cubital venous blood was collected from the two groups of patients in the morning during the obstetric examination, centrifuged at 3,500 r/min for 10 min to take the upper serum, and placed in the refrigerator at -80°C for later use. Use CA8000 automatic blood coagulation analyzer (Syames, Japan) and supporting kits to measure coagulation function related indexes, including prothrombin time (PT), thrombin time (TT), fibrinogen (Fib), activated thrombin Original time (APTT).

Oxidative Stress Indicators

Take the sera of the two groups of patients in 1.5.2, and ELISA kit (Jiangsu Kejing Biological Company) to detect the serum levels of lipid peroxide (LPO), malondialdehyde (MDA), and superoxide dismutase (SOD).

Vascular Endothelial Function

Take the serum of the two groups of patients in 1.5.2, use the BS-800 automatic biochemical analyzer (Zhengzhou Nanbei Instrument Equipment Co.Ltd.) to detect serum endothelin 1 (ET-1), nitric oxide (NO) and ET-1/ NO level.

Judgment of Clinical Efficacy

Compare the clinical effects of the therapy group and the control group. Significantly effective: after therapy, the patient's systolic blood pressure is less than or equal to 140 mmHg, and the diastolic blood pressure is less than or equal to 90 mmHg; or the patient's systolic blood pressure drops >30 mmHg, and the diastolic blood pressure drops >15 mmHg; the patient's dizziness, headache and abdominal discomfort and other clinical symptoms have basically disappeared, and no postpartum complications appear. Effective: after therapy, the patient's systolic blood pressure is $\geqq$140 and $\leqq$150 mmHg, and the diastolic blood pressure is $\geqq$90 and $\leqq$100 mmHg. The clinical symptoms such as dizziness, headache, and abdominal discomfort are significantly improved, and no postpartum complications occur. Ineffective: after therapy, the patient has systolic blood pressure $\geqq$150 mmHg, diastolic blood pressure $\geqq$100 mmHg, clinical symptoms are not improved or even worsened, with mild edema and proteinuria.

Adverse Reactions

Observe and record the occurrence of adverse pregnancy outcomes such as premature birth, postpartum hemorrhage, fetal distress, and very low birth weight infants in the two groups.

Statistical Methods

Graphpad priam 8.0 software was used for data analysis, and the measurement data were expressed as mean $\pm$ standard deviation. The t-test was in accordance with the normal distribution, and the Wilcoxon test was not in accordance with the normal distribution. The measurement data used χ^2, and $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of Blood Pressure Levels Between the Two Groups

Before therapy, there was no significant difference in systolic blood pressure and diastolic blood pressure between the two groups ($P > 0.05$). After therapy, the systolic blood pressure and diastolic blood pressure of the two groups were significantly decreased, and the therapy group was significantly lower than the control group ($P < 0.05$) (**Figure 1**).

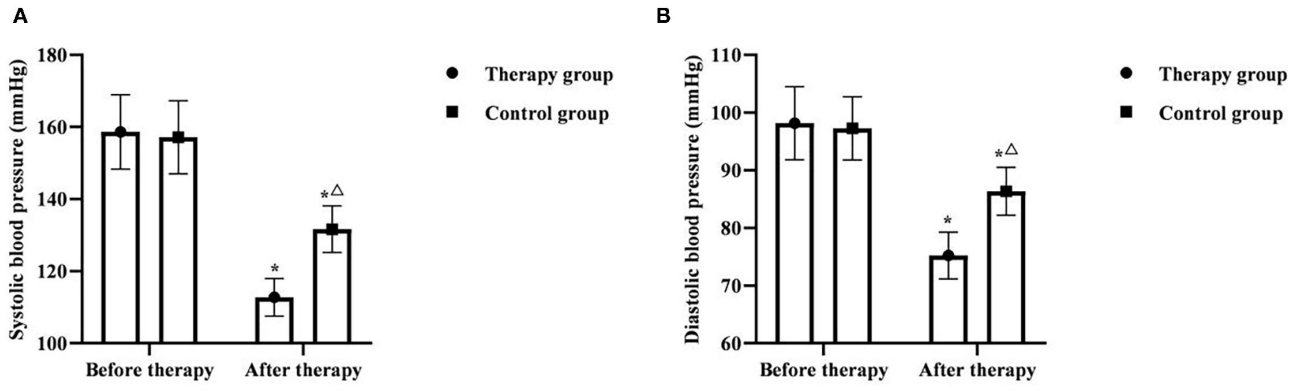


FIGURE 1 | Comparison of blood pressure levels between the two groups ($x \pm s$, $n = 55$). **(A)** was comparison of systolic blood pressure between the two groups. **(B)** was comparison of diastolic blood pressure between the two groups. $^{*}P < 0.05$ was compared with the same group before therapy, $^{\Delta}P < 0.05$ was compared with the control group after therapy.

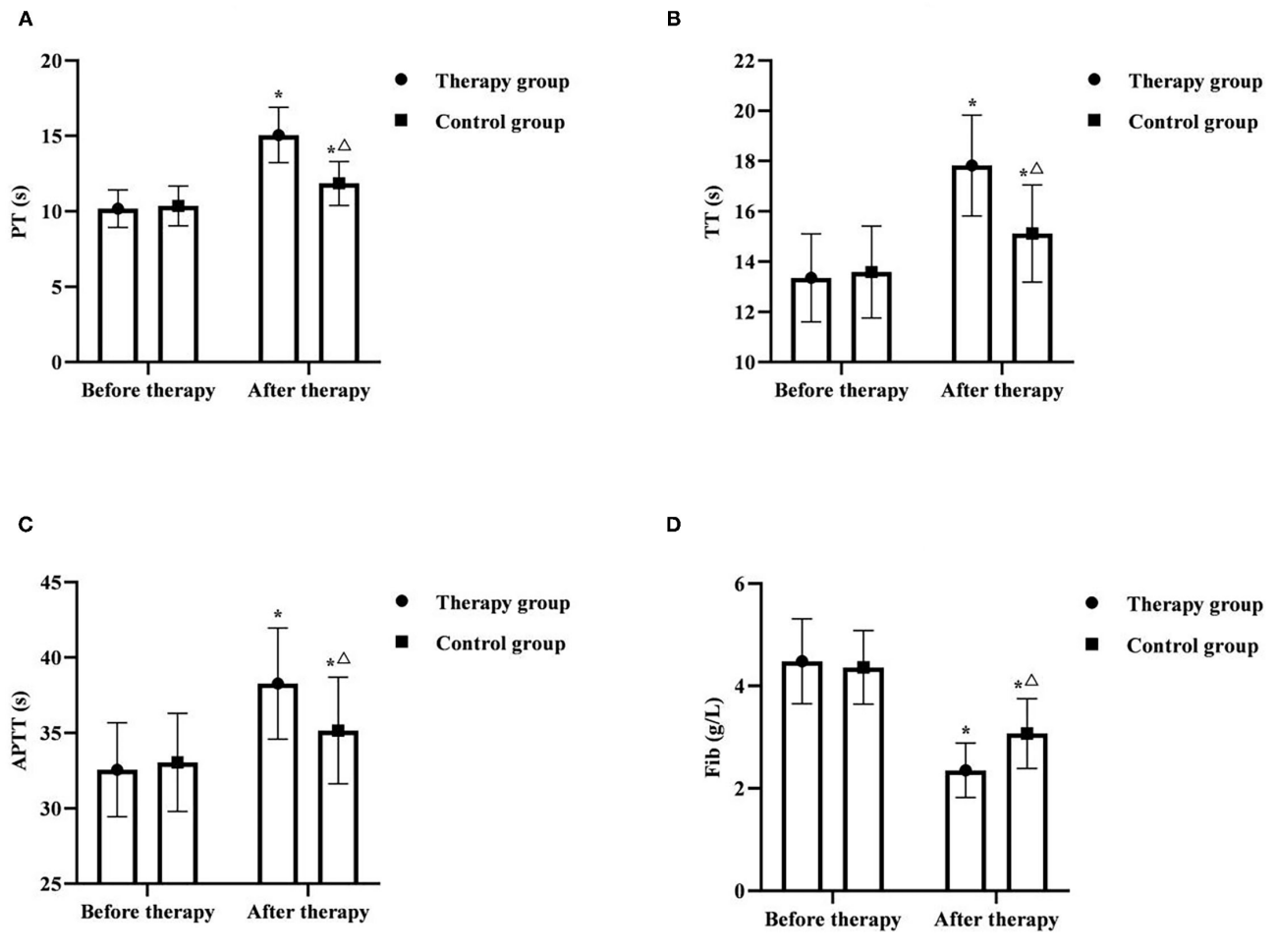


FIGURE 2 | Comparison of coagulation indexes between the two groups ($x \pm s$, $n = 55$). **(A)** was comparison of PT between the two groups. **(B)** was comparison of TT between the two groups. **(C)** was comparison of APTT between the two groups. **(D)** was comparison of Fib between the two groups. $^{*}P < 0.05$ was compared with the same group before therapy, $^{\Delta}P < 0.05$ was compared with the control group after therapy.

Comparison of Coagulation Indexes Between the Two Groups

Before therapy, there was no significant difference in PT, TT, APTT, and Fib between the two groups ($P > 0.05$). After therapy, PT, TT, and APTT in two groups were significantly increased, and Fib was significantly decreased, and PT, TT, APTT in the therapy group were higher than those in the control group, and Fib was lower than that in the control group ($P < 0.05$) (**Figure 2**).

Comparison of Oxidative Stress Indicators Between the Two Groups

Before therapy, there was no significant difference in LPO, MDA and SOD between the two groups ($P > 0.05$). After therapy, LPO and MDA in two groups were significantly decreased, and SOD was significantly increased, and LPO and MDA in the therapy group were lower than those in the control group, and SOD was higher than that in the control group ($P < 0.05$) (**Figure 3**).

Comparison of Vascular Endothelial Function Between the Two Groups

Before therapy, there was no significant difference in ET-1, NO, ET-1/NO between the two groups ($P > 0.05$). After therapy, ET-1 in two groups were significantly increased, and NO and ET-1/NO was significantly decreased, and ET-1 in the therapy group was higher than that in the control group, and NO and ET-1/NO were lower those in the control group ($P < 0.05$) (**Figure 4**).

Comparison of Clinical Efficacy Between the Two Groups

The total clinical effective rate of patients in the therapy group was 94.5%, and the total clinical effective rate of patients in the control group was 81.8%. Compared with the clinical efficacy between the groups, the therapy group was significantly better than the control group, and the difference was statistically significant ($P < 0.05$) (**Table 1** and **Figure 5**).

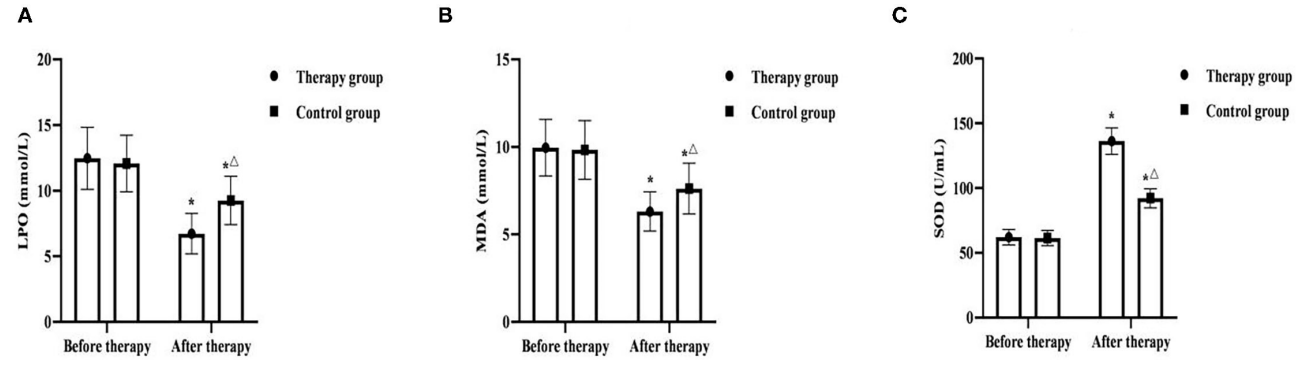


FIGURE 3 | Comparison of oxidative stress indicators between the two groups ($x \pm s$, $n = 55$). **(A)** was comparison of LPO between the two groups. **(B)** was comparison of MDA between the two groups. **(C)** was comparison of SOD between the two groups. $^{*}P < 0.05$ was compared with the same group before therapy, $^{\Delta}P < 0.05$ was compared with the control group after therapy.

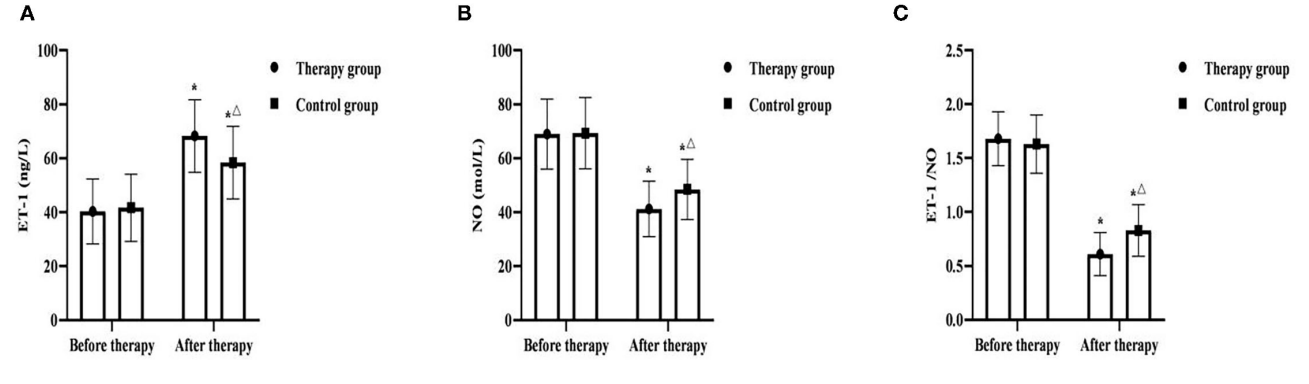


FIGURE 4 | Comparison of vascular endothelial function between the two groups ($x \pm s$, $n = 55$). **(A)** was comparison of ET-1 between the two groups. **(B)** was comparison of NO between the two groups. **(C)** was comparison of ET-1/NO between the two groups. $^{*}P < 0.05$ was compared with the same group before therapy, $^{\Delta}P < 0.05$ was compared with the control group after therapy.

Comparison of Adverse Reactions Between the Two Groups

The total incidence of adverse reactions in the therapy group was 7.3%, and the total incidence of adverse reactions in the control group was 21.8%. The incidence of adverse reactions between the groups was significantly lower in the therapy group than in the control group, and the difference was statistically significant ($P < 0.05$) (**Table 2** and **Figure 6**).

DISCUSSION

Pregnancy hypertension refers to a state in which both increased blood pressure and pregnancy coexist. It has a serious impact on the health of pregnant women and fetuses. If they cannot be effectively controlled in time, they will cause serious consequences with maternal or perinatal death (9). Therefore, how to effectively treat pregnancy-induced hypertension has always been the focus of clinical research. At present, drug therapy is the main treatment method used in clinical practice. The purpose of treatment is mainly to relieve spasm, expand blood volume, reduce blood pressure, sedation, diuresis and termination of pregnancy. However, in the course of drug treatment, certain drugs will inevitably cause a certain degree of harm to the fetus. Therefore, it is necessary to be cautious in the choice of drugs during treatment. Magnesium sulfate is the drug of choice for the treatment of hypertension in pregnancy. It can inhibit the central nervous system and block the conduction at the peripheral neuromuscular joints. It can calm, relieve spasm and relax skeletal muscles; it can also reduce intracranial pressure and relax peripherals. Vascular smooth muscle destroys sympathetic ganglion impulse conduction, promotes vasodilation and lowers blood pressure; in addition, magnesium sulfate also has the effect of accelerating protein metabolism, anti-inflammatory and de-seeding, thereby effectively alleviating the symptoms of proteinuria and edema in patients (10). However, the use of magnesium sulfate alone is prone to adverse reactions, and its use has certain limitations. It has been reported that the combined use of magnesium sulfate and nifedipine tablets can improve the effective rate of clinical treatment. Nifedipine is a calcium antagonist, which can relax vascular smooth muscle, expand blood vessels, reduce peripheral

TABLE 1 | Comparison of clinical efficacy between the two groups ($n = 55$, %).

Group	Markedly effective	Efficient	Invalid	Total effective
Therapy group	45 (81.82)	7 (12.73)	3 (5.45)	52 (94.55)
Control group	30 (54.55)	15 (27.27)	10 (18.18)	45 (81.82)
χ^2				4.274
P				0.039

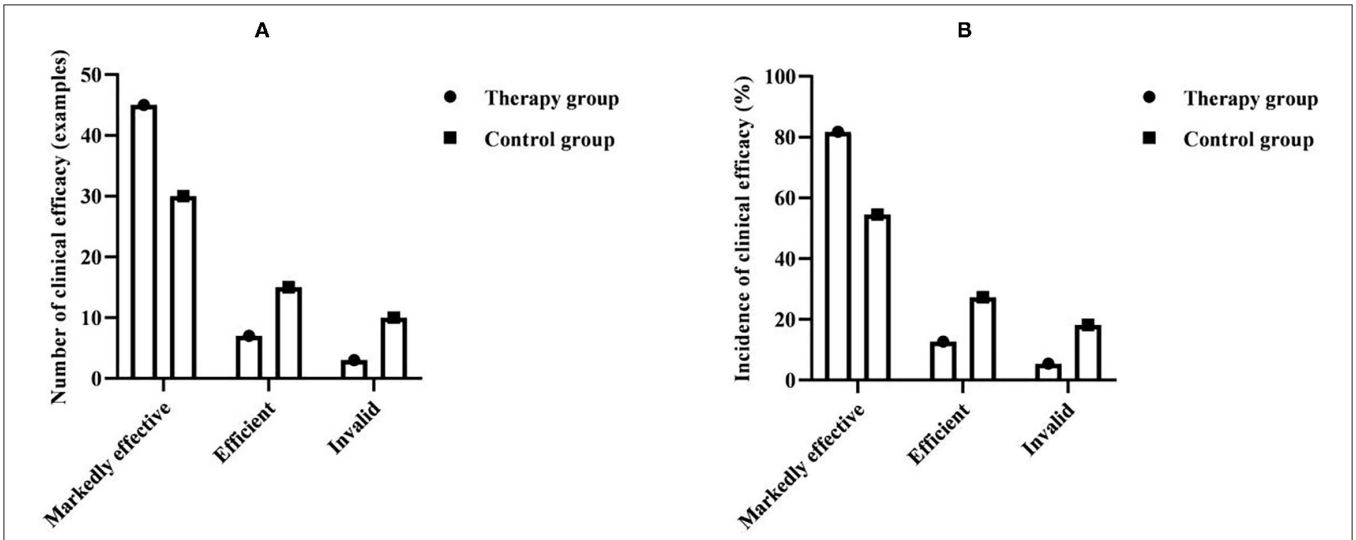


FIGURE 5 | Comparison of clinical efficacy between the two groups ($n = 55$, %). **(A)** Comparison of the number of clinical efficacy between the two groups. **(B)** Comparison of the incidence of clinical efficacy between the two groups.

TABLE 2 | Comparison of adverse reactions between the two groups ($n = 55$, %).

Group	Premature birth	Postpartum hemorrhage	Fetal distress	Very low birth weight infant	Total incidence
Therapy group	3 (5.45)	0 (0.00)	1 (1.82)	0 (0.00)	4 (7.27)
Control group	5 (9.09)	3 (5.45)	3 (5.45)	1 (1.82)	12 (21.82)
χ^2					4.681
P					0.031

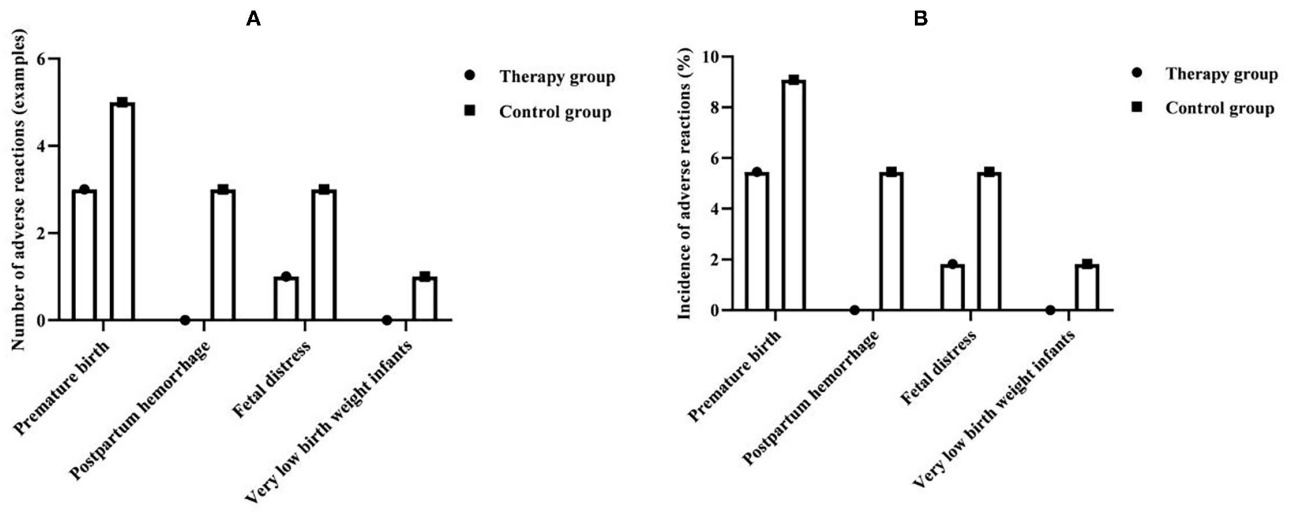


FIGURE 6 | Comparison of adverse reactions between the two groups. **(A)** Comparison of the number of adverse reactions between the two groups. **(B)** Comparison of the incidence of adverse reactions between the two groups.

vascular resistance, lower blood pressure, and it can reduce afterload, suitable for long-term use, and can make up for the defects of magnesium sulfate (11). The results of this study showed that the blood pressure and clinical efficacy of patients in the therapy group were significantly better than those in the control group, and the difference was statistically significant ($P < 0.05$). The results of this study are consistent with the above reports.

When the body's blood coagulation function is abnormal, the blood coagulation function and anticoagulant function in the body will be out of balance (12). The coagulation indexes (TT, PT, Fib, APTT) selected in this study are commonly used indexes for clinical coagulation function tests. TT can indicate the abnormal state of the endogenous coagulation system, PT can indicate the abnormal state of the exogenous coagulation system, Fib can show whether its content in human plasma is at a normal level, and APTT can show the abnormal degree of thrombin activity. It was shown that the blood of patients with pregnancy-induced hypertension was in a hypercoagulable state, with lower TT, PT and APTT levels and higher Fib levels than those of normal pregnant women. The results of this study showed that after therapy, serum TT, PT and APTT levels were higher in the treatment group than in the control group, and Fib levels were lower than in the control group. It was suggested that the combination of nifedipine tablets and magnesium sulfate was effective in improving hypercoagulability in patients with pregnancy-induced hypertension, and was more effective than magnesium sulfate alone. SONG (13) and others have confirmed that nifedipine combined with magnesium sulfate has a good therapeutic effect on patients with pregnancy-induced hypertension, and the clinical effect is significant.

Studies have found that the occurrence and development of hypertension are closely related to the excessive production of reactive oxygen species leading to oxidative stress or the body's ability to resist internal antioxidants (14). In patients with pregnancy-induced hypertension, the activity and content of antioxidant enzymes are found to be low, such as SOD, on the contrary, a large amount of peroxidation products are generated in the body, such as LPO and MDA. Therefore, it is of great significance to explore the level of oxidative stress in patients. The results of this study showed that the oxidative stress level of the two groups of patients after therapy was significantly improved compared with that before treatment, and the serum LPO and MDA of the therapy group were lower than those of the control group, and the SOD level was higher than that of the control group, suggesting that nifedipine tablets combined with magnesium sulfate. It can improve the oxidative stress response of patients with pregnancy-induced hypertension, enhance the body's antioxidant capacity, and reduce the degree of endothelial damage. Vascular endothelial cell injury is one of the pathologies of pregnancy-induced hypertension. After injury, vascular endothelial cells secrete too much vasoconstrictor factor ET, and less secrete vasodilator factor NO (15). ET-1 is the most active endogenous vasoconstrictor peptide found so far, which can promote the proliferation of vascular smooth muscle cells and contract blood vessels. In normal pregnancy, ET-1 is at a normal level, and its increase will cause systemic arteriole spasm, promote the secretion of aldosterone and angiotensin, increase peripheral vascular resistance, and increase blood pressure. The possible mechanism for the increase of ET-1 is that there are endothelial cytotoxic factors that can cause vascular endothelial cell damage in patients with pregnancy-induced hypertension, release a large amount of ET-1 to promote vasoconstriction, and ischemia and hypoxia further aggravate endothelial cell damage, and then form a vicious circle (16). NO is a very active vasodilator released by vascular endothelial cells. It has the effect of inhibiting platelet adhesion, aggregation and vascular smooth

muscle cell growth, and can maintain high blood flow and low blood pressure during healthy pregnancy. Studies have reported that the plasma nitrite level in healthy non-pregnant women is lower than that in healthy pregnant women. The level of NO increases significantly in the first trimester and decreases in the third trimester, and returns to normal after delivery, suggesting a significant increase in NO release during pregnancy (17). The dynamic balance between NO and ET can affect the integrity of endothelial cell function to a large extent, and endothelial cell damage can lead to an imbalance between NO and ET (18, 19). Therefore, the abnormal changes in serum ET-1 and NO levels can reflect abnormal vascular endothelial function. The increase in serum ET-1 level and the decrease in NO concentration are one of the mechanisms of the pathogenesis of pregnancy-induced hypertension. Zhang et al. (20) and other studies have confirmed that nifedipine tablets combined with magnesium sulfate in the treatment of hypertension during pregnancy can increase the effective rate of treatment, improve the patient's hemodynamics, and at the same time regulate the patient's plasma ET-1 and NO levels, and improve the function of vascular endothelial cells, and safe and effective. The results of this study showed that after therapy, ET-1 in two groups were significantly increased, and NO and ET-1/NO was significantly decreased, and ET-1 in the therapy group was higher than that in the control group, and NO and ET-1/NO were lower those in the control group. It was suggested that nifedipine tablets combined with magnesium sulfate can improve the degree of vascular endothelial cell damage in patients with pregnancy-induced hypertension by improving serum ET-1 and NO levels, which is consistent with the above view.

In summary, nifedipine tablets combined with magnesium sulfate in the treatment of pregnancy-induced hypertension can improve the coagulation function of patients, reduce oxidative stress damage, regulate the levels of ET-1 and NO in patients' serum, and improve clinical efficacy.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Weifang People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XY and QZ made equal contributions, including the design of the study, the evaluation of the results, and the writing of the paper. QZ guided the whole study as the supervisor of the whole study. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Djokic V, Jankovic S, Labudovic-Borovic M, Rakocevic J, Stanisic J, Rajkovic J, et al. Pregnancy-induced hypertension decreases Kv1.3 potassium channel expression and function in human umbilical vein smooth muscle. *Eur J Pharmacol.* (2020) 882:173281. doi: 10.1016/j.ejphar.2020.173281
2. Kyozuka H, Murata T, Fukuda T, Endo Y, Yamaguchi A, Yasuda S, et al. Immunoglobulin E levels and pregnancy-induced hypertension: Japan Environment and Children's Study. *Sci Rep.* (2021) 11:8664. doi: 10.1038/s41598-021-88227-2
3. Bakouei F, Delavar MA, Mashayekh-Amiri S, Esmailzadeh S, Taheri Z. Efficacy of n-3 fatty acids supplementation on the prevention of pregnancy induced-hypertension or preeclampsia: A systematic review and meta-analysis. *Taiwan J Obstet Gynecol.* (2020) 59:8–15. doi: 10.1016/j.tjog.2019.11.002
4. Wang HY, Liu ZP, Suo DM. Comparison of the effects of labetalol and nifedipine on hypersensitivity C-reactive protein, angiotensin II and prostaglandin E2 in patients with pregnancy-induced hypertension. *Guangdong Med.* (2019) 40:4.
5. Li YH, Qiao JL. The effect of nifedipine combined with labetalol on heart and kidney function and hemodynamics in patients with hypertension during pregnancy. *J Inner Mongolia Med College.* (2019) 41:243–5.
6. Shi CL. The effect of nifedipine combined with magnesium sulfate on hypertension and heart and kidney function of pregnant women during pregnancy. *J Clin Med Pra.* (2020) 24:4.
7. Chen R, Yao XY. The clinical efficacy of Danshen ligustrazine injection combined with conventional treatment in patients with hypertension-preeclampsia during pregnancy. *Chinese Patent Med.* (2019) 41:6.
8. Wang YH, Lu AJ, Liu CG. Clinical observation of Shenxiong injection combined with magnesium sulfate and labetalol in the treatment of hypertension during pregnancy. *World Trad Chin Med.* (2020) 15:5. doi: 10.3969/j.issn.1673-7202.2020.06.014
9. Socha MW, Malinowski B, Puk O, Dubiel M, Wiciński M. The NLRP3 inflammasome role in the pathogenesis of pregnancy induced hypertension and preeclampsia. *Cells.* (2020) 9:1642. doi: 10.3390/cells9071642
10. Xiang C, Zhou X, Zheng X. Magnesium sulfate in combination with nifedipine in the treatment of pregnancy-induced hypertension. *Pak J Med Sci.* (2020) 36:21–210 doi: 10.12669/pjms.36.2.706
11. Karemore MN, Avari JG. Formulation, optimization, and in vivo evaluation of gastroretentive drug delivery system of nifedipine for the treatment of preeclampsia. *AAPS PharmSciTech.* (2019) 20:200. doi: 10.1208/s12249-019-1391-2
12. Zhu H, Xuan RR, Liu LP. Discussion on the value of blood coagulation function detection in patients with pregnancy-induced hypertension and gestational diabetes. *Chin Gene Pract.* (2019) 17:3.
13. Song J, Lan R, Gong H, Zheng L, Yang Y, Yi D, et al. Magnesium sulfate combined with nifedipine is effective in pregnancy-induced hypertension and reduces levels of serum β2-microglobulin and retinol binding protein 4. *Iran J Public Health.* (2019) 48:2308–10. doi: 10.18502/ijph.v48i12.3569
14. Zhang Q, Zhang P, Li L. The effect of Xintongding combined with Labetalol on hemorheology, oxidative stress and inflammatory endothelial factors in patients with hypertension during pregnancy. *J Hainan Med Univer.* (2019) 25:4. doi: 10.13210/j.cnki.jhmu.20190510.002
15. Liu F, Long Y, Han MG. The role of apolipoprotein C4 in endothelial cell injury in hypertension during pregnancy. *Chin J Lab Med.* (2019) 42:5. doi: 10.3760/cma.j.issn.1009-9158.2019.08.011
16. Ou M, Zhao H, Ji G, Zhao X, Zhang Q. Long noncoding RNA MALAT1 contributes to pregnancy-induced hypertension development by enhancing oxidative stress and inflammation through the regulation of the

miR-150-5p/ET-1 axis. *FASEB J.* (2020) 34:6070–85. doi: 10.1096/fj.201902280R
17. Zhao K, Chang Q, Zhang Q. The application of dynamic monitoring of serum ADM, ET-1, and NO levels in the evaluation of the condition of patients with hypertension during pregnancy. *Heilongjiang Med Sci.* (2019) 42:2. doi: 10.3969/j.issn.1008-0104.2019.04.088
18. Shen T, Liang YJ, Ming Q. The clinical efficacy of hyperbaric oxygen therapy on patients with pregnancy-induced hypertension and the effect of serum endothelin-1 and nitric oxide levels. *Chin J Maritime Med Hyperbaric Med.* (2019) 26:4. doi: 10.3760/cma.i.issn.1009-6906.2019.06.022
19. Chen HH, Zhuang LM, Ji ZJ. Study on the correlation between prognosis evaluation of pulmonary hypertension caused by COPD and ET-1, H2S, NO. *Labeled Immunoassay Clinic.* (2019) 26:6. doi: 10.11748/bjmy.issn.1006-1703.2019.04.016
20. Zhang T, Chen Y, Qiu XF. Clinical study of nifedipine combined with magnesium sulfate in the treatment of patients with hypertension during pregnancy. *Chin J Clin Pharmacol.* (2020) 36:4. doi: 10.13699/j.cnki.1001-6821.2020.14.012

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Yu and Zhou. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers in Surgery

ORIGINAL RESEARCH
published: 28 March 2022
doi: 10.3389/fsurg.2022.863286

Correlation Between Hypothyroidism During Pregnancy and Glucose and Lipid Metabolism in Pregnant Women and Its Influence on Pregnancy Outcome and Fetal Growth and Development

Da Xu[1] *and Haolin Zhong*[2]*

[1] *Department of Endocrinology, Zhuji People's Hospital, Zhuji, China,* [2] *Department of Obstetrics, Zhuji Maternal and Child Health Care Hospital, Zhuji, China*

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Fang Wei,
Central South University, China
Lihong Chen,
The First Affiliated Hospital of Fujian Medical University, China

***Correspondence:**
Haolin Zhong
172477152@qq.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *27 January 2022*
Accepted: *21 February 2022*
Published: *28 March 2022*

Citation:
Xu D and Zhong H (2022) Correlation Between Hypothyroidism During Pregnancy and Glucose and Lipid Metabolism in Pregnant Women and Its Influence on Pregnancy Outcome and Fetal Growth and Development. Front. Surg. 9:863286. doi: 10.3389/fsurg.2022.863286

Purpose: To observe the correlation between hypothyroidism during pregnancy and glucose and lipid metabolism in pregnant women and its influence on a pregnancy outcome and fetal growth and development.

Methods: About 152 patients with hypothyroidism during pregnancy in our hospital from June 2017 to June 2020 were selected as the observation group and divided into the overt hypothyroidism (OH) group, the subclinical hypothyroidism (SCH) group, and the low T_4 group. Another 60 pregnant women with normal antenatal examination and normal thyroid function were selected as the normal group. The glucose and lipid metabolism indexes of each group were compared. The pregnant women in the OH group and the SCH group were given levothyroxine intervention, and the pregnancy outcome and infant development of the two groups were compared.

Results: The fasting blood glucose and hemoglobin A1c, triglyceride and low-density lipoprotein of the OH group and the SCH group were higher than the low T_4 group and the normal group, and the OH group was higher than the SCH group ($p < 0.05$). The incidence of premature delivery and premature rupture of membranes at term (PROM at term) in the hypothyroidism non-control group was higher than the hypothyroidism control group ($p < 0.05$). The mental development index and the psychomotor development index in the hypothyroidism non-control group were lower than the hypothyroidism control group ($p < 0.05$).

Conclusion: Pregnant women with hypothyroidism during pregnancy are more prone to glucose and lipid metabolism disorder, which increases the risk of premature delivery and PROM at term, and has certain influence on the intellectual development and psychomotor development of infants.

Keywords: hypothyroidism during pregnancy, glucose metabolism, lipid metabolism, pregnancy outcome, fetal growth and development

INTRODUCTION

Thyroid dysfunction is one of the common endocrine complications in pregnancy, especially hypothyroidism in pregnancy. Thyroid hormone (TH) is the most important endocrine hormone in the body, which can promote the synthesis of protein, RNA, DNA, and special enzymes in fetal tissues and cells, TH can regulate the metabolism of carbohydrates, calcium, phosphorus, fat, and other energy substances in pregnant women and fetus, and promote the growth and development of fetal bones and reproductive organs, and is very important to maintain the normal development and maturity of fetus (1, 2). During pregnancy, the hypothalamus-pituitary-thyroid regulatory system of pregnant women is in a stress state, and, during pregnancy, it is in a special endocrine state, which leads to the decrease of TH synthesis and the defect of thyroid receptor function, resulting in the decrease of the utilization rate of TH (3). Hypothyroidism can lead to a series of related clinical symptoms such as hypometabolism in pregnant women, with listlessness, fatigue, lethargy, pale face, rough skin, and decreased heart rate as the main manifestations (4). The incidence of hypothyroidism is high among women of childbearing age. The incidence of overt hypothyroidism (OH) in pregnant women is 1–2%, that of subclinical hypothyroidism (SCH) is 2–5%, and that of isolated low T_4 is 8–10% (5). Generally speaking, hypothyroidism is often ignored by people because the onset of hypothyroidism is hidden. In recent years, some scholars have suggested that hypothyroidism during pregnancy may affect maternal glucose and lipid metabolism and offspring development, which seriously endangers maternal and infant health (6). In this study, we observed the glucose and lipid metabolism and a pregnancy outcome of pregnant women with hypothyroidism during pregnancy, and followed up the fetus in order to improve the clinical outcome of pregnant women and fetus.

MATERIALS AND METHODS

Object

About 152 patients with hypothyroidism during pregnancy in our hospital from June 2017 to June 2020 were selected as the observation group. Inclusion criteria: age > 18 years old; the first gestational week was <28 weeks; single pregnancy; the patient had a formal birth examination in the department of obstetrics of our hospital and delivered in our hospital. Exclusion criteria: a history of thyroid disease before pregnancy; pre-pregnancy with abnormal glucose and lipid metabolism-related diseases; in the past 3 months, patient has taken drugs that affect thyroid hormones or glucose and lipid metabolism indexes; the fetus was lost before 28 weeks of gestation; complicated with serious organic diseases; lost or dropped out of the study. Another 60 pregnant women with normal antenatal examination and normal thyroid function were selected as the normal group. All the subjects were informed and agreed, and this study was reviewed by the ethics committee.

Research Methods

In the second trimester of pregnancy ($14–27^{+6}$ weeks of pregnancy), in the morning, 3 ml of fasting venous blood was collected from all the subjects, and the blood was centrifuged at 3,500 r/5 min for 5 min at room temperature, and the serum was separated. The levels of serum-free triiodothyronine (FT_3), free tetraiodothyronine (FT_4), and thyroid-stimulating hormone (TSH) were detected by an automatic chemiluminescence instrument. Fasting blood glucose (FBG) and hemoglobin A1c (HbA1c) were measured. Triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured.

According to the diagnostic criteria of hypothyroidism during pregnancy (7), patients with hypothyroidism were divided into: the (1) OH group: serum TSH > 3.6 mIU/L and FT_4 decreased, or serum TSH > 10 mIU/L regardless of whether FT_4 was normal or not; the (2) SCH group: serum TSH > 3.6 mIU/L, the serum FT_4 level was normal; the (3) Low T_4 group: the TSH level was normal, but the serum FT_4 level was lower than normal.

From the date of the diagnosis, the pregnant women with SCH and OH were treated with levothyroxine sodium tablets (specification: 50 ug), and FT_3, FT_4, and TSH were detected every 4 weeks. The therapeutic target of serum TSH was: 2–3. mIU/L in the second trimester. The dosage of levothyroxine sodium tablets had large individual variability, which required clinicians to evaluate factors, such as the cause of hypothyroidism, pre-pregnancy TSH levels, and other factors before treatment, and adjust the dosage according to individual circumstances. Pregnant women with hypothyroidism will not be treated; only FT_3, FT_4, and TSH will be detected every month, and then treated if the disease meets the requirements of SCH or OH. According to the level of serum TSH of the pregnant women before labor, they were divided into the hypothyroidism control group, and the serum TSH was kept in the target range through treatment; in the uncontrolled hypothyroidism group, the serum TSH was not controlled within the target range due to various reasons, such as the pregnant women's disobedience to the doctor's advice and refusal for treatment.

Evaluation Methods

All the subjects were followed up until delivery, and adverse pregnancy outcomes, such as premature delivery (delivery between >28 weeks and <37 weeks of gestation), abortion (termination of pregnancy due to pregnancy <28 weeks and fetal weight < 1,000 g), premature rupture of membranes at term (PROM at term) (After 37 weeks of gestation, the membranes rupture naturally), infants of low-birth weight (fetal birth weight < 2,500 g), and fetal distress (fetal heart rate, <120 beats/min or >160 beats/min on auscultation test) were recorded.

Within 18 months of live births, infants' intelligence development and psychomotor development were measured by Bayley scales of infant development (BSID) (revised edition of Chinese cities), and mental development index (MDI) and psychomotor development index (PDI) were calculated (8). MDI was used to test the infant's response to stimuli, hand-eye coordination, language, exploratory activities, cognitive ability, etc.; PDI was used to test the gross motor and fine motor of

all parts of the infant's body. MDI included 163 items and PDI included 81 items. The larger the index, the better the infant's development. The test results show that the developmental quotient ≤69 was diagnosed as developmental retardation. The infants were tested in a testing room by specially trained testers.

Statistical Methods

SPSS22.0 software was used for analysis, and the measured data were expressed by $\bar{x} \pm s$ and compared by t-test. The counting data were expressed as % and compared by χ^2 test. $p < 0.05$, the difference was statistically significant.

RESULTS

Incidence of Hypothyroidism During Pregnancy

There were 152 cases in the observation group, including 56 pregnant women with OH, 53 pregnant women with SCH, and 43 cases with low T_4. During the study period, no pregnant women with low T_4 changed into SCH or OH. After the treatment, hypothyroidism was controlled in 85 cases and uncontrolled in 24 cases among the 109 pregnant women with SCH or OH.

Comparison of Blood Glucose Levels in Each Group

The FBG and HbA1c of the OH group and the SCH group were higher than the low T_4 group and the normal group, and the OH group was higher than the SCH group ($p < 0.05$), as shown in **Figure 1**.

Comparison of Blood Lipid Levels in Each Group

The TG and LDL of the OH group and the SCH group were higher than the low T_4 group and the normal group, and the OH group was higher than the SCH group ($p < 0.05$), as shown in **Figure 2**.

Comparison of Adverse Pregnancy Outcomes Between the Two Groups

The incidence of premature delivery and PROM at term in the hypothyroidism non-control group was higher than the hypothyroidism control group ($p < 0.05$), as shown in **Table 1**.

Comparison of Fetal Growth and Development Between the Two Groups

The MDI and PDI in the hypothyroidism non-control group were lower than the hypothyroidism control group ($p < 0.05$), as shown in **Figure 3**.

DISCUSSION

Studies have shown that severe thyroid dysfunction is closely related to female infertility, poor pregnancy outcomes, and offspring stunting (9). At present, during pregnancy, thyroid function can be evaluated by detecting serum FT_3, FT_4, and TSH levels. Some scholars believe that hypothyroidism in early pregnancy does not increase the risk of dysglycemia and dyslipidemia, while the levels of FT_4 and TSH in the second trimester are related to glucose and lipid metabolism (10). Therefore, by detecting the levels of FT_3, FT_4, and TSH in pregnant women in the second trimester, we divided the patients with hypothyroidism into the OH group, the SCH group, and the low T_4 group, observed the glucose and lipid metabolism in pregnant women, and discussed the influence of hypothyroidism on a pregnancy outcome and fetal growth and development.

In this study, FBG, HbA1c, TG, and LDL in the OH group and the SCH group are higher than the low T_4 group and the normal group, and the increase in the OH group is more significant, which indicates that pregnant women with hypothyroidism during pregnancy are more prone to glucose and lipid metabolism disorder. TH has a two-way characteristic in regulating glucose metabolism of the body. On the one hand, it can increase blood glucose by promoting the decomposition and utilization of glycogen, enhancing gluconeogenesis and increasing the rate of glucose metabolism. On the other hand, it can increase glycolysis by increasing insulin

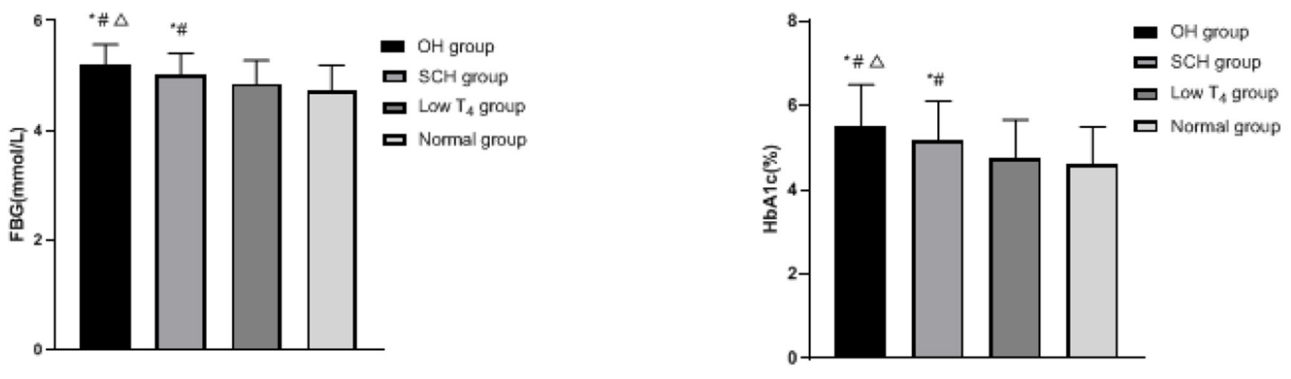


FIGURE 1 | Comparison of blood glucose levels in each group; compared with the normal group, $^{*}p < 0.05$; compared with the low T_4 group, $^{\#}p < 0.05$; compared with the SCH group, $^{\Delta}p < 0.05$.

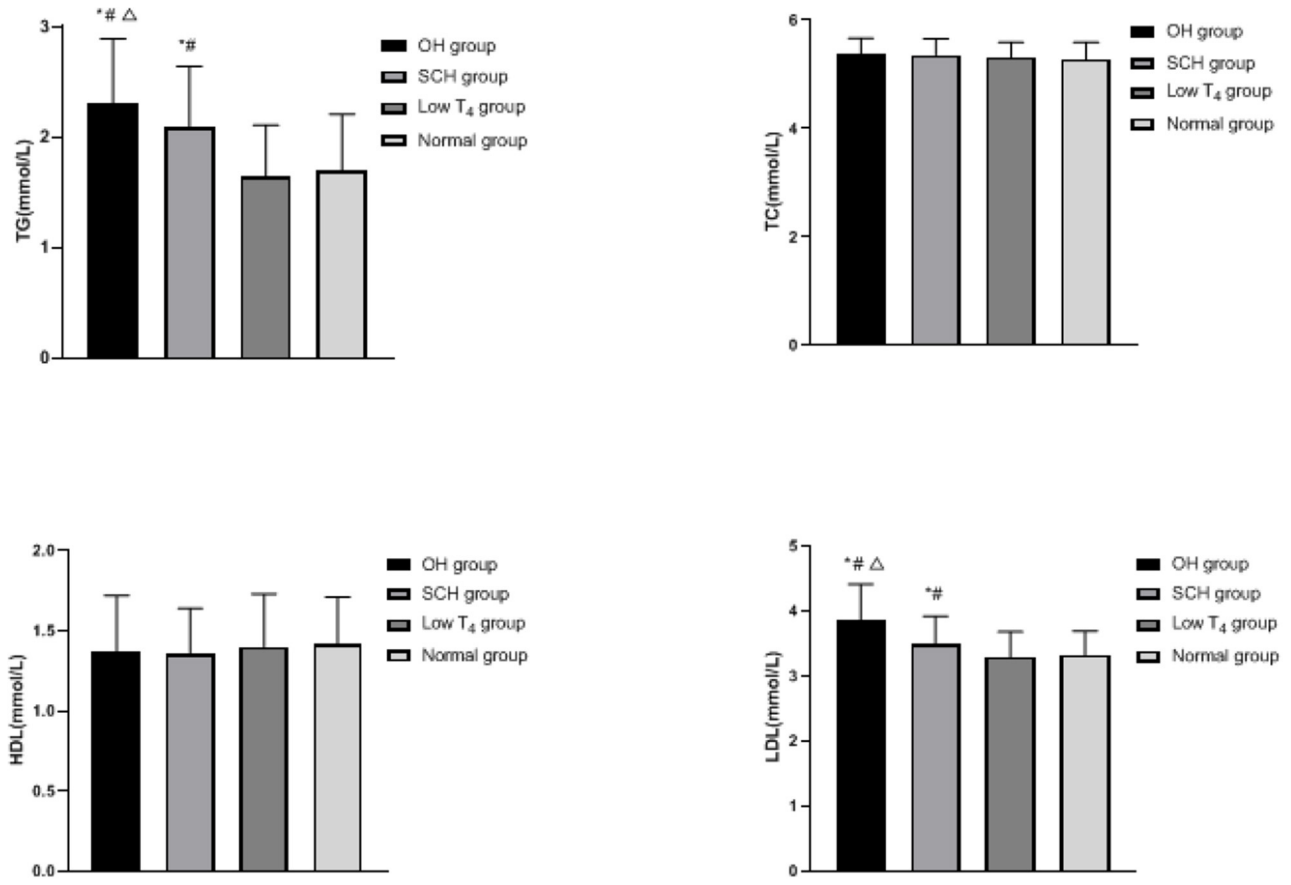


FIGURE 2 | Comparison of blood lipid levels in each group: compared with the normal group, $^{*}p < 0.05$; compared with the low T_4 group, $^{\#}p < 0.05$; compared with the SCH group, $^{\Delta}p < 0.05$.

TABLE 1 | Comparison of adverse pregnancy outcomes between the two groups (*n*,%).

Group	Premature delivery	Abortion	PROM at term	Infant of low-birth weight	Fetal distress
Hypothyroidism non-control group ($n = 24$)	3 (12.50%)	2 (8.33%)	5 (20.83%)	1 (4.17%)	3 (12.50%)
Hypothyroidism control group ($n = 85$)	2 (2.35%)	2 (2.35%)	6 (7.06%)	3 (3.53%)	7 (8.24%)
χ^2value	4.403	1.894	3.914	0.021	0.409
P-value	0.036	0.169	0.048	0.883	0.523

secretion, thereby reducing blood glucose (11, 12). For patients with hypothyroidism, most patients will have positive thyroid peroxidase antibody, TH decreased and abnormal immune function, which will further affect the utilization of insulin in peripheral tissues. The phenomenon of insulin resistance in pregnant women will lead to abnormal glucose metabolism and promote the change of fasting glucose tolerance, and thus lead to the increase of blood glucose (13). Jia's team found that maternal glucose metabolism during pregnancy was more sensitive to changes of thyroid hormone than that during non-pregnancy, and the incidence of gestational diabetes in pregnant women with hypothyroidism was higher than that in pregnant women with normal thyroid function (14). In addition, hypothyroidism is also closely related to the fat metabolism of pregnant women. The main reasons are as follows: (1) TH has influence on the fat synthesis, transportation, and degradation. Compared with the normal population, the cholesterol transport level in the patients with hypothyroidism decreased, the carrying capacity of apolipoprotein to TG and LDL was affected, and the activity of lipoprotein decreased, resulting in the decrease of cholesterol

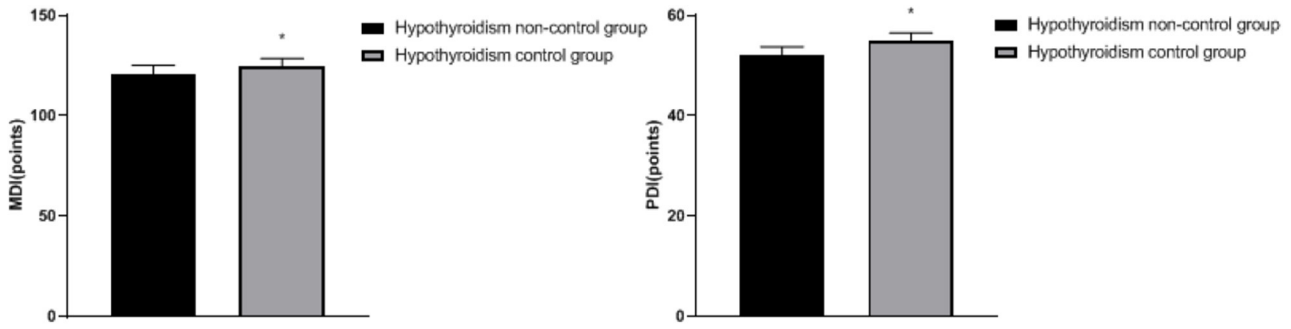


FIGURE 3 | Comparison of fetal growth and development between the two groups: compared with the hypothyroidism non-control group, $^*p < 0.05$.

clearance and degradation, so the concentration of TG and LDL in blood increased. (2) By regulating the expression of the LDL receptor and the activity of lipoprotein lipase on the surface of liver cells, the occurrence of hypothyroidism can interfere with the reverse transport process of cholesterol in liver epithelial cells by promoting the occurrence of oxidative stress disorder *in vivo*, and lead to the decrease of LDL receptor sensitivity, the decrease of the number and activity of the LDL receptor on the surface of liver cells, the decrease of LDL clearance and degradation, the accumulation of LDL, and the abnormality of serum lipid metabolism. (3) Hypothyroidism will cause a large amount of free fatty acids to flow into the liver, which will increase the synthesis of LDL in the liver, and eventually lead to the increase of TG and LDL content (15–17).

This study also found that treatment with levothyroxine sodium tablets significantly improved thyroid function of patients with hypothyroidism during pregnancy, and the risk of premature delivery and PROM was lower. Without treatment for hypothyroidism during pregnancy, the metabolism of blood glucose and blood lipid may be disordered, and TH is directly involved in placenta development, and OH or SCH may lead to mild deficiency of TH, which may lead to premature birth of newborn (18). At the same time, due to the influence of gestational diabetes mellitus, lower genital tract infection, mechanical stimulation, the increase of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) cytokines, and other factors, PROM at term has become one of the clinical adverse pregnancy outcomes (19). Adipose is involved in the energy metabolism of pregnant and lying-in women. IL-6 and TNF-α are endocrine hormones secreted by adipose tissue. The serum of TSH can regulate the endocrine function of adipose tissue to a certain extent (20). However, in the body of pregnant women with OH or SCH, the serum TSH level is obviously increased, which can promote the secretion of leptin, adiponectin, IL-6, TNF-α, and other inflammatory factors in adipose tissue, leading to PROM at term (21).

In addition, TH not only affects the proliferation and migration of neurons in cerebral cortex, and the uplift of hippocampus and inner pleural ganglion but also influences the formation of axons and dendrites, and myelination (22). During pregnancy, the fetus needs TH to ensure the development of normal nervous system and other organ systems, and TH plays a key role in the development and maturation of the fetal brain (23). Once hypothyroidism occurs during pregnancy, the increase of TSH level may inhibit the secretion of human chorionic gonadotropin by placenta to a certain extent, resulting in an irreversible influence on the development of placenta and fetus and damages the development of fetal nervous system (24). Moreover, long-term hypothyroidism will make the abnormal blood glucose and blood lipid levels of pregnant women for a long time, resulting in the damage of the blood vessel wall and the decrease of blood flow supply, which will further lead to the decrease of blood flow to various organs of the body, resulting in the lack of oxygen supply to cells, and, in severe cases, placenta aging will occur, resulting in the limitation of fetal growth and development (25). The above research is consistent with our results. We have observed that, after hypothyroidism control, infants' intelligence and psychomotor development are better.

CONCLUSION

To sum up, pregnant women with hypothyroidism during pregnancy are more prone to glucose and lipid metabolism disorder, which increases the risk of premature delivery and PROM at term, and has certain influence on the intellectual development and psychomotor development of infants. The results suggest that doctors should screen thyroid function during pregnancy, pay attention to the changes of glucose and lipid metabolism indexes of pregnant women with hypothyroidism, and actively give treatment according to the actual situation of patients so as to improve the maternal and child outcomes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Zhuji People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors of this study made equal contributions, including study design, inclusion of cases, data detection and statistics, and writing of the paper. HZ was the supervisor of the entire study. All authors contributed to the article and approved the submitted version.

REFERENCES

1. Donnay S, Fajardo C, Fernández-García JC, Torres T, Bandrés O, Domínguez JR, et al. Diagnosis, treatment, and management of gestational hypothyroidism. The TIROGEST study. *Endocrinol Diabetes Nutr.* (2020) 67:36–42. doi: 10.1016/j.endinu.2019.03.008
2. López-Muñoz E, Mateos-Sánchez L, Mejía-Terrazas GE, Bedwell-Cordero SE. Hypothyroidism and isolated hypothyroxinemia in pregnancy, from physiology to the clinic. *Taiwan J Obstet Gynecol.* (2019) 58:757–63. doi: 10.1016/j.tjog.2019.09.005
3. Shinohara DR, Santos TDS, de Carvalho HC, Lopes LCB, Günther LSA, Aristides SMA, et al. Pregnancy Complications Associated With Maternal Hypothyroidism: a systematic review. *Obstet Gynecol Surv.* (2018) 73:219–30. doi: 10.1097/OGX.0000000000000547
4. Li N, Yang J, Chen X, Huang J, Lai M, Fang F, et al. Postpartum follow-up of patients with subclinical hypothyroidism during pregnancy. *Thyroid.* (2020) 30:1566–73. doi: 10.1089/thy.2019.0714
5. Martínez M, Soldevila B, Lucas A, Velasco I, Vila L, Puig-Domingo M. Hypothyroidism during pregnancy and its association to perinatal and obstetric morbidity: a review. *Endocrinol Diabetes Nutr.* (2018) 65:107–13. doi: 10.1016/j.endien.2017.11.016
6. Lei Y, Yang J, Li H, Zhong H, Wan Q. Changes in glucose-lipid metabolism, insulin resistance, and inflammatory factors in patients with autoimmune thyroid disease. *J Clin Lab Anal.* (2019) 33:e22929. doi: 10.1002/jcla.22929
7. Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum. *Thyroid.* (2017) 27:315–89. doi: 10.1089/thy.2016.0457
8. Yang X, Zhu ZH, Zhang M, Li DY, Liu DL, Cheng Y, et al. [Study of the relevant factors of behavioral development among 30-month-old infants in rural area of Shaanxi Province]. *Zhonghua Yu Fang Yi Xue Za Zhi.* (2017) 51:628–34. doi: 10.3760/cma.j.issn.0253-9624.2017.07.010
9. Yoshioka W, Amino N, Ide A, Kang S, Kudo T, Nishihara E, et al. Thyroxine treatment may be useful for subclinical hypothyroidism in patients with female infertility. *Endocr J.* (2015) 62:87–92. doi: 10.1507/endocrj.EJ14-0300
10. Liu Y, Chen H, Jing C, Li F. The association between maternal subclinical hypothyroidism and growth, development, and childhood intelligence: a meta-analysis. *J Clin Res Pediatr Endocrinol.* (2018) 10:153–61. doi: 10.4274/jcrpe.4931
11. Li P, Lin S, Cui J, Chen X, Meng Z, Fan J. Impact of early pregnancy subclinical hypothyroidism on gestational diabetes mellitus: a retrospective study of 7,536 cases. J *Womens Health.* (2021) 31:293–8. doi: 10.1089/jwh.2020.8825
12. Huang K, Xu Y, Yan S, Li T, Xu Y, Zhu P, et al. Isolated effect of maternal thyroid-stimulating hormone, free thyroxine and antithyroid peroxidase antibodies in early pregnancy on gestational diabetes mellitus: a birth cohort study in China. *Endocr J.* (2019) 66:223–31. doi: 10.1507/endocrj.EJ18-0340
13. Biondi B, Kahaly GJ, Robertson RP. Thyroid dysfunction and diabetes mellitus: two closely associated disorders. *Endocr Rev.* (2019) 40:789–824. doi: 10.1210/er.2018-00163
14. Jia M, Wu Y, Lin B, Shi Y, Zhang Q, Lin Y, et al. Meta-analysis of the association between maternal subclinical hypothyroidism and gestational diabetes mellitus. *Int J Gynaecol Obstet.* (2019) 144:239–47. doi: 10.1002/ijgo.12751
15. Zhou J, Dong X, Liu Y, Jia Y, Wang Y, Zhou J, et al. Gestational hypothyroidism elicits more pronounced lipid dysregulation in mice than pre-pregnant hypothyroidism. *Endocr J.* (2020) 67:593–605. doi: 10.1507/endocrj.EJ19-0455
16. Liu H, Peng D. Update on dyslipidemia in hypothyroidism. *Endocr Connect.* (2022) 11:e210002. doi: 10.1530/EC-21-0002
17. Li X, Wang Y, Guan Q, Zhao J, Gao L. The lipid-lowering effect of levothyroxine in patients with subclinical hypothyroidism: A systematic review and meta-analysis of randomized controlled trials. *Clin Endocrinol (Oxf).* (2017) 87:1–9. doi: 10.1111/cen.13338
18. Consortium on Thyroid and Pregnancy—Study Group on Preterm Birth, Korevaar TIM, Derakhshan A, Taylor PN, Meima M, Chen L, et al. Association of thyroid function test abnormalities and thyroid autoimmunity with preterm birth: a systematic review and meta-analysis. *JAMA.* (2019) 322:632–41. doi: 10.1001/jama.2019.10931
19. Li W, Zhao X, Li S, Chen X, Cui H, Chang Y, et al. Upregulation of TNF-α and IL-6 induces preterm premature rupture of membranes by activation of ADAMTS-9 in embryonic membrane cells. *Life Sci.* (2020) 260:118237. doi: 10.1016/j.lfs.2020.118237
20. Milani AT, Khadem-Ansari MH, Rasmi Y. Effects of thyroid-stimulating hormone on adhesion molecules and pro-inflammatory cytokines secretion in human umbilical vein endothelial cells. *Res Pharm Sci.* (2018) 13:546–56. doi: 10.4103/1735-5362.245966
21. Zhou J, Cheng G, Pang H, Liu Q, Liu Y. The effect of 131I-induced hypothyroidism on the levels of nitric oxide (NO), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), total nitric oxide synthase (NOS) activity, and expression of NOS isoforms in rats. *Bosn J Basic Med Sci.* (2018) 18:305–12. doi: 10.17305/bjbms.2018.2350
22. Lecorguillé M, Léger J, Forhan A, Cheminat M, Dufourg MN, Heude B, et al. Pregnancy outcomes in women with preexisting thyroid diseases: a French cohort study. *J Dev Orig Health Dis.* (2021) 12:704–13. doi: 10.1017/S2040174420001051
23. Camm EJ, Inzani I, De Blasio MJ, Davies KL, Lloyd IR, Wooding FBP, et al. Thyroid hormone deficiency suppresses fetal pituitary-adrenal function near term: implications for the control of fetal maturation and parturition. *Thyroid.* (2021) 31:861–9. doi: 10.1089/thy.2020.0534
24. Batistuzzo A, Ribeiro MO. Clinical and subclinical maternal hypothyroidism and their effects on neurodevelopment, behavior and cognition. *Arch Endocrinol Metab.* (2020) 64:89–95. doi: 10.20945/2359-3997000000201
25. Davies KL, Smith DJ, El-Bacha T, Stewart ME, Easwaran A, Wooding PFP, et al. Development of cerebral mitochondrial respiratory function is impaired by thyroid hormone deficiency before birth in a region-specific manner. *FASEB J.* (2021) 35:e21591. doi: 10.1096/fj.202100075R

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Xu and Zhong. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers | Frontiers in Surgery

ORIGINAL RESEARCH
published: 01 April 2022
doi: 10.3389/fsurg.2022.882712

Validity and Reliability of the Secondary Traumatic Stress Scale—Chinese Version

*Yi He[1], Zhiqun Liu[2], Juan Zhang[3], Jiapei Yao[4], Huan Xiao[1] and Huan Wan[5]**

[1] Department of Otolaryngology Head and Neck Surgery, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, China, [2] Department of Respiratory Therapy, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, China, [3] Department of Biliary Surgery, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, China, [4] Department of Orthopedics, The Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University, Changzhou, China, [5] Department of Nursing, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University), Changsha, China

Objectives: To test the validity and reliability of the Secondary Traumatic Stress Scale—Chinese version in clinical nurses.

Methods: According to the translation principles of the Brislin Scale, the original scale was translated, back translated and cross-culturally adapted to form the Chinese version of the Secondary Traumatic Stress Scale. Nurses in three general hospitals in Changsha, Hunan province were surveyed by convenient sampling method from July 2020 to September 2021. Exploratory factor analysis, confirmatory factor analysis, content validity and criterion validity was used to evaluate the validity of the scale. Internal consistency Cronbach's α coefficient, split-half reliability and test-retest reliability were used to evaluate the reliability of the scale.

Results: A total of 678 nurses were included in the study. There were 460 people in sample 1 and 218 people in sample 2. Two common factors were extracted by exploratory factor analysis. The cumulative contribution was 65.560%. The two-factor structure model was good (χ^2/df = 3.137, CFI = 0.928, IFI = 0.929, GFI = 0.842, TLI = 0.917, RMSEA = 0.099). The I-CVI of the scale was 0.8–1.0. The S-CVI/Ave was 0.94. The Cronbach's alpha coefficient is 0.956. The broken half reliability is 0.920. The retest reliability is 0.910.

Conclusion: This study identified two components of the Secondary Traumatic Stress Scale—Chinese version, which has 2 dimensions and 17 items. With good validity and reliability, it is suitable for the assessment of secondary traumatic stress among clinical nurses in the Chinese context.

Keywords: secondary traumatic stress, validity, reliability, scale, Chinesization

OPEN ACCESS

Edited by:
Weiguo Li,
Harbin Institute of Technology, China

Reviewed by:
Tingting Wu,
Zhejiang Lab, China
Qing Li,
Heart Health Research Center (HHRC), China

***Correspondence:**
Huan Wan
184997982@qq.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *24 February 2022*
Accepted: *08 March 2022*
Published: *01 April 2022*

Citation:
He Y, Liu Z, Zhang J, Yao J, Xiao H and Wan H (2022) Validity and Reliability of the Secondary Traumatic Stress Scale—Chinese Version. Front. Surg. 9:882712. doi: 10.3389/fsurg.2022.882712

INTRODUCTION

Secondary traumatic stress (STS) is a pattern of psychological symptoms in which the helper exhibits disturbing or painful psychological symptoms during or after helping without directly experiencing a traumatic event (1). STS was originally described as Compassion fatigue (CF) (2). But it does not include the concept of empathy. They should therefore be defined and measured differently (3, 4). Symptoms of STS include exhaustion, hyperarousal, avoidance and numbness. Similar to Post-traumatic stress disorder (PTSD) (5). The difference is that PTSD occurs in individuals who have direct exposure to traumatic events (6), whereas STS occurs in

professionals who have indirect exposure to traumatic individuals (1). At the beginning, STS had some similarities with PTSD and CF. Researchers often assess STS using measures of PTSD or the Occupational Quality of Life Scale (ProQOL) (7). Neither was specifically designed for that purpose. The Secondary Traumatic Stress Scale (STSS) (1) was compiled by Bride BE in 2004 according to the concept of STS proposed by Figley. It measures intrusion, avoidance, and arousal symptoms triggered by indirect exposure to traumatic events. Its psychometric properties have been validated (8). Over the past decade, STSS has become the standard tool for assessing STS. It has been used by doctors, nurses, midwives, respiratory therapists, mental health workers and other social workers in many regions (9–12). It has been translated into Hungarian (13), French (14), German (15), Japanese (16) and other languages.

The stimulation induced by STS was short in duration. STS can suddenly occur without much warning (17). The incidence of STS may be high for frontline mental health professionals and social workers (including nurses, mental psychiatrists, first responders, and victim advocates, etc.) (5, 18, 19). Because they frequently work with victims of all forms of trauma, such as listening to trauma victims describe the physical and psychological horrors they have experienced, providing a variety of services including emotional support, in-person counseling and psychological education information. As a key member of the medical treatment team, nurses are usually the first people to contact patients and their families. Nurses are also the main personnel to observe patients' pain and distress symptoms. Their professional clinical competence is the basic requirement to provide safe and effective care for patients. A large number of studies have shown that STS is common among nurses (20, 21). STS can have a wide range of impacts on personal and professional life, including various somatization symptoms, sleep disorders, depression, anxiety, interpersonal relationship damage and other aspects (22). Most of them are negative, which may affect the ability level and nursing quality of nurses (23). This will affect patient satisfaction and even the stable development of the hospital. Improving the mental health of nursing staff can effectively improve the nursing level (24). Therefore, it is necessary to assess the STS of clinical nurses effectively.

Although the compassion fatigue scale has been sinicized and put into use by scholars. Zakeri (25) pointed out that we should study STS and compassion fatigue as independent but related structures. It also focuses on understanding the factors related to STS in nurses. So as to help them reduce STS. Currently, there is a lack of assessment tools to directly measure STS among nursing staff in China, which is not conducive to understanding the current situation of STS among nursing staff in China, nor to promoting corresponding social support systems and using positive coping mechanisms to reduce STS. Given the potential harmful effects of STS and the fact that effective interventions depend on accurate assessment. The introduction of STSS can help to quickly identify the mental state of nursing staff. To provide a basis for timely and accurate targeted interventions. Therefore, this study aims to sinicize STSS and evaluate the validity and reliability of the Chinese version of STSS (C-STSS) in nursing staff. To provide a reliable tool for assessing STS of clinical nursing staff.

METHODS

Participants

The participants included 678 clinical nurses from three general hospitals in Changsha, Hunan province (Hunan Provincial People's Hospital, Hunan Provincial Second People's Hospital, Changsha Xingsha Hospital). All of them had worked for more than one year.

Sample 1: A total of 460 clinical nurses were included.
Sample 2: A total of 218 clinical nurses were included.

The proposal of this research was approved by the ethics committee of Hunan Provincial People's Hospital (The first affiliated hospital of Hunan normal university). All subjects gave informed consent to this study.

Measures

Secondary Traumatic Stress (STSS)

The scale is a self-rating scale. The frequency of STS-related symptoms in the previous 7 days was assessed. It consists of three subscales of intrusion, avoidance and arousal, with 17 items in total. Likert grade 5 scoring method was adopted. The higher the score was, the higher the frequency of symptoms appeared. A total score below 28 is classified as "no STS". 28-37 is "mild STS". 38-43 is "moderate STS". 44-48 is "high STS". More than 49 is "severe STS". The Cronbach's α coefficients of the total scale were 0.94. The α coefficients of the three subscales were 0.83, 0.89 and 0.85 (8).

Post-traumatic Stress Disorder Scale Civilian Version (PCL-C)

There are 17 items in this scale. It includes three dimensions: reexperience, avoidance and over-arousal. To assess individual PTSD symptoms and their severity. Likert 5-level scoring method is adopted, with a total score of 17-85. The higher the score, the more severe the PTSD degree (26). The Cronbach's α coefficient of the scale in this study was 0.956.

Chinese Version of the Compassion Fatigue Scale (C-CFS)

A total of 30 items. It is mainly used for measuring the clinical nurses in satisfaction, traumatic stress, job burnout, intrusive thoughts and fears of five aspects. Likert grade 5 scoring method was adopted. Score 1-5 points from "none" to "always". A few items are scored backwards. The higher the score prompt more sympathy for the degree of fatigue (27). The Cronbach's α coefficient of the scale in this study was 0.930.

Procedures

Translating-back translation scale using Brislin's intercultural translation model. Firstly, two bilingual experts were invited to translate STSS. One was a doctor of nursing who was familiar with psychological terms. The other was a non-medical person. Then, the research team members compared and merged the Chinese versions translated by the two experts. The differences were discussed with two experts. Form proofread version STSS. Then, a nursing master candidate with overseas study experience and a bilingual expert were invited to translate the Chinese proofread version of STSS back into English. In order to ensure

TABLE 1 | The personal and demographic information of the participating in the study.

Sample 1	Variable	Number (*n*)	Percentage (%)	Sample 2	Variable	Number (*n*)	Percentage (%)
Age	<25y old	117	25.4	Age	<25y old	24	11.0
	25–30y old	143	31.1		25–30y old	66	30.3
	30–40y old	157	34.1		30–40y old	113	51.8
	>40y old	43	9.3		>40y old	15	6.9
Gender	Male	15	3.3	Gender	Male	17	7.8
	Female	445	96.7		Female	201	92.2
Type of education	High school degree	100	21.7	Type of education	High school degree	19	8.7
	Bachelor degree	351	76.3		Bachelor degree	185	84.9
	Master degree or above	9	2.0		Master degree or above	14	6.4
Professional qualification	Primary	300	65.2	Professional qualification	Primary	123	56.4
	Intermediate	135	29.3		Intermediate	83	38.1
	Senior	25	5.4		Senior	12	5.5

the quality of translation, they were not informed that they were doing translation work. A bilingual expert and research team members will compare and discuss the translated version with the original version to form the first version of STSS.

In order to ensure the pertinence and effectiveness of the scale after Chinese version, five experts were invited to form a cultural debugging group (doctor of psychology, master of psychology and doctor of nursing) through face-to-face discussion or E-mail to debug the preliminary STSS. Comments and suggestions were put forward based on whether the meaning of each item in the questionnaire was clear, whether the language expression was simple, accurate, direct and easy to understand. Then the items were revised and integrated again.

The convenience sampling method was used to conduct a preliminary survey in June 2020. 40 clinical nurses who met the inclusion and exclusion criteria were selected for the preliminary experiment. The internal consistency reliability of the C-STSS was calculated according to the results of the preliminary experiment. The results showed that all 40 clinical nurses could understand the meaning of each item in the scale. The average time to complete the questionnaire was 5-10min. The analysis of the investigation results of the 40 subjects showed that the Cronbach's α coefficient of the C-STSS was 0.943.

Data Collection

The convenience sampling method was used to investigate the clinical nursing staff in three general hospitals by using questionnaire star in two stages. Before data collection, use uniform standard guidance language. It is stipulated that the questionnaire can be submitted only after all items have been answered to avoid missing selection. The same client can only submit once. In the first stage, 460 valid questionnaires (sample 1) were collected. 218 valid questionnaires (sample 2) were collected in the second stage. A total of 678 questionnaires were collected.

Statistical Methods

In this study, frequency and percentage were used to describe the general data of the research object. SPSS 26.0 was used for exploratory factor analysis of sample 1 (n = 460). The content validity, internal consistency reliability, half-fold reliability and retest reliability of the scale were evaluated. AMOS 21.0 was used for confirmatory factor analysis and criterion validity analysis of sample 2 (n = 218). Test level $\alpha = 0.05$.

RESULTS

Demographics

Table 1 displays the demographics of both samples. A total of 460 clinical nurses were included in Sample 1. 15 cases were male (3.3%). Female 445 cases (96.7%). A total of 218 clinical nurses were included in Sample 2. 17 cases were male (7.8%). Female 201 cases (92.2%).

Validity

Structural Validity

Exploratory Factor Analysis

The results of Bartlett's sphericity test showed that the KMO value was 0.968. The Bartlett's sphericity test χ^2 value was 5,767.238. The degree of freedom was 136 ($P < 0.001$). It suggests that the data in this study are suitable for factor analysis. Principal component analysis (PCA) was used to extract factors with characteristic roots >1 without limiting the number of factors. Run a lithograph at the same time. Two common factors were extracted, with a cumulative contribution rate of 65.560%. The maximum variance orthogonal rotation method was adopted for exploratory factor analysis. The factor load matrix was rotated. There is no item with factor load < 0.40 in the corresponding common factor. And no items with a common degree < 0.2. Therefore, the questionnaire with 17 items and 2 common factors was finally formed. The cumulative variance contribution rate was 65.560% (**Table 2**). Factors are defined according to the items and meanings contained in each common factor. Factor 1 stress (Including items 1, 4, 5, 7, 8, 9, 11, 15, 16, 17. A total of 10 items. Cronbach's α 0.718). Factor 2 invasion and avoidance (Including items 2, 3, 6, 10, 12, 13, 14. A total of 7 items. Cronbach's α 0.696).

TABLE 2 | C-STSS exploratory factor analysis results ($n = 460$).

Item	$\bar{x} \pm SD$	Factor 1	Factor 2	Common degrees
I was less active than usual.	3.18 ± 1.007	0.799		0.690
I felt discouraged about the future.	2.79 ± 1.024	0.780		0.721
I had little interest in being around others.	2.64 ± 1.025	0.746		0.686
I had trouble concentrating.	2.70 ± 0.941	0.746		0.712
I felt jumpy.	2.86 ± 0.996	0.720		0.710
I felt emotionally numb.	2.66 ± 0.977	0.679		0.622
I expected something bad to happen.	2.55 ± 0.974	0.630		0.702
I had trouble sleeping.	2.93 ± 1.052	0.617		0.457
I was easily annoyed.	2.73 ± 0.992	0.601		0.600
I noticed gaps in my memory about patient sessions.	2.63 ± 0.920	0.552		0.397
I wanted to avoid working with some patients.	2.31 ± 0.959		0.813	0.767
I avoided people, places, or things that reminded me of my work with patients.	2.36 ± 0.952		0.756	0.721
I had disturbing dreams about my work with patients.	2.16 ± 0.953		0.745	0.667
My heart started pounding when I thought about my work with patients.	2.61 ± 0.998		0.737	0.623
It seemed as if I was reliving the trauma(s) experienced by my patient(s).	2.35 ± 0.997		0.733	0.650
Reminders of my work with patients upsets me.	2.50 ± 0.955		0.733	0.738
I thought about my work with patients when I didn't intend to.	2.66 ± 0.928		0.716	0.682
Eigenvalue		5.717	5.429	
Explanatory variance percentage		33.627	31.933	
Cumulative contribution rate				65.560

Confirmatory Factor Analysis

AMOS was used to perform confirmatory factor analysis on the relevant data of sample 2 ($n = 218$). The fitting indexes of the model were as follows. The χ^2/ DF was 3.137. The CFI was 0.928. The GFI was 0.842. The IFI was 0.929. The TLI was 0.917. The RMR was 0.048. The RMSEA was 0.099.

Content Validity

In this study, 10 experts from psychology related fields were invited to form an expert group to score the scale with level 4 Content Validity Index (CVI). All the experts had been engaged in psychology-related treatment and nursing or research for more than 5 years. Members of the expert panel evaluated each item of the questionnaire. Finally calculated the Item-Content Validity Index (I-CVI) of the C-STSS. I-CVI ranged from 0.80 to 1.00. The scale-content Validity Index (S-CVI) was 0.94. The results are shown in **Table 3**.

TABLE 3 | Content validity of C-STSS ($n = 17$).

Item	I-CVI
I felt emotionally numb.	0.9
My heart started pounding when I thought about my work with patients.	0.9
It seemed as if I was reliving the trauma(s) experienced by my patient(s).	0.8
I had trouble sleeping.	0.8
I felt discouraged about the future.	1.0
Reminders of my work with patients upsets me.	1.0
I had little interest in being around others.	0.9
I felt jumpy.	1.0
I was less active than usual.	1.0
I thought about my work with patients when I didn't intend to.	0.9
I had trouble concentrating.	0.9
I avoided people, places, or things that reminded me of my work with patients.	1.0
I had disturbing dreams about my work with patients.	1.0
I wanted to avoid working with some patients.	1.0
I was easily annoyed.	1.0
I expected something bad to happen.	0.9
I noticed gaps in my memory about patient sessions.	0.9
S-CVI/Ave	0.94

Criterion Correlation Validity

PCL-C and C-CFS are used as calibration tools of C-STSS. The total score of STSS and its two factors (stress, invasion and avoidance) were positively correlated with the total score of PCL-C and its subscales (re-experience, avoidance and over-arousal) ($P<0.01$). It was positively correlated with the total score of C-CFS and its four factors (traumatic stress, job burnout, intrusive thinking, fear) ($P < 0.01$) (**Table 4**).

Reliability

The results of this study show that the Cronbach's α coefficient of C-STSS is 0.956. The Cronbach's α coefficient of stress dimension is 0.931. The Cronbach's α coefficient of invasion and avoidance dimension is 0.926. All were >0.70. The half-reliability of the C-STSS is 0.934. The half-reliability of the two dimensions is 0.920. Forty nurses were selected for retest at intervals of 2 weeks for convenience. The retest reliability of The C-STSS was

TABLE 4 | Correlation between C-STSS score and criteria [r, ($n = 218$)].

Scale	C-STSS score	Stress	Invasion and evasion
PCL-C	0.881**	0.875**	0.800**
Re-experience	0.767**	0.724**	0.750**
Avoidance	0.828**	0.809**	0.772**
Over-arousal	0.799**	0.849**	0.647**
C-CFS	0.629**	0.580**	0.635**
Satisfaction	0.061	0.077	0.033
Traumatic stress	0.709**	0.620**	0.766**
Job burnout	0.729**	0.682**	0.723**
Intrusive thinking	0.704**	0.605**	0.774**
Fear	0.661**	0.666**	0.587**

**$P < 0.01$.

0.910. The retest reliability of the two dimensions was 0.753 and 0.888 respectively.

DISCUSSION

With the transformation of biology-psychology-social medicine model, strengthening the construction of mental health service system and standardization of management related policies. The concern for the mental state of clinical medical workers has become a widespread concern in the society (28). As the susceptible population of STS, the inappropriate psychological stress of nursing staff not only affects their physical and mental health, but also affects the quality of nursing service (29, 30). Therefore, it is particularly important to select appropriate and reliable assessment tools for early identification of related symptoms. The purpose of this study is to provide a reliable tool for the evaluation of STS for clinical nurses by sinicizing STSS and testing the reliability and validity of the application of STSS in clinical nurses.

Validity refers to the accuracy, validity and correctness of the measurement content of an evaluation scale. Including structure validity and content validity (31). Exploratory factor analysis was used to verify the structural validity of the C-STSS in this study. Principal component analysis was used to extract the common factor and generate the gravel map of the factor structure. The item could be considered to be in the factor when the factor load value and common degree ≥0.40. The exploratory factor analysis results of this study showed that the C-STSS extracted two common factors and retained all the items in the original scale, with a cumulative contribution rate of 65.560%. Finally, a questionnaire with 2 dimensions and 17 items was formed. One less than the three dimensions in the original scale. The item distribution was not completely consistent with the original scale. The reasons may be as follows: ①regional cultural differences; ②differences in research objects, such as gender, age, position, economic status, etc.; ③time difference. By careful analysis of the items contained in the two dimensions of C-STSS, it can be found that the first dimension—stress dimension (items 1, 4, 5, 7, 8, 9, 11, 15, 16, 17) mainly describes the influence of STS on helpers' daily life and psychological state (including sleep, mood, concentration, enthusiasm, etc.). And dimension 2—invasion and avoidance dimension (items 2, 3, 6, 10, 12, 13, 14) mainly describe the content related to the trauma victims they help.

In order to further confirm the rationality of this dimension division, this study conducted an in-depth analysis of the dimensions of the scale and the distribution of items contained in it. The results showed that the validity of all dimensions and the overall validity of the C-STSS was good. The I-CVI of The C-STSS ranged from 0.80 to 1.00. Both >0.80. The S-CVI/Ave was 0.94. Greater than 0.90. This indicates that each item of the scale had high content validity. The results of internal correlation analysis showed that the correlation coefficient between each item of the scale and the total score of the scale was 0.616–0.834. The correlation coefficient between stress dimension and the total table was 0.965. The correlation coefficient between invasion and avoidance dimension and the total table was 0.932. The correlation coefficient between the two dimensions was 0.806. All of them were statistically significant ($P < 0.001$). This shows that the internal consistency of the scale is good. In addition, the correlation coefficients between the two dimensions and the total table are higher than those between the two dimensions, indicating that each dimension is consistent with the overall concept and relatively independent. Finally, according to the fitting results of the model by confirmatory factor analysis, it can be seen that all fitting indexes reach the ideal standard. The model fits well.

Reliability is to evaluate the stability, equality and internal consistency of the results measured by the scale. Including internal and external reliability. The greater the reliability of the scale, the smaller the standard error of measurement (32). The internal consistency reflects the internal reliability among the measurement items. It checks whether each item of the scale measures the same content. The results of this study show that the Cronbach's α coefficient of The C-STSS is 0.956. The Cronbach's α coefficient of stress dimension is 0.931. The Cronbach's α coefficient of invasion and avoidance dimension is 0.926. All >0.70. Indicating that the C-STSS has good internal consistency. The half-fold reliability of C-STSS is 0.934. The half-fold reliability of both dimensions is 0.920. Indicating that the scale has good internal relevance. The most commonly used evaluation index of external reliability is retest reliability. The retest reliability of The C-STSS is 0.910, >0.80. The retest reliability of the 2 dimensions is 0.753 and 0.888, which indicating that the scale has good cross-time stability. Therefore, the C-STSS has good internal and external reliability and is reliable.

CONCLUSIONS

Due to specific occupational factors, long-term exposure of nurses to stressors may result in job dissatisfaction or burnout. Especially in the context of the COVID-19 epidemic in the past 2 years, their work intensity and psychological stress often exceed load. The psychological problems of medical workers

have become a topic of general concern. The psychosomatic health of nursing staff needs more attention and intervention. The C-STSS is an easy-to-implement scale with 17 items. It has a high level of internal consistency reliability and validity. All the evaluation indexes of the scale meet the requirements of measurement, which can be used for the evaluation of STS of clinical medical staff. The application of this scale in China has certain significance.

Limitations

The sampling sites in this study are only in Changsha city of Hunan Province. It doesn't represent all caregivers in the country. The sample range can be expanded in the future to further verify its applicability. In addition, the subjects were all nursing staff. Cannot represent other social workers such as: mental health professionals, child protection workers, etc. The scale can be further expanded by studying other social workers.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan Normal University). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YH, ZL, and JZ conceived the study concept and designed the study. HW and HX participated in data collection. YH and JY analyzed the data. YH wrote the initial draft of the manuscript and corrected the manuscript. All the authors read and approved the final version of the article.

ACKNOWLEDGMENTS

The authors would like to thank all the staff and organizations that supported this survey: Hunan Provincial People's Hospital, Hunan Provincial Second People's Hospital, and Changsha Xingsha Hospital.

REFERENCES

1. Brian EB, Margaret MR, Charles RF. Development and validation of the secondary traumatic stress scale. *Res Soc Work Pract.* (2004) 14:27–35. doi: 10.1177/1049731503254106
2. Figley C, Charles R. *Treating Compassion Fatigue[M]*. New York, NY: Bruner-Routledge (2002).
3. Roberts F, Teague B, Lee J, Rushworth I. The prevalence of burnout and secondary traumatic stress in professionals and volunteers working with forcibly displaced people: a systematic review and two meta-analyses. *J Trauma Stress.* (2021) 34:773–85. doi: 10.1002/jts.22659
4. Steinheiser M. Compassion fatigue among nurses in skilled nursing facilities: discoveries and challenges of a conceptual model in research. *Appl Nurs Res.* (2018) 44:97–9. doi: 10.1016/j.apnr.2018.10.002
5. Benuto LT, Yang Y, Ahrendt A, Cummings C. The secondary traumatic stress scale: confirmatory factor analyses with a national sample of victim advocates. *J Interpers Violence.* (2021) 36:2572–91. doi: 10.1177/0886260518759657
6. Ozer EJ, Best SR, Lipsey TL, Weiss DS. Predictors of posttraumatic stress disorder and symptoms in adults: a meta-analysis. *Psychol Bull.* (2003) 129:52–73. doi: 10.1037/0033-2909.129.1.52
7. Lee H, Baek W, Lim A, Lee D, Pang Y, Kim O. Secondary traumatic stress and compassion satisfaction mediate the association between stress and burnout among Korean hospital nurses: a cross-sectional study. *BMC Nurs.* (2021) 30:115. doi: 10.1186/s12912-021-00636-w
8. Ting L, Jacobson JM, Sanders S, Bride BE, Harrington D. The secondary traumatic stress scale: confirmatory factor analyses with a national sample of mental health social workers. *J Hum Behav Soc Environ.* (2005) 11:177–94. doi: 10.1300/J137v11n03_09
9. Johansen AB, Kristiansen E, Bjelland I, Tavakoli S. Secondary traumatic stress in norwegian sud-therapists: symptoms and related factors. *Nordisk Alkohol Nark.* (2019) 36:522–31. doi: 10.1177/1455072519847014
10. Burr KL, O'Brien P, Brown JM, Penfil SH, Hertzog JH. Occupational-induced secondary traumatic stress and posttraumatic stress disorder in respiratory therapists. *Respir Care.* (2020) 65:1019–23. doi: 10.4187/respcare.06840
11. Craun SW, Bourke ML, Bierie DM, Williams KS. A longitudinal examination of secondary traumatic stress among law enforcement. *Victims Offend.* (2014) 9:299–316. doi: 10.1080/15564886.2013.848828
12. Teel J, Reynolds M, Bennett M, Roden-Foreman JW, McShan E, Hamilton R, et al. Secondary traumatic stress among physiatrists treating trauma patients. *Proc (Bayl Univ Med Cent).* (2019) 32:209–14. doi: 10.1080/08998280.2018.1559694
13. Kegye A, Takács S, Ries B, Zana Á, Hegedus K. A szakmai élet minoségét méro kérdoív (professional quality of life scale) magyar változatának validálása [validation of the hungarian version of the professional quality of life Scale]. *Orv Hetil.* (2018) 159:1441–9. doi: 10.1556/650.2018.31126
14. Jacobs I, Charmillot M, Martin Soelch C, Horsch A. Validity, reliability, and factor structure of the secondary traumatic stress scale-french version. *Front Psychiatry.* (2019) 10:191. doi: 10.3389/fpsyt.2019.00191
15. Daniels J. SekundäreTraumatisierung. *Psychotherapeut.* (2008) 53:100–7. doi: 10.1007/s00278-008-0585-y
16. Kitano M, Shoji K, Nakaita I, Sano S, Tachibana S, Bride BE, et al. Validity and reliability of the secondary traumatic stress Scale-Japanese version. *Neuropsychopharmacol Rep.* (2021) 41:476–84. doi: 10.1002/npr2.12207
17. Mangoulia P, Koukia E, Alevizopoulos G, Fildissis G, Katostaras T. Prevalence of secondary traumatic stress among psychiatric nurses in Greece. *Arch Psychiatr Nurs.* (2015) 29:333–8. doi: 10.1016/j.apnu.2015.06.001
18. Okoli CTC, Seng S, Otachi JK, Higgins JT, Lawrence J, Lykins A, et al. A cross-sectional examination of factors associated with compassion satisfaction and compassion fatigue across healthcare workers in an academic medical centre. *Int J Ment Health Nurs.* (2020) 29:476–87. doi: 10.1111/inm.12682
19. Acquadro Maran D, Zito M, Colombo L. Secondary traumatic stress in italian police officers: the role of job demands and job resources. *Front Psychol.* (2020) 11:1435. doi: 10.3389/fpsyg.2020.01435
20. Morrison LE, Joy JP. Secondary traumatic stress in the emergency department. *J Adv Nurs.* (2016) 72:2894–906. doi: 10.1111/jan.13030
21. Ratrout HF, Hamdan-Mansour AM. Secondary traumatic stress among emergency nurses: prevalence, predictors, and consequences. *Int J NursPract.* (2020) 26:e12767. doi: 10.1111/ijn.12767
22. Missouridou E. Secondary posttraumatic stress and nurses' emotional responses to patient's trauma. *J Trauma Nurs.* (2017) 24:E3–E4. doi: 10.1097/JTN.0000000000000280
23. Greinacher A, Derezza-Greeven C, Herzog W, Nikendei C. Secondary traumatization in first responders: a systematic review. *Eur J Psychotraumatol.* (2019) 10:1562840. doi: 10.1080/20008198.2018.1562840

24. Molnar BE, Sprang G, Killian KD, Gottfried R, Emery V, Bride BE. Advancing science and practice for vicarious traumatization/secondary traumatic stress: a research agenda. *Traumatology.* (2017) 23:129–42. doi: 10.1037/trm0000122
25. Zakeri MA, Bazmandegan G, Ganjeh H, Zakeri M, Mollaahmadi S, Anbariyan A, et al. Is nurses' clinical competence associated with their compassion satisfaction, burnout and secondary traumatic stress? a cross-sectional study. *Nurs Open.* (2020) 8:354–63. doi: 10.1002/nop2.636
26. Wang MC, Sui SG, Li JH, Dai XY. Psychometric properties of the PTSD checklist-civilian version among junior school students from earthquake-hit region. *Chinese J Behav Med Brain Sci.* (2010) 6:566–8. doi: 10.3760/cma.j.issn.1674-6554.2010.06.032
27. Chen HY, Wang WH. Reliability and validity of the chinese version of the compassion fatigue scale. *Chin Nurs Manag.* (2013) 13:39–41. doi: 10.3969/j.issn.1672-1756.2013.04.012
28. "Healthy China 2030". *Plan outline of the CPC Central Committee and The State Council[EB/OL].* Available online at: http://www.gov.cn/zhengce/2016-10/25/content_5124174.htm (accessed October 25, 2016).
29. Tracey C Arnold. An evolutionary concept analysis of secondary traumatic stress in nurses. *Nurs Forum.* (2020) 55:149–56. doi: 10.1111/nuf.12409
30. Bock C, Heitland I, Zimmermann T, Winter L, Kahl KG. Secondary traumatic stress, mental state, and work ability in nurses-results of a psychological risk assessment at a university hospital. *Front Psychiatry.* (2020) 11:298. doi: 10.3389/fpsyt.2020.00298
31. Qu S, Shi XX, Xie ZJ, Ding RJ, Zheng MJ. Validity and reliability of the Patient Health Questionnaire and the Generalized Anxiety Scale for screening depressive anxiety in patients with non-cardiac chest pain. *Chin Ment Health J.* (2021) 35:376–381. doi: 10.3969/j.issn.1000-6729.2021.05.005
32. Huang L, Chen QL, Luo L, Wang Y, Hou WL, Hu RF. Validity and reliability of the Chinese version of the Richards-Campbell Sleep Questionnaire. *Chinese J Ment Health.* (2018) 32:401–6. doi: 10.3969/j.issn.1000-6729.2018.05.009

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 He, Liu, Zhang, Yao, Xiao and Wan. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers | Frontiers in Surgery

ORIGINAL RESEARCH
published: 01 April 2022
doi: 10.3389/fsurg.2022.850099

Oblique Lumbar Interbody Fusion Using a Stand-Alone Construct for the Treatment of Adjacent-Segment Lumbar Degenerative Disease

*Wang Kai, Cheng Cheng, Qingyu Yao, Can Zhang, Fengzeng Jian and Hao Wu**

Department of Neurosurgery, Xuanwu Hospital of Capital Medical University, Beijing, China

Objective: Adjacent-segment disease (ASD) is common in patients undergone previous lumbar fusion. A typical revision treatment from posterior approach requires management of postoperative scar tissue and previously implanted instrumentation. An oblique lumbar interbody fusion (OLIF) approach allows surgeon to reduce the potential risk of posterior approach. This study aimed to analyze the clinical and radiographic efficacy of stand-alone OLIF for the treatment of lumbar adjacent-segment disease.

Methods: A total of 13 consecutive patients who underwent stand-alone OLIF for the treatment of adjacent-segment disease from December 2016 to January 2019 were reviewed. Visual analog scale (VAS) of back pain and leg pain and the Oswestry Disability Index (ODI) before surgery and at last postoperative clinic visits were obtained. Radiography, CT and MRI before and at last follow-up after surgery was evaluated in all patients.

Results: During the study period, 13 cases were successfully treated with stand-alone OLIF. The mean follow-up was 17.7 ± 8.3 months. The back pain VAS improved from 6.2 ± 1.0 to 2.0 ± 1.1 ($P < 0.01$), and the leg pain VAS improved from 7.0 ± 1.9 to 1.0 ± 0.9 ($P < 0.01$). ODI improved from 28.0 ± 7.5 to 10.8 ± 4.0 ($P < 0.01$). The disc height (DH) increased from 9 ± 2 to 12 ± 2 mm ($P < 0.01$), the cross-sectional area (CSA) of spinal canal increased from 85 ± 26 to 132 ± 24 mm^2 ($P < 0.01$), the foraminal height increased from 17 ± 2 to 21 ± 3 mm ($P < 0.01$) and the CSA of foramen increased from 95 ± 25 to 155 ± 36 mm^2 ($P < 0.01$). Cage subsidence was observed in 2 cases.

Conclusions: Stand-alone OLIF provides a safe and effective alternative way to treat ASD.

Keywords: oblique lumbar interbody fusion, stand-alone, adjacent-segment disease, visual analog scale, Oswestry Disability Index

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Yang Liu,
The First Medical Center of Chinese PLA General Hospital, China
Jiangang Liu,
The Second Affiliated Hospital of Shandong First Medical University, China

****Correspondence:***
Hao Wu
haoo13901@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *07 January 2022*
Accepted: *03 March 2022*
Published: *01 April 2022*

Citation:
Kai W, Cheng C, Yao Q, Zhang C, Jian F and Wu H (2022) Oblique Lumbar Interbody Fusion Using a Stand-Alone Construct for the Treatment of Adjacent-Segment Lumbar Degenerative Disease. Front. Surg. 9:850099. doi: 10.3389/fsurg.2022.850099

INTRODUCTION

Adjacent-segment disease (ASD) is a common phenomenon following lumbar spinal fusion (1). The development of adjacent segment disease is undoubtedly multifactorial. While some studies attribute this to increased motion and biomechanical forces on the unfused segments, it is also clear that patient characteristics, including age, sex and previously lumbar degeneration could

predispose the patient to further degeneration (2–5). Many studies have shown that the rate of ASD is ∼3% per year (6). The patients developing ASD experience axial pain, radiculopathy or neurogenic claudication (3, 7).

Operative management to achieve decompression and stabilization for symptomatic ASD should be considered after failure of non-operative management (6). Traditionally, this is performed posteriorly with laminectomy, extension of the instrumentation and fusion level. However, this method requires extensive soft tissue dissection to expose the previously implanted hardware, adding to prolonged operation time, blood loss, postoperative pain and prolonging recovery with high associated health care costs (3, 8, 9). In addition, exposing the previous laminectomy site poses a higher risk of dural violations and Cerebrospinal Fluid (CSF) leakage due to postoperative scar tissue (3, 10). As minimally invasive lateral lumbar interbody fusion has become increasingly popular over the past decade, it offers the surgeon an alternative strategy for revision surgery to avoid these risks (3). It allows the surgeon to achieve indirect decompression and interbody fusion. The effectiveness of indirect decompression relies on distraction across the intervertebral space to stretch the spinal ligaments and enlarge the central canal as well as increase the foraminal space for the exiting nerve root (11–13). However, the transpsoas approach is associated with direct muscle injury and a risk of injury to the lumbar plexus as it courses through the psoas (14–16). The oblique lumbar interbody fusion (OLIF) was introduced as an alternative procedure to the transpsoas approach, allowing for psoas preservation and avoids the lumbar plexus (17, 18). Several studies have reported promising results of OLIF for primary surgery of lumbar degenerative disease (12, 13, 18–20). However, there are few reports of stand-alone OLIF for treatment of ASD (21). The radiographic indirect decompression effect of spinal canal and foramen, namely the CSA of spinal canal and foramen, has not been evaluated yet.

Here, we report a consecutive series of patients who had undergone stand-alone OLIF without additional instrumentation to achieve indirect decompression and stabilization for ASD and evaluate the clinical and radiographic efficacy of this approach.

PATIENT AND METHODS

Study Population

This is a retrospective study. A total of 13 consecutive patients who had undergone stand-alone OLIF for ASD after lumbar fusion in Xuanwu Hospital between December 2016 and January 2019 were included in this study based on the following inclusion criteria: (I) clinical and radiographic findings as reported by Cheh et al. were consistent with progressive degeneration at the adjacent spinal level with associated new back and/or leg symptoms (2); (II) refractory to conservative measures including NSAIDs and epidural injection; (II) single-level stand-alone OLIF for the treatment of ASD to a lumbar fusion construct. Patients were excluded from the study if they had undergone surgery for a non-degenerative etiology such as infection or trauma. Medical records, operative reports and radiographic imaging studies were retrospectively reviewed.

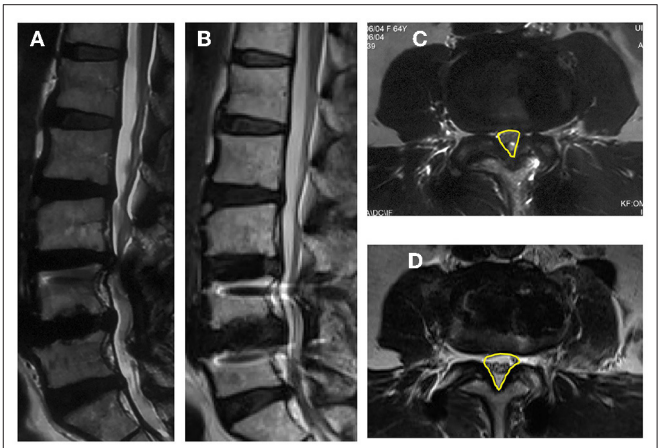


FIGURE 1 | Images obtained in a 62-year-old woman who had an L4–L5 posterior instrumented fusion 6 years earlier. She experienced new back and leg pain and intermittent claudication due to adjacent-segment degeneration and stenosis for 3 months. **(A)** Pre-operative sagittal MRI; **(B)** Sagittal MRI at last follow-up post-operative; **(C)** Pre-operative axial MRI through the L3–4 and CSA (the yellow contour line illustrates); **(D)** Post-operative axial MRI through the L3–4 and CSA (the yellow contour line illustrates).

Surgical Technique

A stand-alone procedure was defined by the absence of instrumentation at the OLIF level. The OLIF procedures were performed using the OLIF (DePuy Synthes, Raynham, MA, USA), as similarly described in previous reports (18). The patient was put in the right lateral decubitus position with spine flex to increase the distance between the iliac crest and the rib cage. A 4-cm skin incision was made about 5 cm anterior to the mid portion of an intervertebral disc of interest, parallel to the fibers of the external oblique. The retroperitoneal space is accessed by blunt dissection. The peritoneal content was mobilized anteriorly and the psoas muscle was retracted posteriorly, revealing the intervertebral disc. After confirming the segment of intervertebral disc with fluoroscopy, we incised the annulus, remove the disc material with curettes and rongeurs and prepare the endplates. An appropriately sized polyetheretherketone (PEEK) cage (DePuy Synthes, Raynham, MA, USA) is then filled with allogeneic bone graft and hydroxyapatite containing bone morphogenetic protein (BMP) mixed with bone marrow which is aspirated from iliac crest. Neither posterior fixation nor lateral fixation was applied. All patients were allowed to ambulate by Boston brace on the second postoperative day. The Boston brace was recommended for removal after 12 weeks.

Outcome Measures

Back and leg pain was evaluated according to the visual analog scale (VAS). The Oswestry Disability Index (ODI) before surgery and at last routine postoperative clinic visits were also compared. Achievement of minimum clinically important difference (MCID) was evaluated using following thresholds: ODI 10, back pain VAS 2.1, leg pain VAS 2.8. Radio (22, 23) graph, Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) before and at last follow-up after surgery was

evaluated in all patients. Axial CSA of the spinal canal at the ASD level were evaluated by T2-weighted MRI (**Figure 1**). DH, height of intervertebral foramen, and CSA of intervertebral foramen were evaluated with CT (**Figure 2**). Averages of the anterior and posterior heights of the disk were used for disk height; and largest diameter of foramen was used for evaluation. Segmental lordosis (SL) was determined by measuring the sagittal Cobb angle between the upper endplate of the upper vertebral body in relation to the lower endplate of the lower vertebral body fused. Lumbar lordosis (LL) was determined by measuring the sagittal Cobb angle between the upper endplate of the L1 and S1 vertebra. All diameters and CSAs were measured using a picture archiving and communication systems (PACS). Grading of severity of lumbar spinal stenosis based on reports by Schizas et al. (24). Radiograph at last follow-up was used to evaluate subsidence (25). CT images obtained at last follow-up were reviewed to assess bridging bone to determine if bony fusion had occurred. Fusion criteria on CT studies included the presence of bony trabeculation across the fusion level and lack of bony lucency at the graft/vertebral body junction (26–28). Evaluation of bone fusion was blinded and performed by 3 surgeons. Fusion was identified if at least 2 of the observers concurred. Complications during surgery and follow-up periods are detected by assessment and physical examination according to past reports and patient self-reports (18, 29, 30). Data on perioperative and postoperative complications in the patients were collected and reviewed.

RESULTS

The 13 consecutive patients were included in this study. The mean patient age was 68.5 ± 8.7 years. The mean BMI (Body Mass Index) was 26.5 ± 3.2 Kg/m^2. All of the cases were successfully treated with stand-alone OLIF. The mean operation time was 64.9 ± 18.9 mins. The mean blood loss was 22.3 ± 8.6 mL. Hospital stay post operation was 3.8 ± 0.8 days. The mean follow-up was 17.7 ± 8.3 months. The mean follow-up time after operation was 17.7 ± 8.3 months. Demographic and operative characteristics of the patients was shown in **Table 1**.

Low back pain, leg pain evaluated by VAS were significantly improved at last follow-up after surgery compared with before surgery ($P < 0.01$, **Table 2**). ODI was also significantly improved at last follow-up months after surgery compared with before surgery ($P < 0.01$, **Table 2**). The percentage attainment of MCID at last follow-up for back pain VAS, leg pain VAS and ODI was 100, 100, and 84.62%, respectively.

The DH, the axial CSA of spinal canal, the foraminal height and the CSA of foramen were significantly enlarged at last follow-up compared those before surgery ($P < 0.01$, **Figure 2**). Segmental lordosis improved from a mean of 5.4° ± 7.7° to 8.7° ± 4.5° ($P < 0.05$) between the preoperative and final follow-up radiographs. Global lumbar lordosis (L1–S1) increased from 34.8° ± 13.5° to 40.8° ± 10.0° ($P < 0.05$) comparing preoperative and last follow-up radiographs (**Figure 2**). All of the 13 patients achieved bony fusion during their follow-up period (**Table 1**).

Grade I cage subsidence at 2 levels was observed in 2 of the patients by their last follow-up (**Figure 3**). However, at their last follow-up, the clinical symptoms were significantly relieved, and improved VAS, ODI scores were achieved. The OLIF procedures in the lumbar spine are associated with transient or permanent symptoms in the thigh. Due to retrospective direction of observation, these data were not consistently available and thus were not included in the study. However, thigh numbness, pain, dysesthesias, or weakness indicative of a lumbosacral plexopathy was not seen in any of the patients by their last follow-up visit. No patients experienced infection or injuries to the great abdominal vessels, abdominal viscera and ureters.

DISCUSSION

Adjacent-segment degeneration is an undeniable phenomenon after lumbar fusion surgery. The incidence of clinically symptomatic ASD following lumbar fusion is about 3% annually (6, 31). This risk is increased in older patients, male patients and with pre-existing facet or disk degeneration. Additional risk factors include multi-level constructs and floating fusion (5, 32). Disruption of sagittal or coronal balance and ligamentous disruption can accelerate degeneration of adjacent segments in the lumbar spine (31, 33). Given this high incidence, spinal surgeons are facing a growing population of patients in need of treatment for ASD.

One clinical question that arises is whether or not ASD can be managed non-operatively. Within our review, no study directly compared non-operative with operative management for ASD. However, from a clinical perspective, it stands to reason that non-operative treatment would first be implemented and operative treatment undertaken only after failure of non-operative treatment, just as in primary lumbar pathology (6). However, it is unclear how effective non-operative care is, because there are no studies directly comparing non-operative care with surgical intervention for ASD. Thus, clinical judgment, best available evidence, and patient preference are the current cornerstones that guide treatment (6).

Another issue to address is the type of operative treatment to choose. ASD may be associated with kyphosis, severe disc collapse, listhesis, or hypertrophied ligamentum flavum causing adjacent segment stenosis. However, there is absence of literature directly comparing one type of operative treatment with another type.

For cases involving only neural entrapment without axial symptoms, the surgeon may choose limited decompression. A potential benefit of laminectomy alone is that minimally invasive surgery (MIS) may be performed. However, this approach risks iatrogenic destabilization adjacent to a fused construct and increases the risk of recurrent ASD (31). A more typical approach is to perform revision posterior surgery with both a laminectomy and extension of the instrumentation and fusion to the rostral levels (3, 34, 35). In the setting of symptomatic ASD with radiographic evidence, patients often have significant improvement in pain and quality of life with 2 years minimum follow up (6, 34, 36). However, revision surgery through a previous lumbar incision can be cumbersome in the setting of scar tissue and violation of natural landmarks from the initial

TABLE 1 | Summary of patient demographics and surgical characteristics.

Patient No.	Sex	Age (yrs)	BMI (Kg/m^2)	Comorbidities	Prior operation	Time before revision (mos)	Symptoms before revision	Level	Radiographic findings	Time of operation (mins)	Blood loss (mL)	Hospital stay post revision (days)	Follow-up (mos)	Fusion	Subsidence
1	M	61	24.22	HT	TLIF L4/5, L5S1	16	Low back pain, pain in bilateral lower extremities	L3/4	Spinal canal (Grade C), bilateral foraminal stenosis	45	30	4	33	Yes	No
2	M	80	29.41	HT, DM	TLIF L3/4	48	Low back pain, Intermittent claudication.	L2/3	Loss of intervertebral height, spondylolisthesis, lumbar spinal stenosis (Grade C), LDH	100	35	5	25	Yes	No
3	M	81	24.46	HT	PLIF L3/4, 4/5	156	Low back pain	L2/3	Loss of intervertebral height, spondylolisthesis, lumbar spinal stenosis (Grade A3), bilateral foraminal stenosis	105	40	4	25	Yes	Grade 1
4	F	66	24.44	CHD	TLIF L4/5	26	Pain in left lower extremity, intermittent claudication	L3/4	Lumbar spinal stenosis (Grade B), left foraminal stenosis	40	20	3	22	Yes	Grade 1
5	F	79	29.78	HT	TLIF L4/5, L5S1	104	Low back pain, pain in left lower extremity	L3/4	Lumbar spinal stenosis (Grade C), left foraminal stenosis, lumbar instability	67	25	3	26	Yes	No
6	F	64	25.07	HT, DM	TLIF L4/5	24	Pain in right lower extremity	L3/4	Loss of intervertebral height, lumbar spinal stenosis (Grade B), right foraminal stenosis, LDH	60	20	4	22	Yes	No
7	F	71	24.17	HT	PDF L3/4, 4/5	180	Low back pain, intermittent claudication	L2/3	Lumbar spinal stenosis (Grade B), lumbar instability	56	20	3	16	Yes	No
8	M	57	25.83	CHD, DM	TLIF L4/5, L5S1; Endoscopic discectomy L3/4	108	Low back pain, pain in right lower extremity, intermittent claudication	L3/4	Loss of intervertebral height, spondylolisthesis, lumbar spinal stenosis (Grade C), bilateral foraminal stenosis, effusion of facet joints	75	20	4	10	Yes	No
9	M	65	27.66	HT	TLIF L5S1	60	Low back pain, pain in right lower extremity	L4/5	Loss of intervertebral height, spondylolisthesis, lumbar spinal stenosis (Grade A3), bilateral foraminal stenosis	60	20	5	8	Yes	No
10	F	54	34.6	HT	TLIF L4/5 and PDF L5S1; Removal of implants	28	Low back pain, pain in right lower extremity, intermittent claudication	L3/4	Loss of intervertebral height, lumbar spinal stenosis (Grade D), left foraminal stenosis	65	20	3	8	Yes	No

(Continued)

TABLE 1 | Continued

Patient No.	Sex	Age (yrs)	BMI (Kg/m^2)	Comorbidities	Prior operation	Time before revision (mos)	Symptoms before revision	Level	Radiographic findings	Time of operation (mins)	Blood loss (mL)	Hospital stay post revision (days)	Follow-up (mos)	Fusion	Subsidence
11	M	68	25.71	HT, DM	PLIF L3/4, 4/5	41	Low back pain, pain in bilateral lower extremities	L2/3	Loss of intervertebral height, spondylolisthesis, lumbar spinal stenosis (Grade B), bilateral foraminal stenosis	60	20	3	13	Yes	No
12	M	68	22.49	HT, DM	TLIF L4/5, L5S1	52	Low back pain, pain in left lower extremity	L3-4	Loss of intervertebral height, spondylolisthesis, lumbar spinal stenosis (Grade A3), left foraminal stenosis	58	10	3	9	Yes	NO
13	M	77	26.47	HT, DM	TLIF L4/5, L5S1	144	Low back pain, pain in left lower extremity, intermittent claudication	L3/4	Loss of intervertebral height, spondylolisthesis, lumbar spinal stenosis (Grade D), left foraminal stenosis LDH	53	10	5	13	Yes	No

CHD, Coronary heart disease; DM, Diabetes mellitus; HT, Hypertension; LDH, lumbar disc herniation; PDF, Posterior decompression and fusion; PLIF, Posterior Lumbar Interbody Fusion; TLIF, Transforaminal lumbar Interbody fusion.

TABLE 2 | Clinical outcomes.

Parameter	Value preop	Value postop	*p*
VAS, back	6.2 ± 1.0	2.0 ± 1.1	<0.01
VAS, leg	7.0 ± 1.9	1.0 ± 0.9	<0.01
ODI	28.0 ± 7.5	10.8 ± 4.0	<0.01

surgery. This can lead extensive soft tissue dissection, adding to surgical blood loss, severe postoperative pain, prolonging operation time and recovery with high associated health care (8). In addition, exposing the previous laminectomy site poses a higher risk of dural violations and CSF leakage due to postoperative scar tissue (10, 37, 38).

The standard of care in ASD remains structural stabilization, or extension of the construct, and decompression (34, 35). Thus, other approach has been proposed to avoid the disadvantages. Chen et al. introduced cortical bone trajectory screws fixation with minimal invasive interbody cage fusion for lumbar adjacent segment disease to negates removal of pre-existing instruments and reduce the wound length, blood loss and soft tissue damage compared with traditional surgery (33). Minimally invasive lateral interbody fusion is another viable option for the treatment of ASD. It is an entirely different access route to the spine, which could avoid previous lumbar incision and disruption of the posterior tension band. Minimally invasive lateral interbody fusion of the adjacent segment and posterior extension of fusion could achieve clinical and radiographic improvement of ASD (33). Du et al. reported lateral lumbar interbody fusion (LLIF) with unilateral pedicle screw fixation for the treatment of ASD (39). Wang et al. reported LLIF without supplemental pedicle screw fixation and Palejwala et al. reported LLIF using a stand-alone construct for the treatment of ASD (3, 7). All of above studies shows significantly reduced pain and favorable radiographic results treated by LLIF (3, 7, 33, 39). However, the LLIF approach is associated with access-related thigh pain caused by direct muscle injury and has an added a risk of injury to the lumbar plexus (40–43). Furthermore, high rates of transient anterior thigh symptoms are found despite real-time electromyography monitoring (16). Thus, OLIF has been applied recently to avoid invasion of the psoas muscle and lumbar plexus (17, 18).

Zhu et al. compared stand-alone oblique lumbar interbody fusion with posterior lumbar interbody fusion for revision of rostral adjacent segment disease and concluded that OLIF was effective and safe for the treatment of rostral ASD following prior posterior lumbar fusion, and is superior to PLIF in terms of perioperative parameters, short-term clinical outcomes, and DH restoration, with similar fusion and reduction rates (21). In our study, we reviewed a consecutive series of patients who had undergone OLIF using a stand-alone construct for the treatment of ASD. This approach achieved satisfied clinical outcomes (**Table 2**). It also achieved radiographic indirect decompression by enlarging the DH, the axial CSA of spinal canal, the foraminal height and the CSA of foramen (**Figure 2**). Besides, it showed the advantage of being minimally invasive. The mean

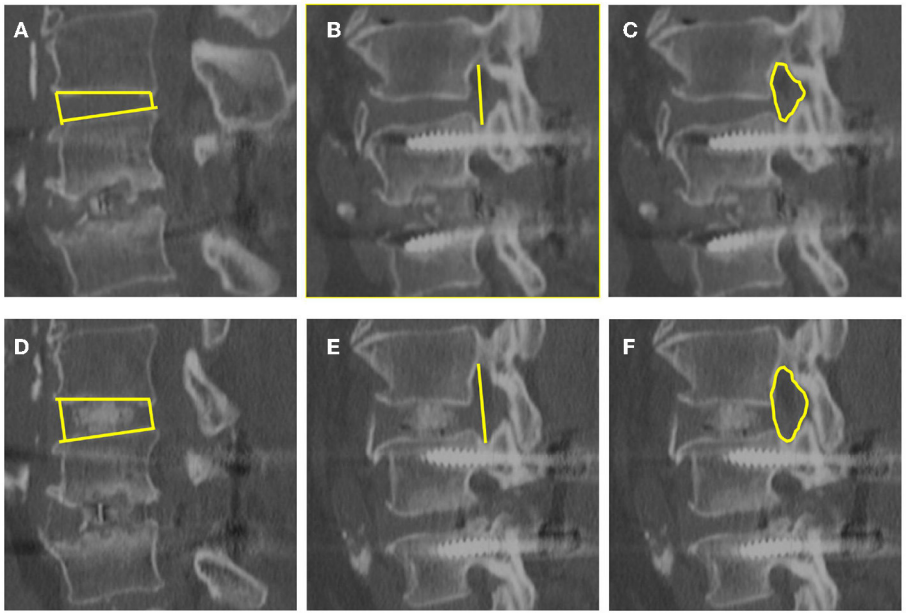


FIGURE 2 | Images obtained in the same patient. Disk height **(A,D)**, foraminal height **(B,E)**, and foraminal CSA **(C,F)** were evaluated with CT before and at last follow-up after surgery. **(A–C)** are before surgery, and **(D–F)** are at last follow-up after surgery.

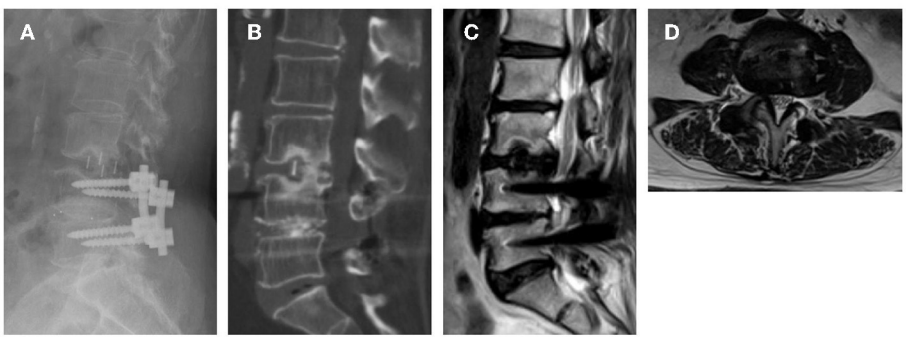


FIGURE 3 | Images obtained in a 66-year-old woman who had an L4–L5 posterior instrumented fusion 26 month ago. She experienced new leg pain and intermittent claudication due to adjacent-segment degeneration and stenosis for 2 months. **(A)** 18 months follow-up reviewed Grade I subsidence; **(B)** CT confirmed bony fusion was achieved; **(C,D)** Indirect decompression of spinal canal was maintained.

blood loss of 28.3 ± 8.2 ml, the mean operation time of 69.5 ± 27.4 min and the mean hospital stay of 3.8 ± 0.8 days demonstrate that this approach is likely to cause less morbidity than a posterior approach to the spine. There is no need to involve a laminectomy and extension of instrumentation as a standard posterior revision surgery do. Thus, CSF leakage and the management of previously implanted spinal instrumentation could be avoided. Another advantage of this approach is that the posterior spinal elements, including the facet joint capsules, are not disrupted; thus, additional degeneration at the supra adjacent level may also be less likely to occur (3). Moreover, this procedure improves SL and global LL after lateral surgery. Thus, its application in patients may have potential benefits for sagittal imbalance.

A major concern regarding the use of stand-alone OLIF is that the construct may not be strong enough to promote fusion, and prevent the interbody cages from subsidence. As we all know, indirect neural decompression in OLIF was achieved by reduction of disc bulging and elongation of the hypertrophied ligamentum flavum through the restoration of DH (12). Cage subsidence caused by endplate damage, improper cage size, and osteoporosis may affect indirect neural decompression and interbody fusion. However, low-grade subsidence is likely an expected outcome, while high-grade subsidence may result in persistent symptoms or reoperation (25, 44). Moreover, stand-alone construct has shown evidence of solid arthrodesis and improvements in clinical symptoms and fusion rate was not affected by incidence of subsidence (25, 45–47). Careful attention

to proper endplate preparation without violation of the cortical endplate is also critical to minimizing settling (3). In our study, Grade I cage subsidence was observed in 2 of the patients by their last follow-up. However, the bony fusion was achieved and the clinical symptoms were improved as well. Therefore, we believe indirect decompression could be maintain as long as bony fusion was achieved and high-grade subsidence was avoided.

There are several limitations to this study. With regard to the relief of neurological symptoms of stenosis, the OLIF approach relies entirely on indirect decompression by elevating intervertebral disc height, which expands the neuroforamen and tensions the ligaments to open the central canal. While we found excellent clinical and radiographic results, one might expect this approach to be occasionally inadequate in cases of severe stenosis, as well as in cases without severe disc collapse. A larger study with a wider variety of specific pathologies would be helpful to validate this technique across the broad spectrum of ASD. Another limitation relates to our ability to ascertain definitive fusion. In this series, we used reconstructed CT scans to identify bridging bone between the treated vertebral bodies as the determinant of fusion. However, a follow-up longer than 2 years would also be helpful as well, as an osseous nonunion would likely become more apparent clinically or radiographically over more protracted periods of time.

CONCLUSION

This limited study suggests that OLIF using a stand-alone construct may be a safe and effective alternative way in treating ASD following a previous lumbar fusion. The approach can achieve adequate indirect neural decompression, satisfied clinical outcome as well as solid arthrodesis without supplemental fixation.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Xuanwu Hospital of Capital Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

WK is responsible for the writing of the paper. CC is responsible for the search for data and the inclusion of cases. QY is responsible for the design of the study. CZ is responsible for the evaluation of the results. FJ is responsible for the statistics of the data. HW is the instructor of the entire study. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported by the Beijing Natural Science Foundation of China, the Beijing Natural Science Foundation of China Joint Project (KZ20191025028).

REFERENCES

1. Hilibrand AS, Robbins M. Adjacent segment degeneration and adjacent segment disease: the consequences of spinal fusion? *Spine J.* (2004) 4:190S−4S doi: 10.1016/j.spinee.2004.07.007
2. Cheh G, Bridwell KH, Lenke LG, Buchowski JM, Daubs MD, Kim Y, et al. Adjacent segment disease followinglumbar/thoracolumbar fusion with pedicle screw instrumentation: a minimum 5-year follow-up. *Spine.* (2007) 32:2253–7 doi: 10.1097/BRS.0b013e31814b2d8e
3. Wang MY, Vasudevan R, Mindea SA. Minimally invasive lateral interbody fusion for the treatment of rostral adjacent-segment lumbar degenerative stenosis without supplemental pedicle screw fixation. *J Neurosurg Spine.* (2014) 21:861–6 doi: 10.3171/2014.8.SPINE13841
4. Radcliff K, Curry P, Hilibrand A, Kepler C, Lurie J, Zhao W, et al. Risk for adjacent segment and same segment reoperation after surgery for lumbar stenosis: a subgroup analysis of the Spine Patient Outcomes Research Trial (SPORT). *Spine.* (2013) 38:531–9 doi: 10.1097/BRS.0b013e31827c99f0
5. Lawrence BD, Wang J, Arnold PM, Hermsmeyer J, Norvell DC, Brodke DS. Predicting the risk of adjacent segment pathology after lumbar fusion: a systematic review. *Spine.* (2012) 37:S123–32 doi: 10.1097/BRS.0b013e31826d60d8
6. Chou D, Dekutoski M, Hermsmeyer J, Norvell DC. The treatment of lumbar adjacent segment pathology after a previous lumbar surgery: a systematic review. *Spine.* (2012) 37:S180–8 doi: 10.1097/BRS.0b013e31826d613d
7. Palejwala SK, Sheen WA, Walter CM, Dunn JH, Baaj AA. Minimally invasive lateral transpsoas interbody fusion using a stand-alone construct for the treatment of adjacent segment disease of the lumbar spine: review of the literature and report of three cases. *Clin Neurol Neurosurg.* (2014) 124:90–6 doi: 10.1016/j.clineuro.2014.06.031
8. Parker SL, Shau DN, Mendenhall SK, McGirt MJ. Factors influencing 2-year health care costs in patients undergoing revision lumbar fusion procedures. *J Neurosurg Spine.* (2012) 16:323–8 doi: 10.3171/2011.12.SPINE11750
9. Smorgick Y, Baker KC, Bachison CC, Herkowitz HN, Montgomery DM, Fischgrund JS. Hidden blood loss during posterior spine fusion surgery. *Spine J.* (2013) 13:877–81 doi: 10.1016/j.spinee.2013.02.008
10. Khan IS, Sonig A, Thakur JD, Bollam P, Nanda A. Perioperative complications in patients undergoing open transforaminal lumbar interbody fusion as a revision surgery. *J Neurosurg Spine.* (2013) 18:260–4 doi: 10.3171/2012.11.SPINE12558
11. Oliveira L, Marchi L, Coutinho E, Pimenta L. A radiographic assessment of the ability of the extreme lateral interbody fusion procedure to indirectly decompress the neural elements. *Spine.* (2010) 35:S331–7 doi: 10.1097/BRS.0b013e3182022db0
12. Sato J, Ohtori S, Orita S, Yamauchi K, Eguchi Y, Ochiai N, et al. Radiographic evaluation of indirect decompression of mini-open anterior retroperitoneal lumbar interbody fusion: oblique lateral interbody fusion

for degenerated lumbar spondylolisthesis. *Eur Spine J.* (2017) 26:671–8 doi: 10.1007/s00586-015-4170-0
13. Fujibayashi S, Hynes RA, Otsuki B, Kimura H, Takemoto M, Matsuda S. Effect of indirect neural decompression through oblique lateral interbody fusion for degenerative lumbar disease. *Spine.* (2015) 40:E175–82 doi: 10.1097/BRS.0000000000000703
14. Moller DJ, Slimack NP, Acosta FL Jr, Koski TR, Fessler RG, Liu JC. Minimally invasive lateral lumbar interbody fusion and transpsoas approach-related morbidity. *Neurosurg Focus.* (2011) 31:E4 doi: 10.3171/2011.7.FOCUS11137
15. Hussain NS, Perez-Cruet MJ. Complication management with minimally invasive spine procedures. *Neurosurg Focus.* (2011) 31:E2 doi: 10.3171/2011.8.FOCUS11165
16. Cummock MD, Vanni S, Levi AD, Yu Y, Wang MY. An analysis of postoperative thigh symptoms after minimally invasive transpsoas lumbar interbody fusion. *J Neurosurg Spine.* (2011) 15:11–8 doi: 10.3171/2011.2.SPINE10374
17. Mayer HM. A new microsurgical technique for minimally invasive anterior lumbar interbody fusion. *Spine.* (1997) 22:691–9 doi: 10.1097/00007632-199703150-00023
18. Silvestre C, Mac-Thiong JM, Hilmi R, Roussouly P. Complications and morbidities of mini-open anterior retroperitoneal lumbar interbody fusion: oblique lumbar interbody fusion in 179 patients. *Asian Spine J.* (2012) 6:89–97 doi: 10.4184/asj.2012.6.2.89
19. Ohtori S, Orita S, Yamauchi K, Eguchi Y, Ochiai N, Kishida S, et al. Mini-open anterior retroperitoneal lumbar interbody fusion: oblique lateral interbody fusion for lumbar spinal degeneration disease. *Yonsei Med J.* (2015) 56:1051–9 doi: 10.3349/ymj.2015.56.4.1051
20. Zhang C, Wang K, Jian F, Wu H. Efficacy of oblique lateral interbody fusion in treatment of degenerative lumbar disease. *World Neurosurg.* (2018) 18:32698–6. doi: 10.1016/j.wneu.2018.11.139
21. Zhu G, Hao Y, Yu L, Cai Y, Yang X. Comparing stand-alone oblique lumbar interbody fusion with posterior lumbar interbody fusion for revision of rostral adjacent segment disease: A STROBE-compliant study. *Medicine.* (2018) 97:e12680 doi: 10.1097/MD.0000000000012680
22. Ostelo RW, Deyo RA, Stratford P, Waddell G, Croft P, Von Korff M, et al. Interpreting change scores for pain and functional status in low back pain: toward international consensus regarding minimal important change. *Spine.* (2008) 33:90–4 doi: 10.1097/BRS.0b013e31815e3a10
23. Khan JM, Harada GK, Basques BA, Nolte MT, Louie PK, Iloanya M, et al. Patients with predominantly back pain at the time of lumbar fusion for low-grade spondylolisthesis experience similar clinical improvement to patients with predominantly leg pain: mid-term results. *Spine J.* (2020) 20:276–82 doi: 10.1016/j.spinee.2019.09.021
24. Schizas C, Theumann N, Burn A, Tansey R, Wardlaw D, Smith FW, et al. Qualitative grading of severity of lumbar spinal stenosis based on the morphology of the dural sac on magnetic resonance images. *Spine.* (2010) 35:1919–24 doi: 10.1097/BRS.0b013e3181d359bd
25. Marchi L, Abdala N, Oliveira L, Amaral R, Coutinho E, Pimenta L. Radiographic and clinical evaluation of cage subsidence after stand-alone lateral interbody fusion. *J Neurosurg Spine.* (2013) 19:110–8 doi: 10.3171/2013.4.SPINE12319
26. Santos ER, Goss DG, Morcom RK, Fraser RD. Radiologic assessment of interbody fusion using carbon fiber cages. *Spine.* (2003) 28:991–1001 doi: 10.1097/01.BRS.0000061988.93175.74
27. Buchowski JM, Liu G, Bunmaprasert T, Rose PS, Riew KD. Anterior cervical fusion assessment: surgical exploration versus radiographic evaluation. *Spine.* (2008) 33:1185–91 doi: 10.1097/BRS.0b013e318171927c
28. Ghiselli G, Wharton N, Hipp JA, Wong DA, Jatana S. Prospective analysis of imaging prediction of pseudarthrosis after anterior cervical discectomy and fusion: computed tomography versus flexion-extension motion analysis with intraoperative correlation. *Spine.* (2011) 36:463–8 doi: 10.1097/BRS.0b013e3181d7a81a
29. Abe K, Orita S, Mannoji C, Motegi H, Aramomi M, Ishikawa T, et al. Perioperative complications in 155 patients who underwent oblique lateral interbody fusion surgery: perspectives and indications from a retrospective, multicenter survey. *Spine.* (2017) 42:55–62 doi: 10.1097/BRS.0000000000001650
30. Zeng ZY, Xu ZW, He DW, Zhao X, Ma WH, Ni WF, et al. Complications and prevention strategies of oblique lateral interbody fusion technique. *Orthop Surg.* (2018) 10:98–106 doi: 10.1111/os.12380
31. Radcliff KE, Kepler CK, Jakoi A, Sidhu GS, Rihn J, Vaccaro AR, et al. Adjacent segment disease in the lumbar spine following different treatment interventions. *Spine J.* (2013) 13:1339–49 doi: 10.1016/j.spinee.2013.03.020
32. Cheh G, Lenke LG, Lehman RA Jr, Kim YJ, Nunley R, Bridwell KH. The reliability of preoperative supine radiographs to predict the amount of curve flexibility in adolescent idiopathic scoliosis. *Spine.* (2007) 32:2668–72 doi: 10.1097/BRS.0b013e31815a5269
33. Lee JC, Choi SW. Adjacent segment pathology after lumbar spinal fusion. *Asian Spine J.* (2015) 9:807–17 doi: 10.4184/asj.2015.9.5.807
34. Adogwa O, Carr RK, Kudyba K, Karikari I, Bagley CA, Gokaslan ZL, et al. Revision lumbar surgery in elderly patients with symptomatic pseudarthrosis, adjacent-segment disease, or same-level recurrent stenosis. Part 1. Two-year outcomes and clinical efficacy: clinical article. *J Neurosurg Spine.* (2013) 18:139–46 doi: 10.3171/2012.11.SPINE12224
35. Whitecloud TS, 3rd, Davis JM, Olive PM. Operative treatment of the degenerated segment adjacent to a lumbar fusion. *Spine.* (1994) 19:531–36 doi: 10.1097/00007632-199403000-00007
36. Parker SL, Mendenhall SK, Shau D, Adogwa O, Cheng JS, Anderson WN, et al. Determination of minimum clinically important difference in pain, disability, and quality of life after extension of fusion for adjacent-segment disease. *J Neurosurg Spine.* (2012) 16:61–7 doi: 10.3171/2011.8.SPINE1194
37. Eichholz KM, Ryken TC. Complications of revision spinal surgery. *Neurosurg Focus.* (2003) 15:E1 doi: 10.3171/foc.2003.15.3.1
38. Wang JC, Bohlman HH, Riew KD. Dural tears secondary to operations on the lumbar spine. management and results after a two-year-minimum follow-up of eighty-eight patients. *J Bone Joint Surg Am.* (1998) 80:1728–32 doi: 10.2106/00004623-199812000-00002
39. Du JY, Kiely PD, Al Maaieh M, Aichmair A, Huang RC. Lateral lumbar interbody fusion with unilateral pedicle screw fixation for the treatment of adjacent segment disease: a preliminary report. *J Spine Surg.* (2017) 3:330–7 doi: 10.21037/jss.2017.06.17
40. Bergey DL, Villavicencio AT, Goldstein T, Regan JJ. Endoscopic lateral transpsoas approach to the lumbar spine. *Spine.* (2004) 29:1681–8 doi: 10.1097/01.BRS.0000133643.75795.EF
41. Benglis DM, Vanni S, Levi AD. An anatomical study of the lumbosacral plexus as related to the minimally invasive transpsoas approach to the lumbar spine. *Journal of neurosurgery Spine.* (2009) 10:139–44 doi: 10.3171/2008.10.SPI08479
42. Moro T, Kikuchi S, Konno S, Yaginuma H. An anatomic study of the lumbar plexus with respect to retroperitoneal endoscopic surgery. *Spine.* (2003) 28:423–8 doi: 10.1097/01.BRS.0000049226.87064.3B
43. Davis TT, Bae HW, Mok JM, Rasouli A, Delamarter RB. Lumbar plexus anatomy within the psoas muscle: implications for the transpsoas lateral approach to the L4-L5 disc. *J Bone Joint Surg Am.* (2011) 93:1482–7 doi: 10.2106/JBJS.J.00962
44. Bocahut N, Audureau E, Poignard A, Delambre J, Queinnec S, Flouzat Lachaniette CH, et al. Incidence and impact of implant subsidence after stand-alone lateral lumbar interbody fusion. *Orthop Traumatol Surg Res.* (2018) 104:405–10 doi: 10.1016/j.otsr.2017.11.018
45. Marchi L, Abdala N, Oliveira L, Amaral R, Coutinho E, Pimenta L. Stand-alone lateral interbody fusion for the treatment of low-grade degenerative spondylolisthesis. *ScientificWorldJournal.* (2012) 2012:456346 doi: 10.1100/2012/456346
46. Ahmadian A, Bach K, Bolinger B, Malham GM, Okonkwo DO, Kanter AS, et al. Stand-alone minimally invasive lateral lumbar interbody fusion: multicenter clinical outcomes. *J Clin Neurosci.* (2015) 22:740–6 doi: 10.1016/j.jocn.2014.08.036
47. Chen E, Xu J, Yang S, Zhang Q, Yi H, Liang D, et al. Cage Subsidence and Fusion Rate in Extreme Lateral Interbody Fusion with and without

Fixation. *World Neurosurg.* (2019) 122:e969–77 doi: 10.1016/j.wneu.2018.10.182

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Kai, Cheng, Yao, Zhang, Jian and Wu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers | Frontiers in Surgery

ORIGINAL RESEARCH
published: 05 April 2022
doi: 10.3389/fsurg.2022.874577

Application of Integrated Emergency Care Model Based on Failure Modes and Effects Analysis in Patients With Ischemic Stroke

Yuying Yang[1], *Qing Chang*[2], *Jing Chen*[3], *Xiangkun Zou*[4], *Qian Xue*[2] *and Aixia Song*[2]*

[1] Stroke Center Office, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China, [2] Department of Neurology, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China, [3] Imaging Department, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China, [4] Information Section, The First Affiliated Hospital of Hebei North University, Zhangjiakou, China

Purpose: To explore the application value of an integrated emergency care model based on failure modes and effects analysis (FMEA) in patients with acute ischemic stroke (AIS).

Methods: According to the convenience sampling method, 100 patients with AIS who visited the emergency department in our hospital from October 2018 to March 2019 were randomly selected as the control group and received routine emergency care mode intervention. Another 100 AIS patients who visited the emergency department from April to October 2019 were selected as the intervention group and received the integrated emergency care model based on FMEA. The total time spent from admission to completion of each emergency procedure [total time spent from admission to emergency physician reception (T_{0-1}), total time spent from admission to stroke team reception (T_{0-2}), total time spent from admission to imaging report out (T_{0-3}), total time spent from admission to laboratory report out (T_{0-4}), and total time spent from admission to intravenous thrombolysis (T_{0-5})] was recorded for both groups. The clinical outcome indicators (vascular recanalization rate, symptomatic intracerebral hemorrhage incidence, mortality rate) were observed for both groups. The National Institutes of Health Stroke Scale (NIHSS) score and Barthel score were evaluated for both groups after the intervention. The treatment satisfaction rate of the patients was investigated for both groups.

Results: The total time of T_{0-1}, T_{0-2}, T_{0-3}, T_{0-4}, T_{0-5} in the intervention group (0.55 ± 0.15, 1.23 ± 0.30, 21.24 ± 3.01, 33.30 ± 5.28, 44.19 ± 7.02) min was shorter than that of the control group (1.22 ± 0.28, 4.01 ± 1.06, 34.12 ± 4.44, 72.48 ± 8.27, 80.31 ± 9.22) min ($P < 0.05$). The vascular recanalization rate in the intervention group (23.00%) was higher than that in the control group (12.00%) ($P < 0.05$). There was no statistical significance in the symptomatic intracerebral hemorrhage incidence and mortality rate in the two groups ($P > 0.05$). After intervention, the NIHSS score of the intervention group (2.95 ± 0.91) was lower than that of the control group (6.10 ± 2.02), and the Barthel score (77.58 ± 7.33) was higher than that of the control group (53.34 ± 5.12) ($P < 0.05$). The treatment satisfaction rate in the intervention group (95.00%) was higher than that of the control group (86.00%) ($P < 0.05$).

OPEN ACCESS

Edited by:
Songwen Tan,
Central South University, China

Reviewed by:
Wenjun Gu,
Shanghai Jiaotong University School of Medicine, China
Fenglong Sun,
Capital University of Medical Sciences, China

***Correspondence:**
Aixia Song
tuw20@mails.tsinghua.edu.cn

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *12 February 2022*
Accepted: *04 March 2022*
Published: *05 April 2022*

Citation:
Yang Y, Chang Q, Chen J, Zou X, Xue Q and Song A (2022) Application of Integrated Emergency Care Model Based on Failure Modes and Effects Analysis in Patients With Ischemic Stroke. Front. Surg. 9:874577. doi: 10.3389/fsurg.2022.874577

Conclusion: Through FMEA, the failure mode that affects the emergency time of AIS patients is effectively analyzed and the targeted optimization process is proposed, which are important to enhance the efficiency and success rate of resuscitation of medical and nursing staff and improve the prognosis and life ability of patients.

Keywords: acute ischemic stroke, failure modes and effects analysis, integrated emergency care model, emergency procedures, clinical outcomes

INTRODUCTION

Acute ischemic stroke (AIS) is the most prevalent type of stroke in clinical practice, accounting for more than 80% of strokes, and it is a major public health problem that threatens national health in my country (1). The disease is mostly secondary to systemic diseases such as hypertension (2), atherosclerosis (3), heart disease (4) and coagulation dysfunction (5), and is characterized by a high recurrence rate, high disability rate, high complication rate and high mortality rate. The key to AIS treatment is to restore blood flow to the occluded vessel and save the ischemic penumbra within the treatment time window (i.e., 3 to 4.5 h after the onset of stroke) (6). Intravenous thrombolysis is the highest-level recommendation in current international guidelines for the treatment of ultra-early AIS (7). However, due to the low recognition of early AIS by the public in China, the ineffective pre-hospital treatment by medical and nursing staff, and the delay in in-hospital emergency care, only about 21.5% of patients arrive at the emergency department within 3 h of onset, and the average time from admission to thrombolytic drug treatment is 116 min, of which only about 9% of patients complete thrombolytic treatment within 1 h after admission, much lower than 50% in the United States. And it has been reported that after thrombolysis, 6 % of patients are still at risk of symptomatic intracranial hemorrhage, and 70% of patients still have symptoms of varying degrees of disability (8, 9). The treatment situation of AIS patients in my country is very severe, and the treatment efficiency is not optimistic. It is urgent to formulate an optimization plan to effectively shorten the delay in the hospital as soon as possible.

Failure modes and effects analysis (FMEA) is a commonly used method in foreign countries to actively assess risks to improve the quality of medical management. It integrates failure mode and effect analysis, hazard analysis and critical control points, and root cause analysis. By prospectively quantifying and evaluating the possible failure links of a first aid process, analyzing its failure causes and effects, and formulating targeted solutions accordingly, its essence is a continuous quality improvement process. It has been widely used in medication guidance, diagnosis and treatment process, risk management, surgery and nursing operations, etc., but it is rarely used in my country's emergency nursing model (10, 11). This study explores the application value of the integrated emergency care model based on FMEA in patients with AIS, in order to provide an important theoretical basis for optimizing the in-hospital emergency mode of AIS patients and shortening the delay time of in-hospital emergency care.

MATERIALS AND METHODS

Research Object

According to the convenience sampling method, 100 patients with AIS who visited the emergency department in our hospital from October 2018 to March 2019 were randomly selected as the control group. Another 100 AIS patients who visited the emergency department from April to October 2019 were selected as the intervention group. Inclusion criteria: Those with a suspected AIS diagnosis were screened by the Los Angeles prehospital stroke screen (LAPSS) (12) before diagnosis; During the implementation of the emergency procedures, those who were diagnosed by imaging examinations and met the diagnostic criteria of the Chinese Stroke Society (13) for AIS; Age $\geq$18 years; time from onset to consultation $\leq$3–4.5 h; those who met the requirements of 3.0–4.5 h for intravenous thrombolysis for AIS patients set by the American Heart and Stroke Association (14); patients or their families who had signed relevant informed consent. Exclusion criteria: Those who had been transferred to our hospital after completion of examination or diagnosis in another hospital; those who had undergone major surgical operations in the past 2 weeks; those with other serious primary diseases or mental illnesses; those with absolute contraindications to thrombolysis therapy. Statistical software was used to analyze the general data of the two groups of patients, and there was no statistical difference, which was comparable ($P > 0.05$). As seen in **Table 1**.

Care Methods

Control group: intervention with routine emergency nursing mode was given. It mainly included emergency triage nurse pre-screening, notification of physician consultation, preliminary diagnosis and treatment of patients, various auxiliary examinations for patients, doctor's assessment of patient's condition, doctor-patient conversation to decide whether to implement intravenous thrombolysis, preparation for thrombolysis treatment, interfacing with neurology/neurosurgery and other routine treatment procedures.

Intervention group: intervention with integrated emergency care model based on FMEA was given. Step I: a 10 person stroke emergency care team was formed. Nursing experts with rich experience and strong nursing ability were included in emergency department, neurology department, radiology department, laboratory department and other departments. Step II: a total of 8 special seminars for a month was carried out. During the meeting, the stroke team was given training on FMEA management method, AIS emergency procedures

TABLE 1 | General information of two groups of patients.

Information	Control group ($n = 100$)	Intervention group ($n = 100$)	t/χ^2	P
Age (M ± SD, years old)	67.96 ± 6.95	66.58 ± 7.24	1.375	0.171
Male [*n* (%)]	49 (49.00)	54 (54.00)	0.501	0.479
History of hypertension [*n* (%)]	56 (56.00)	52 (52.00)	0.322	0.570
History of diabetes [*n* (%)]	33 (33.00)	35 (35.00)	0.089	0.765
History of hyperlipidemia [*n* (%)]	29 (29.00)	24 (24.00)	0.642	0.423
History of coronary heart disease [*n* (%)]	13 (13.00)	15 (15.00)	0.166	0.684
History of atrial fibrillation [*n* (%)]	17 (17.00)	18 (18.00)	0.035	0.852
History of transient cerebral ischemic attack [*n* (%)]	5 (5.00)	7 (7.00)	0.355	0.552
History of stroke [*n* (%)]	12 (12.00)	10 (10.00)	0.204	0.651
History of smoking [*n* (%)]	29 (29.00)	33 (33.00)	0.374	0.541
History of drinking [*n* (%)]	19 (19.00)	22 (22.00)	0.276	0.599

and other related knowledge. During this period, the stroke team analyzed the causes of failure and the risk priority number (RPN) for possible failure modes in the AIS emergency procedure, and indicated the presence of high-risk links when the RPN score was >125. RPN was the product of event severity (S), occurrence (O) and detection indexes (D). After analysis, there were the following 6 high-risk links in the emergency process of AIS patients in our hospital: (1) Preliminary triage, (2) Families payment, examination appointment and medication collection, (3) Families send for examinations, (4) Doctor-patient communication to decide whether to thrombolize, (5) Emergency nurses dispense drugs, (6) Thrombolysis preparations. The FMEA of each high-risk link as shown in **Table 2**. Step III: For the above-mentioned high-risk links, priority should be given to developing targeted and optimized care processes to reduce the harm of failure modes. The corresponding optimization measures for each high-risk link as shown in **Table 3**. The problems that emerged during the implementation of the optimized process were discussed and improved to ensure continuous improvement of the quality of emergency care. The optimized integrated emergency care model of this study as shown in **Figure 1**.

Observation Index

The total time spent from admission to completion of each emergency procedure was recorded for both groups. Including the total time spent from admission to emergency physician reception (T_{0-1}), total time spent from admission to stroke team reception (T_{0-2}), total time spent from admission to imaging report out (T_{0-3}), total time spent from admission to laboratory report out (T_{0-4}), and total time spent from admission to intravenous thrombolysis (T_{0-5}).

The clinical outcome indicators were observed for both groups. Including vascular recanalization rate, symptomatic intracerebral hemorrhage incidence, mortality rate.

The National Institutes of Health Stroke Scale (NIHSS) score was evaluated for both groups after the intervention. It was divided into 11 scoring items such as consciousness level and dysarthria. The total score was 42, and the lower the score, the lighter the neurological impairment.

The Barthel score was evaluated for both groups after the intervention. The total score was 100, measuring the patient's self-care in 10 dimensions, such as walking up and down stairs, dressing and bathing. The higher the total score, the less dependent the patient was.

The treatment satisfaction rate of the patients was investigated for both groups. The survey scale was self-administered by the stroke team, with a Cronhach' s α coefficient of 0.84 and a split-half reliability of 0.88, and was surveyed before the patients were discharged. There were four items: health education, basic care, nursing attitude, and nursing skills. The total score of 90∼100 was very satisfied, 70∼89 was satisfied, 60∼69 was generally satisfied, and <60 was dissatisfied. Overall satisfied rate = (very satisfied + satisfied) number of people /total number of people ×100%.

Statistical Methods

SPSS 22.0 software was used. Enumeration data were expressed as ratios, and the χ^2 test was used for comparison between groups. Measurement data conforming to normal distribution were expressed as mean ± standard deviation (M ± SD), and *t*-test was used for comparison between groups. Statistical significance was expressed as $P < 0.05$.

RESULTS

The Total Time of Each Procedure in the Two Groups of Patients

The total time of T_{0-1}, T_{0-2}, T_{0-3}, T_{0-4}, T_{0-5} in the intervention group (0.55 ± 0.15, 1.23 ± 0.30, 21.24 ± 3.01, 33.30±5.28, 44.19 ± 7.02) min was shorter than that of the control group (1.22 ± 0.28, 4.01 ± 1.06, 34.12 ± 4.44, 72.48 ± 8.27, 80.31 ± 9.22) min ($P < 0.05$). As seen in **Figure 2**.

Clinical Outcome Indicators in the Two Groups of Patients

The vascular recanalization rate in the intervention group (23.00%) was higher than that in the control group (12.00%) ($P < 0.05$). There was no statistical significance in the symptomatic

TABLE 2 | FMEA for emergency care of AIS patients.

High-risk link	Failure modes	Failure reasons	Risk analysis			
			S	O	D	PRN
1	Inappropriate assessment by triage nurses	The triage nurses were inexperienced, lacked the concept of "time window," and had no specific clinical pathways and plans	7.20	8.40	7.50	453.60
2	Round-trip delay, information blocking	Departments were far apart, families were not familiar with the layout of the hospital and the diagnosis and treatment process, the hospital lacked signs and the information platform was weak, and the hospital stipulated that payment, examination appointment, and medicine need to queue up	8.20	7.80	7.50	479.70
3	Forwarding or pending delay	Lack of AIS green channels, inspections and reports did not specify that AIS would be prioritized	7.50	8.40	7.60	478.80
4	Delayed or poor communication	Untimely or inadequate health education and conservative attitude of physicians toward thrombolysis	7.80	9.00	7.80	547.56
5	Dispensing medicines not on time	There were many cases and diseases in the emergency department, and nurses lacked the concept of "time window", and there was no special clinical path and plan	8.80	7.50	7.50	495.00
6	Delayed transfer to the cath lab and delayed thrombolysis preparation	Cath lab might be in use, delayed arrival of medical staff, delayed preparation for thrombolysis	8.20	7.60	9.00	560.88

TABLE 3 | Corresponding optimization measures for each high-risk link of AIS patients.

High-risk link	Optimization measures
1	Regularly train and assess the knowledge of AIS and thrombolysis for emergency nurses, and formulate the "Emergency AIS Thrombolysis Process Emergency Plan".
2	Set up functions such as "one-click payment, appointment inspection, and report viewing" on the hospital's WeChat platform, and taking medicines is carried out by nurses in the hospital.
3	Set up a green channel for AIS transfer, the patient's delivery is carried out by professional nurses trained in transfer, and the specimen delivery should be labeled as "stepped up".
4	At the time of admission, the possibility of thrombolysis is informed and relevant knowledge is popularized. The electronic bulletin screen in the consultation room broadcasts relevant knowledge and notifications of thrombolysis to help patients or their families understand and decide as soon as possible.
5	Set up a special post for thrombolysis nurses to be responsible for thrombolysis treatment of patients.
6	A spare cath lab and a green channel for AIS thrombolysis are set up. After confirming the patient's thrombolysis, open the cath lab and the green channel immediately, and transfer the patient to the cath lab accompanied by doctors and nurses.

intracerebral hemorrhage incidence and mortality rate in the two groups ($P > 0.05$). As seen in **Figure 3**.

NIHSS and Barthel Scores in the Two Groups of Patients

After intervention, the NIHSS score of the intervention group (2.95 ± 0.91) was lower than that of the control group (6.10 ± 2.02), and the Barthel score (77.58 ± 7.33) was higher than that of the control group (53.34 ± 5.12) ($P < 0.05$). As seen in **Figure 4**.

The Treatment Satisfaction Rate in the Two Groups of Patients

The treatment satisfaction rate in the intervention group (95.00%) was higher than that of the control group (86.00%) ($P < 0.05$).As seen in **Figure 5**.

DISCUSSION

Once AIS patients develop symptoms, the most direct and effective treatment method is early intravenous thrombolysis. For patients with acute onset within 4.5 h, timely and effective thrombolytic therapy can not only effectively reduce the irreversible damage to brain tissue caused by cerebral hemorrhage, but even help patients fully recover to normal levels (15, 16). It is speculated that the degree of prognostic recovery in AIS patients is closely related to the reperfusion time of ischemic brain tissue (17). Based on this, from the onset of the patient to the process of receiving thrombolytic therapy, the waiting time is saved to the maximum extent for the patient, which can create more survival and recovery opportunities for the patient, thereby improving the overall treatment effect. This study focuses on the scientific emergency nursing model, in order to make up for the insufficiency of the current emergency nursing process and improve the clinical treatment efficiency and cure rate of AIS

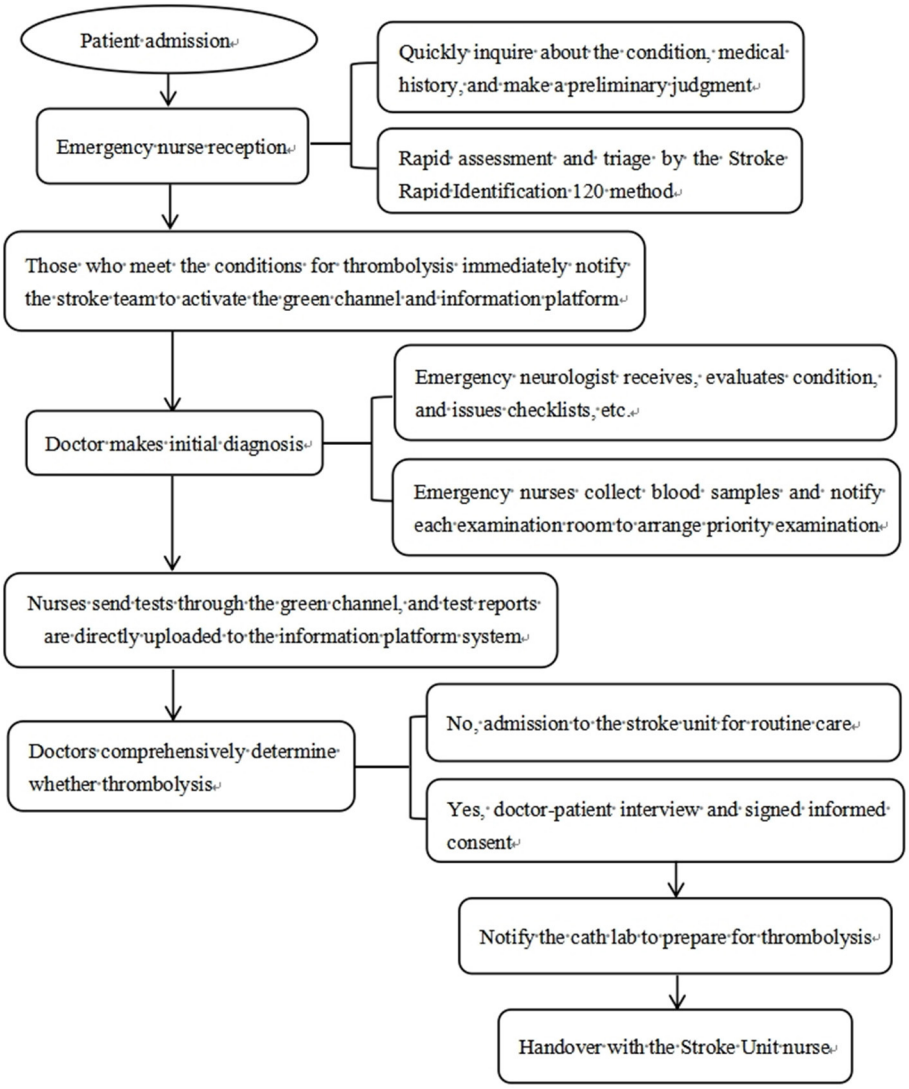


FIGURE 1 | Flow chart of the integrated emergency care model based on FMEA of AIS patients.

patients by reconstructing the relevant links such as inspection, evaluation, nursing and treatment of AIS patients.

In the results of this study, the total time spent from admission to emergency physician, total time spent from admission to stroke team, total time spent from admission to imaging report, total time spent from admission to test report, and total time spent from admission to intravenous thrombolysis in the intervention group were shorter than that of the control group. It is suggested that the integrated emergency care model based on FMEA can effectively shorten the treatment time of each emergency process of AIS patients. Under the conventional nursing mode, the emergency nursing of AIS patients has problems such as unreasonable treatment process, insufficient understanding of the concept of golden time window by nursing staff, and no green channel. These are the main reasons for the lack of effective treatment or unsatisfactory treatment effect in AIS patients within the golden time window (18, 19). FMEA is a scientific and systematic quality control management method (20). The application of the integrated emergency care model based on FMEA in this study. Through the quantification of RPN, the stroke team identified 6 potential high-risk links in the hospital's emergency procedures. The failure causes and optimization measures are also analyzed. Among them, the training and management of comprehensive quality and competence of nursing staff can help strengthen their knowledge about thrombolysis and improve the shortcomings of previous emergency nurses such as insufficient awareness of time window and improper triage; Advance science and electronic education to patients or their families will help to promote their cooperation and help them make thrombolysis decisions as soon as possible; The establishment of an in-hospital information platform realizes the full time-course sharing of information and data among

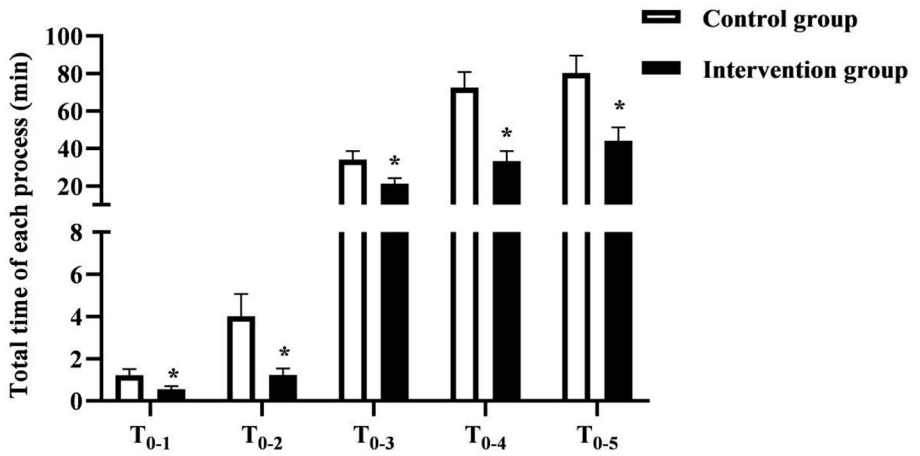


FIGURE 2 | The total time of each procedure in the two groups of patients. * was the comparison of similar items between groups, $P < 0.05$.

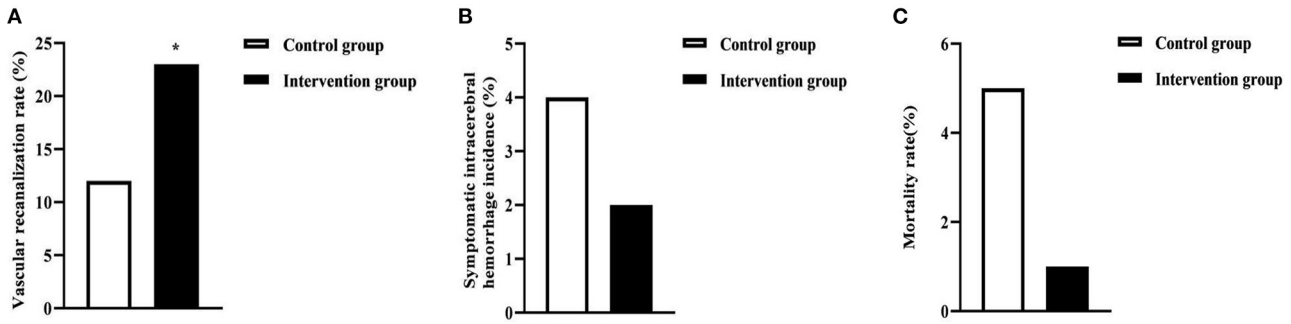


FIGURE 3 | Clinical outcome indicators in the two groups of patients. **(A)** was the vascular recanalization rate. **(B)** was the symptomatic intracerebral hemorrhage incidence. **(C)** was the mortality rate. * was the comparison of similar items between groups, $P < 0.05$.

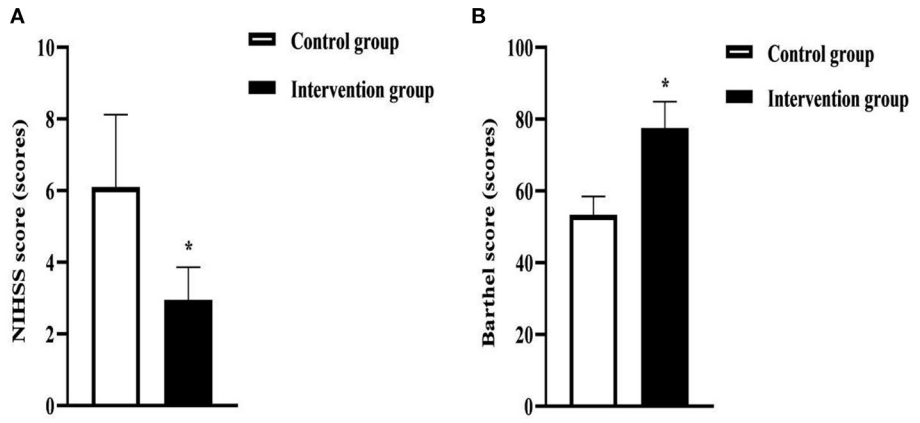


FIGURE 4 | NIHSS and Barthel scores in the two groups of patients. **(A)** was the NIHSS score. **(B)** was the Barthel score. * was the comparison of similar items between groups, $P < 0.05$.

departments, and solves the problems of message lag, repeated information collection, tedious verification work, and poor communication between doctors, nurses, and patients among departments; The opening of the AIS emergency green channel, expedited appointments for relevant examinations, delivery of examinations and medication pickup by professionally trained

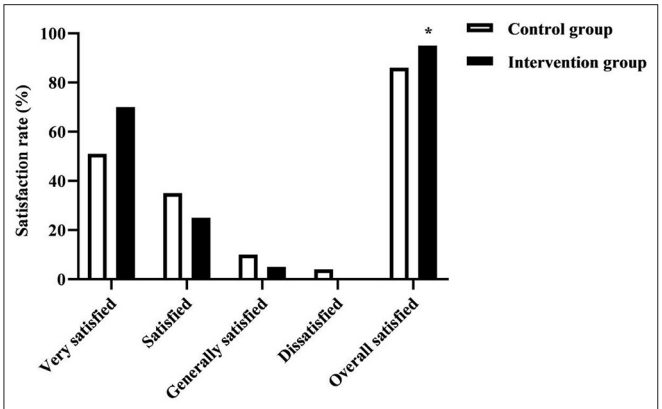


FIGURE 5 | The treatment satisfaction rate in the two groups of patients. * was the comparison of similar items between groups, $P < 0.05$. The intervention group was no dissatisfied.

nurses, etc. greatly reduce the waiting time and ineffective round trip time for each process; The setting of a special post for thrombolytic nurses reduces the reaction time of patients with thrombolytic drugs; Focused discussion and improvement of problems that arise during the implementation of the optimized process will help ensure continuous improvement in the quality of emergency care.

After the implementation of the integrated emergency care model based on FMEA in this study, it was found through statistical analysis that the vascular recanalization rate of patients increased by 11%. This may be because the construction of an integrated emergency care model based on FMEA has effectively shortened the delay time of each emergency procedure for patients, thus ensuring that as many patients as possible can complete thrombolytic therapy within the treatment time window. In the results of this study, there was no significant difference between the intervention group and the control group in the symptomatic intracerebral hemorrhage incidence and mortality rate. This may be because, even if intravenous thrombolysis is completed within the time window, 6% of patients with AIS are still at risk of symptomatic intracerebral hemorrhage after treatment (21). This further suggests that after the optimization of the emergency procedure in this study, although the overall treatment rate of patients was effectively improved, it was still much lower than that in developed countries such as the United States, and the safety and efficacy of patients receiving thrombolytic therapy still need to be improved.

The results of this study also suggested that the NIHSS score of the intervention group after intervention was lower than that of the control group, and the Barthel score was higher than that of the control group. The treatment satisfaction rate in the intervention group was higher than that in the control group. This suggests that the handover application of the integrated emergency nursing model based on FMEA in AIS patients has certain positive significance and practicability. AIS has acute onset and rapid progression, and early and timely professional emergency care is of great significance to block the progression of the disease, reduce the degree of brain damage, and improve its prognosis (22, 23). In this study, the integrated emergency care model based on FMEA was implemented. The reduction of in-hospital delay time significantly improved the efficiency of emergency care for AIS patients, which allows the majority of patients who are admitted in time to receive thrombolytic therapy within the "time window", which ensures that the embolized vessels are opened and the blood supply to the ischemic semidark zone tissues is restored within a short period of time after the onset of the disease. The early suppression of disease progression and the significant improvement in vascular recanalization rates resulted in a corresponding improvement in the prognosis of the patients' quality of survival.

CONCLUSION

Nursing management is an essential and important link in stroke emergency procedures. Through FMEA, the failure mode that affects the emergency time of AIS patients is effectively analyzed and the targeted optimization process is proposed, which are important to enhance the efficiency and success rate of resuscitation of medical and nursing staff and improve the prognosis and life ability of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of The First Affiliated Hospital of Hebei North University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YY and QC are the mainly responsible for the writing of the article. JC is mainly responsible for research design. XZ and QX are mainly responsible for data analysis. AS is responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by Zhangjiakou Science and Technology Research Plan Project (No. 1921065D).

REFERENCES

1. Wu J, Dou Y, Liu W, Zhao Y, Liu X. Osteocalcin improves outcome after acute ischemic stroke. *Aging*. (2020) 12:387–96. doi: 10.18632/aging.102629
2. Gasecki D, Kwarciany M, Kowalczyk K, Narkiewicz K, Karaszewski B. Blood pressure management in acute ischemic stroke. *Curr Hypertens Rep*. (2020) 23:3. doi: 10.1007/s11906-020-01120-7
3. Xu S, Kamato D, Little PJ, Nakagawa S, Pelisek J, Jin ZG. Targeting epigenetics and non-coding RNAs in atherosclerosis: from mechanisms to therapeutics. *Pharmacol Ther*. (2019) 196:15–43. doi: 10.1016/j.pharmthera.2018.11.003
4. Maida CD, Norrito RL, Daidone M, Tuttolomondo A, Pinto A. Neuroinflammatory mechanisms in ischemic stroke: focus on cardioembolic stroke, background, and therapeutic approaches. *Int J Mol Sci*. (2020) 21:6454. doi: 10.3390/ijms21186454
5. Song Y, Fan H, Tang X, Luo Y, Liu P, Chen Y. The effects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on ischemic stroke and the possible underlying mechanisms. *Int J Neurosci*. (2021) 26:1–20. doi: 10.1080/00207454.2021.1897588
6. Alper BS, Foster G, Thabane L, Rae-Grant A, Malone-Moses M, Manheimer E. Thrombolysis with alteplase 3–4.5 h after acute ischaemic stroke: trial reanalysis adjusted for baseline imbalances. *BMJ Evid Based Med*. (2020) 25:168–71. doi: 10.1136/bmjebm-2020-111386
7. Mendelson SJ, Prabhakaran S. Diagnosis and management of transient ischemic attack and acute ischemic stroke: a review. *JAMA*. (2021) 325:1088–98. doi: 10.1001/jama.2020.26867
8. Gusev EI, Martynov MY, Yasamanova AN, Nikonov AA, Markin SS, Semenov AM. Tromboliticheskaia terapiia ishemicheskogo insul'ta [Thrombolytic therapy of ischemic stroke]. *Zh Nevrol Psikhiatr Im S S Korsakova*. (2018) 118:4–14. doi: 10.17116/jnevro20181181224
9. Li KHC, Jesuthasan A, Kui C, Davies R, Tse G, Lip GYH. Acute ischemic stroke management: concepts and controversies. A narrative review. *Expert Rev Neurother*. (2021) 21:65–79. doi: 10.1080/14737175.2021.1836963
10. Liu HC, Zhang LJ, Ping YJ, Wang L. Failure mode and effects analysis for proactive healthcare risk evaluation: a systematic literature review. *J Eval Clin Pract*. (2020) 26:1320–37. doi: 10.1111/jep.13317
11. Rusu I, Thomas TO, Roeske JC, Mescioglu I, Melian E, Surucu M. Failure mode and effects analysis of linac-based liver stereotactic body radiotherapy. *Med Phys*. (2020) 47:937–47. doi: 10.1002/mp.13965
12. O'Brien W, Crimmins D, Donaldson W, Risti R, Clarke TA, Whyte S, et al. FASTER (face, arm, speech, time, emergency response): experience of central coast stroke services implementation of a pre-hospital notification system for expedient management of acute stroke. *J Clin Neurosci*. (2012) 19:241–5. doi: 10.1016/j.jocn.2011.06.009
13. Dong Q, Dong Y, Liu L, Xu A, Zhang Y, Zheng H, et al. The Chinese Stroke Association scientific statement: intravenous thrombolysis in acute ischaemic stroke. *Stroke Vasc Neurol*. (2017) 2:147–59. doi: 10.1136/svn-2017-000074
14. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart association/American stroke association. *Stroke*. (2013) 44:870–947. doi: 10.1161/STR.0b013e318284056a
15. Lin L, Li W, Liu CC, Wu Y, Huang SH, Li XS, et al. Safety and preliminary efficacy of intravenous tirofiban in acute ischemic stroke patient without arterial occlusion on neurovascular imaging studies. *J Neurol Sci*. (2017) 383:175–9. doi: 10.1016/j.jns.2017.10.041
16. Wei XE, Zhou J, Li WB, Zhao YW, Li MH, Li YH. MRI based thrombolysis for FLAIR-negative stroke patients within 4.5-6h after symptom onset. *J Neurol Sci*. (2017) 372:421–7. doi: 10.1016/j.jns.2016.11.010
17. Baird AE, Jackson R, Jin W. Tenecteplase for acute ischemic stroke treatment. *Semin Neurol*. (2021) 41:28–38. doi: 10.1055/s-0040-1722722
18. Zubair AS, Sheth KN. emergency care of patients with acute ischemic stroke. *Neurol Clin*. (2021) 39:391–404. doi: 10.1016/j.ncl.2021.02.001
19. Venema E, Lingsma HF, Chalos V, Mulder MJHL, Lahr MMH, van der Lugt A, et al. Personalized prehospital triage in acute ischemic stroke. Stroke. (2019) 50:313–20. doi: 10.1161/STROKEAHA.118.022562
20. Kim J, Miller B, Siddiqui MS, Movsas B, Glide-Hurst C. FMEA of MR-only treatment planning in the pelvis. *Adv Radiat Oncol*. (2018) 4:168–76. doi: 10.1016/j.adro.2018.08.024
21. Simon E, Forghani M, Abramyuk A, Winzer S, Wojciechowski C, Pallesen LP, et al. Intravenous thrombolysis by telestroke in the 3- to 4.5-h time window. *Front Neurol*. (2021) 12:756062. doi: 10.3389/fneur.2021.756062
22. Kim JY, Lee KJ, Kang J, Kim BJ, Kim SE, Oh H, et al. Acute stroke care in Korea in 2013–2014: national averages and disparities. *J Korean Med Sci*. (2020) 35:167. doi: 10.3346/jkms.2020.35.e167
23. Simpson KN, Simpson AN, Mauldin PD, Palesch YY, Yeatts SD, Kleindorfer D, et al. Observed cost and variations in short term cost-effectiveness of therapy for ischemic stroke in interventional management of stroke (IMS) III. *J Am Heart Assoc*. (2017) 6:e004513. doi: 10.1161/JAHA.116.004513

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Yang, Chang, Chen, Zou, Xue and Song. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

frontiers | Frontiers in Surgery

ORIGINAL RESEARCH
published: 05 April 2022
doi: 10.3389/fsurg.2022.862697

Influence of Contrast Agent Injection Scheme Customized by Dual-Source CT Based on Automatic Tube Voltage Technology on Image Quality and Radiation Dose of Coronary Artery Imaging

Weiling He[1], *Xin Chen*[2], *Rui Hu*[3], *Wenjie Sun*[1] *and Weili Tan*[2]*

[1] *Department of Radiology, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, China,* [2] *Diagnostic Radiology Department, Hunan Cancer Hospital, Changsha, China,* [3] *Interventional Vascular Surgery Department, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha, China*

OPEN ACCESS

Edited by:
Weiguo Li,
Harbin Institute of Technology, China

Reviewed by:
Feng Qin,
Shanghai Jiao Tong University School of Medicine, China
Guilu Tao,
The Second Affiliated Hospital of Dalian Medical University, China
Xiaming Pei,
Hunan Cancer Hospital, China

***Correspondence:**
Weili Tan
tanweili2012@163.com

Specialty section:
This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

Received: *26 January 2022*
Accepted: *21 February 2022*
Published: *05 April 2022*

Citation:
He W, Chen X, Hu R, Sun W and Tan W (2022) Influence of Contrast Agent Injection Scheme Customized by Dual-Source CT Based on Automatic Tube Voltage Technology on Image Quality and Radiation Dose of Coronary Artery Imaging. Front. Surg. 9:862697. doi: 10.3389/fsurg.2022.862697

Objective: To explore the influence of a contrast agent injection scheme customized by dual-source CT based on automatic tube voltage technology on coronary imaging image quality and radiation dose.

Methods: A total of 205 patients who underwent coronary CT angiography (CCTA) in our hospital from June 2021 to September 2021 were selected. 105 patients in the control group who underwent routine scanning according to body mass (BMI) and 100 patients in the observation group who set tube voltage and contrast agent dosage according to automatic tube voltage selection technology. CT values of the aortic root (AO); left anterior descending (LAD) branch; proximal, middle, and distal segments of the right coronary artery (RCA); and proximal and distal segments of left circumflex (LCX) branch were measured. We calculated the signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) of the image. Image quality scoring and effective dose (ED) calculation were carried out.

Results: There was no significant difference in the CT value, SNR value, and CNR value of each part of the artery between the two groups ($P > 0.05$). Image quality scores of the control group and the observation group were 1.28 ± 0.25 and 1.25 ± 0.23, respectively, and there was no significant difference in scores ($P > 0.05$). In the control group, the dosage of comparator was 43.81 ± 6.74 ml, and the ED was 4.92 ± 1.26 mSv. The dosage of contrast agent in the observation group was 34.23 ± 6.39 ml, and ED was 3.05 ± 0.94 mSv. The dosage of contrast agent and ED in the observation group were lower than those in the control group ($P < 0.05$).

Conclusion: The contrast agent injection scheme customized by dual-source CT based on automatic tube voltage technology can meet the clinical requirements of coronary

image quality, reduce the radiation dose and contrast agent consumption, and help doctors choose a more accurate and reasonable examination scheme, which has certain clinical application value.

Keywords: coronary artery, coronary CT angiography, image quality, radiation dosage, aortic root

INTRODUCTION

With the acceleration of population aging, the prevalence trend of cardiovascular risk factors is obvious in China, which leads to increase in the number of cardiovascular diseases. Coronary CT angiography (CCTA) has become an important method for clinical diagnosis and investigation of coronary heart disease because of its fast imaging speed and few complications (1). In the past, traditional CT was limited by detector width, and respiratory artifacts caused more interlaced images, which restricted the examination. However, CCTA can collect accurate and safe clinical information of human tissues and organs in the physiological state during scanning, and its application has gained rapid popularity (2). However, the high radiation dose related to CCTA has become one of the key problems that limit its further promotion and application in routine screening. In past clinical CCTA scanning, to ensure image quality, scanning tube voltage and contrast agent injection dose were usually selected according to the patient's body mass index, which lacked individualized and standardized specifications and needed further research and discussion (3).

Foreign studies have shown that automatic tube voltage selection facilitates CCTA image acquisition, and that it is feasible to customize the contrast injection protocol based on automatically selected tube voltage level (4). CT radiation dose is closely related to scanning parameters. In recent years, research on the relationship between tube current and radiation dose have mostly focused on the automatic tube current setting technology, which is a technology for automatically adjusting tube current according to a scout image and can obviously reduce radiation dose in the abdominal and pelvic scanning. Based on the automatic tube voltage technology, this study adjusts the dosage of a contrast agent to explore the feasibility of CCTA image acquisition and its influence on radiation dose to provide reference for clinical CCTA examination.

DATA AND METHODS

General Information

A total of 205 patients who underwent CCTA in our hospital from June 2021 to September 2021 were selected. Inclusion criteria were patients with suspected coronary heart disease, no history of iodine contrast agent allergy, no history of coronary intervention or coronary artery bypass surgery, good breath-holding training, and nonpregnant or lactating women. Exclusion criteria were severe arrhythmia, cardiac insufficiency, severe hepatic and renal insufficiency, implantation of a pacemaker, and coronary artery bypass grafting. According to different contrast agent injection schemes, 105 patients in the control group were selected tube voltage and contrast agent dosage based on patient body mass, and 100 patients in the observation group were set tube voltage and contrast agent dosage by automatic tube voltage selection technology. There were 107 men and 98 women, with age of 59.26 $\pm$ 9.16 years and BMI of 25.74 $\pm$ 3.09 kg/m^2. This study was approved by the hospital ethics committee and informed consent of the patients and their families.

Research Methods

All examinations were performed by 3rd generation dual-source CT (SOMATOM Definition Force) and prospective ECG gating sequence scanning. The patients took the supine position, and CCTA was performed from the thoracic inlet to the cardiac diaphragmatic surface, with the scanning range ranging from 1 cm below the tracheal bifurcation to the cardiac diaphragmatic surface level. Before the examination, all the patients were trained to hold their breath, including taking nitroglycerin 0.5 mg. A contrast agent (Iohexol injection 370 mg/ml) was injected first, and then physiological saline was injected at the same flow rate; all of which were injected with a double-cylinder high-pressure syringe. When the proximal level of the ascending aorta reaches the trigger threshold of 100 HU, automatic scanning will be delayed for 5 s. Scanning parameter settings were: acquisition layer thickness 0.75 mm, layer spacing 0.4 mm, and rotation time 0.25 s.

For the control group, the dosage of contrast agent was set according to body mass ($<$ 50 kg, 32 ml; 50–59 kg, 36 ml; 60–69 kg, 40 ml; 70–79 kg, 45 ml; $\geq$ 80 kg, 50 ml), and injection time was 12 s. Patients in the observation group used the automatic tube voltage selection technology to set the dosage of contrast agent (70 kV, 33 ml; 80 kV, 36 ml; 90 kV, 42 ml; 100 kV, 46 ml; 110 kV, 52 ml; 120 kV, 55 ml), and injection time was 10 s (5). All the patients' images were transmitted to the image post-processing workstation (Siemens Healthcare, Forchheim, Germany), and multi-planar reformation (MPR), volume rendering (VR), and curved planar reformation (CPR) were performed for image reconstruction and post-processing.

The CT values of the proximal, middle and distal segments of the aortic root (AO), left anterior descending branch (LAD), right coronary artery (RCA), and left circumflex branch (LCX) were measured. The standard deviation of the mean CT value of the AO region of interest (ROI) was taken as the image noise. The ROI should be as large as possible, and we avoided areas, such as coronary vessel wall, calcified plaque, and non-calcified plaque, as much as possible, where the ROI of the aortic root was about 200 mm^2, to ensure the accuracy of the measured CT values. Calculated signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR), SNR = CT value of AO/image noise of AO. CNR = (target blood vessel CT value-fat CT value)/AO image noise.

TABLE 1 | Comparison of general information between the two groups of patients ($n, \bar{x} \pm s$).

Group	Age (years)	Gender (male/female)	Body mass index (kg/m^2)	Heart rate (beats/min)
Control group ($n = 105$)	58.41 ± 8.36	54/51	25.63 ± 2.41	62.19 ± 7.48
Observation group ($n = 100$)	60.15 ± 10.07	53/47	25.86 ± 2.59	63.05 ± 7.82
t/χ^2 value	1.349	0.051	0.659	0.805
P-value	0.179	0.822	0.511	0.421

The coronary artery tree was divided into 18 segments using the newly recommended 18-segment standard modified segmentation method by the American Cardiovascular CT Association, and the distal segment of the occluded vessel was excluded from the analysis (6). Image quality was scored by two senior radiologists through the improved segmentation method of 18-segment standard, with the scoring standard of 1–4 points:1 point: excellent blood vessel display, no ladder-like artifact; 2 points: slight pulsation artifact in the blood vessel; 3 points: moderate artifact in the blood vessel; 4 points: unclear blood vessel display or severe ladder-like artifact that cannot be evaluated. In case of disagreement, an agreement was reached through consultation. We recorded the product of dose length and calculated the effective dose (ED) (7) [ED = dose length product × conversion coefficient k ($k = 0.014\ mSv{\cdot}mGy^{-1}{\cdot}cm^{-1}$)].

For the repeatability test, images of 15 patients were randomly selected from the control group and the observation group. Two physicians performed image quality analysis separately. The Kappa value was used to evaluate the consistency of image quality between the two physicians (*kappa* > 0.8). One week later, another image quality analysis was performed by one of the physicians to calculate intra-examiner consistency (Cronbach's $\alpha = 0.927$).

Statistical Methods

The SPSS 22.0 software was used to process experimental data. Measurement data, such as age, BMI, CT value, SNR, CNR, and ED, of the patients were expressed as mean plus standard deviation ($\bar{x} \pm s$), and the *t*-test was performed for pairwise comparison. Enumeration data, such as gender, of the patients were expressed, in %, and comparison was conducted by the χ^2 test. Test level was $\alpha = 0.05$, and difference was statistically significant when $P < 0.05$.

RESULTS

Comparison of General Data of the Two Groups of Patients

There was no significant differences in general information such as age, gender, BMI and heart rate between the observation group and the control group ($P > 0.05$). As shown in **Table 1**.

TABLE 2 | Comparison of CT of coronary artery segments between the two groups ($n, \bar{x} \pm s$, HU).

Group	AO	LAD-p	LAD-m	LAD-d	RCA-p	RCA-m	RCA-d	LCX-p	LCX-d
Control group ($n = 105$)	491.72 ± 85.13	483.16 ± 68.49	449.71 ± 63.45	412.87 ± 56.27	493.58 ± 81.06	462.71 ± 74.25	446.27 ± 65.37	472.64 ± 78.92	413.27 ± 51.74
Observation group ($n = 100$)	498.26 ± 89.53	470.81 ± 61.28	437.87 ± 59.38	401.52 ± 55.03	486.92 ± 73.54	458.49 ± 69.81	439.61 ± 60.28	465.26 ± 71.23	402.78 ± 50.29
t value	0.454	1.358	1.378	1.459	0.615	0.418	0.757	0.702	1.471
P-value	0.650	0.176	0.170	0.146	0.539	0.675	0.450	0.484	0.143

LAD-p, proximal to the left anterior descending coronary artery; LAD-m, middle segment of the left anterior descending coronary artery; LAD-d, distal left anterior descending coronary artery; RCA-p, proximal right coronary artery; RCA-m, middle right coronary artery; RCA-d, distal right coronary artery; LCX-p, proximal left circumflex branch; LCX-d, distal left circumflex branch.

TABLE 3 | Comparison of signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) between the two groups of patients (n, $\bar{x} \pm s$, HU).

Group	SNR	CNR							
		LAD-p	LAD-m	LAD-d	RCA-p	RCA-m	RCA-d	LCX-p	LCX-d
Control group (n = 105)	28.16 ± 6.24	24.71 ± 6.39	22.74 ± 5.92	21.43 ± 5.58	24.27 ± 6.71	23.04 ± 5.26	23.81 ± 6.33	24.17 ± 6.92	21.93 ± 4.87
Observation group (n = 100)	27.53 ± 5.71	23.19 ± 5.18	21.57 ± 4.86	20.97 ± 4.63	23.69 ± 5.78	22.47 ± 5.09	22.75 ± 5.12	22.86 ± 5.35	20.57 ± 4.42
t value	0.753	1.865	1.542	0.641	0.662	0.788	1.314	1.511	0.553
P value	0.452	0.064	0.125	0.523	0.509	0.431	0.190	0.132	0.581

LAD-p, proximal to the left anterior descending coronary artery; LAD-m, middle segment of the left anterior descending coronary artery; LAD-d, distal left anterior descending coronary artery; RCA-p, proximal right coronary artery; RCA-m, middle right coronary artery; RCA-d, distal right coronary artery; LCX-p, proximal left circumflex branch; LCX-d, distal left circumflex branch.

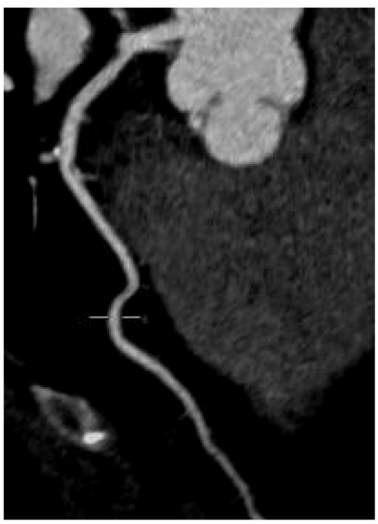


FIGURE 1 | Typical image of left anterior descending curved planar reconstruction in the control group.

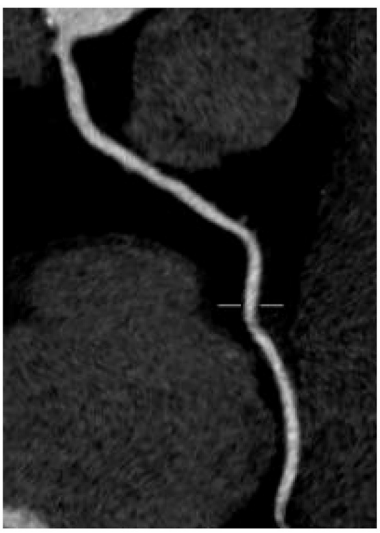


FIGURE 2 | Typical image of right coronary artery curved planar reconstruction in the control group.

CT Comparison of AO and Coronary Artery Segments Between the Two Groups

There is no significant difference in CT values of AO, LAD, RCA, and LCX between the two groups ($P > 0.05$), as shown in **Table 2**.

Comparison of SNR and CNR Between the Two Groups of Patients

There was no significant difference between the two groups in SNR and CNR of LAD, RCA and LCX ($P > 0.05$), as shown in **Table 3**.

Comparison of Image Quality Between the Two Groups of Patients

There was no significant difference in image quality scores between the two groups ($P > 0.05$), as shown in **Figures 1**–**6**. **Figures 1**–**3**: a patient in the control group, male, 55 years old, BMI 25.2 kg/m^2, tube voltage 80 kv and contrast agent dosage 42 ml during scanning; image quality score is 1 point, average CT value of AO is about 603 HU, noise value is 26 HU, and ED is 2.7 mSv. **Figures 4**–**6**: a patient in the observation group, female, 61 years old, BMI 25.8 kg/m^2, tube voltage 80 kv, and contrast agent dosage 35 ml during scanning; image quality score is 2 points, average CT value of AO is 533 HU, noise value is 25 HU, and ED is 1.9 mSv.

Comparison of Contrast Agent Dosage and ED Between the Two Groups of Patients

The dosage of contrast agent and ED in the observation group are lower than those in the control group, and the differences are statistically significant ($P < 0.05$), as shown in **Figures 7**, **8**.

DISCUSSION

With the rapid development of multi-slice spiral CT technology, coronary CTA has become one of the first-choice technologies for screening coronary heart disease safely and reliably. However, the

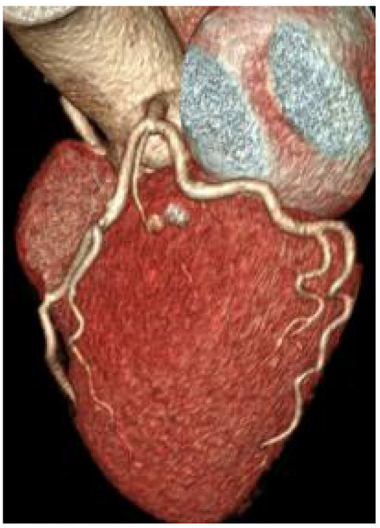


FIGURE 3 | Typical image of coronary CT angiography (CCTA) volume rendering in the control group.

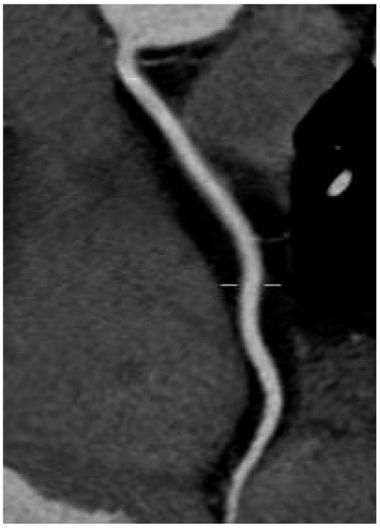


FIGURE 5 | Typical image of right coronary artery curved planar reconstruction in the observation group.

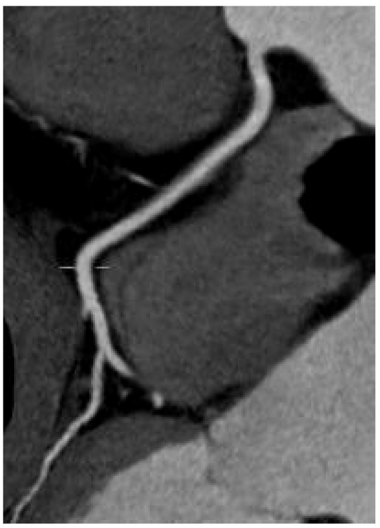


FIGURE 4 | Typical image of left anterior descending curved planar reconstruction in the observation group.

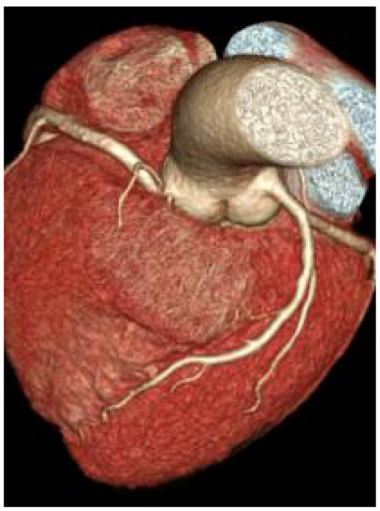


FIGURE 6 | Typical image of CCTA volume rendering in the observation group.

high radiation dose associated with coronary CTA examination and cancer risk, radiation protection, and safety problems caused by ionizing radiation have gradually become the focus of widespread concern in society. On the website of the US Food and Drug Administration, the statement of the American Heart Committee is published, which concludes that a CT radiation dose of 10 msv can cause a malignant tumor in 1/2,000 patients undergoing CT (8). Therefore, how to effectively reduce radiation dose while ensuring image quality has become a research hotspot.

At present, the most commonly used methods to reduce radiation dose include reducing tube voltage and current, reducing scanning length, forward-looking ECG trigger scanning, large pitch scanning, and new reconstruction algorithms. Radiation dose is proportional to the square of the tube voltage, which indicates that reducing tube voltage is the most effective way to reduce radiation dose at present (9, 10). Chen et al. studied head and neck CTA scanning with tube voltage reduced to 70 KV, and image quality score had no obvious change, but radiation dose could be reduced by about 58%, which reflected the advantages of automatic tube voltage technology in reducing radiation dose (11).

Based on the customized scheme of automatic tube voltage technology, the lowest or next lowest tube voltage can be selected for scanning according to inspection purpose, and parameters meeting image quality requirements can be set, which provides

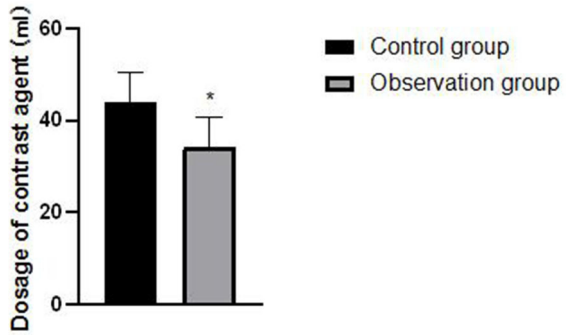


FIGURE 7 | Comparison of contrast agent dosage between the two groups of patients. Compared with the control group, $^*P < 0.05$.

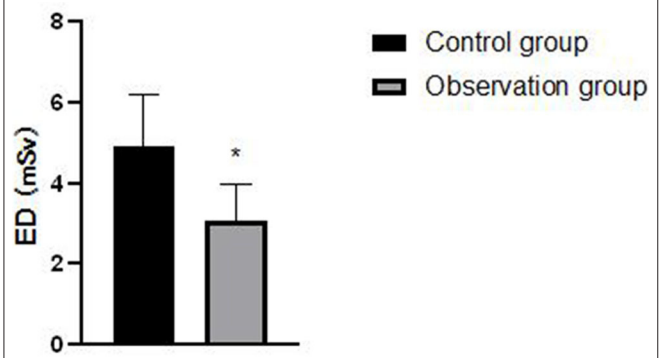


FIGURE 8 | Comparison of effective dose (ED) between the two groups of patients. Compared with the control group, $^*P < 0.05$.

the basis for further reducing the contrast agent (12, 13). The results show that there is no significant difference in the AO, SNR, CT, and CNR values of each segment of the coronary artery between the two groups. It is suggested that the objective image quality of CCTA scanned with the automatic tube voltage technology is consistent with that of the selection of tube voltage and contrast agent dose according to a patient's body mass, and image quality has not been reduced. This is consistent with the research of Ippolito et al. (14).

In the past, CCTA examination was limited by actual situation, and tube voltage was selected empirically according to the body mass of patients. However, for patients with the same body mass range, some patients needed higher tube voltage levels to obtain better scanning images because of differences in body shape and muscle and adipose tissue content distribution, and some patients with larger body mass only needed conventional or even lower tube voltage to meet the examination requirements and obtain better image quality (15, 16). For patients with normal and same body mass range, using the 3rd generation Shuang Yuan CT automatic tube voltage selection technology, the tube voltage of CCTA examination can be intelligently selected, and effects of other patient parameters on the examination besides body mass should be considered, so as to help technicians to more accurately and reasonably select the optimal voltage value suitable for patients. It is necessary to improve the success rate of examination and ensure image quality while effectively controlling or reducing radiation dose (17, 18). In this study, there was no significant difference in image quality scores between the two groups, but the dosage of contrast agent and ED in the observation group were significantly lower than those in the control group. It is suggested that the customized scheme based on automatic tube voltage technology can take into account the influence of other patient parameters except body mass on examination, thus helping technicians to select the best voltage value suitable for patients more accurately and reasonably, and effectively controlling or reducing radiation dose while improving the success rate of examination and ensuring image quality.

Previous studies have shown that the automatic tube voltage technology can automatically adjust tube voltage and make appropriate compensations according to various factors, such as cardiac output, body shape, and chest shape of different patients. At the same time, according to the proportional relationship between radiation dose and tube voltage, the purpose of reducing radiation dose can be achieved by adjusting tube voltage (19). Most the iodine contrast agents used in CCTA examinations are hypertonic, and iodine content is as high as 37%. In the human body, iodine contrast agents are filtered by glomerulus but not absorbed by renal tubules. During the process of glomerular filtration, concentration in the kidney increases, which may lead to a series of adverse reactions, such as renal damage (20). Low contrast agent flow rate and low contrast agent dose usually reduce the enhancement density of coronary arteries. By reducing tube voltage and adjusting the dose of a contrast agent, injection flow rate can be kept at a level slightly lower than that of conventional injection flow rate (6 ml/s), Compton scattering effect can be reduced, and the dose of the contrast agent and radiation can be reduced while meeting image quality requirements.

There are some shortcomings in this study, including the small number of selected cases and lack of gold standard contrast in coronary angiography, which need to be supplemented and further discussed in follow-up research studies.

To sum up, the contrast agent injection scheme customized by dual-source CT based on the automatic tube voltage technology can meet the clinical requirements of coronary imaging image quality, reduce radiation dose and contrast agent consumption at the same time, and help doctors choose a more accurate and reasonable examination scheme, which has certain clinical application value.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Hospital Ethics Committee of the Hunan Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

This work was funded by 2020 Scientific Research Project of Hunan Health Committee (No. 20200059).

REFERENCES

1. Alhailiy AB, Ekpo EU, Kench PL, Ryan EA, Brennan PC, McEntee M. The associated factors for radiation dose variation in cardiac CT angiography. *Br J Radiol*. (2019) 92:793. doi: 10.1259/bjr.20180793
2. Zhang W, Ba Z, Wang Z, Lv H, Zhao J, Zhang Y, et al. Diagnostic performance of low-radiation-dose and low-contrast-dose (double low-dose) coronary CT angiography for coronary artery stenosis. *Medicine*. (2018) 97:11798. doi: 10.1097/MD.0000000000011798
3. Haubold J, Hosch R, Umutlu L, Wetter A, Haubold P, Radbruch A, et al. Contrast agent dose reduction in computed tomography with deep learning using a conditional generative adversarial network. *Eur Radiol*. (2021) 31:6087–95. doi: 10.1007/s00330-021-07714-2
4. Albrecht MH, Nance JW, Schoepf UJ, Jacobs BE, Bayer RR 2nd, Litwin SE, et al. Diagnostic accuracy of low and high tube voltage coronary CT angiography using an X-ray tube potential-tailored contrast medium injection protocol. *Eur Radiol*. (2018) 28:2134–42. doi: 10.1007/s00330-017-5150-z
5. Martin SS, Giovagnoli DA, Abadia AF, Vingiani V, Doeberitz PLVK, Smith HE, et al. Evaluation of a tube voltage-tailored contrast medium injection protocol for coronary CT angiography: results from the prospective volcanic study. *AJR Am J Roentgenol*. (2020) 215:1049–56. doi: 10.2214/AJR.20.22777
6. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the society of cardiovascular computed tomography guidelines committee. *J Cardiovasc Comput Tomogr*. (2014) 8:342–58. doi: 10.1016/j.jcct.2014.07.003
7. Paul J, Banckwitz R, Krauss B, Vogl TJ, Maentele W, Bauer RW. Estimation and comparison of effective dose (E) in standard chest CT by organ dose measurements and dose-length-product methods and assessment of the influence of CT tube potential (energy dependency) on effective dose in a dual-source CT. *Eur J Radiol*. (2012) 81:507–12. doi: 10.1016/j.ejrad.2011.06.006
8. Budoff MJ, Achenbach S, Blumenthal RS, Carr JJ, Goldin JG, Greenland P, et al. Assessment of coronary artery disease by cardiac computed tomography: a scientific statement from the American Heart Association Committee on Cardiovascular Imaging and Intervention, Council on Cardiovascular Radiology and Intervention, and Committee on Cardiac Imaging, Council on Clinical Cardiology. *Circulation*. (2006) 114:1761–91. doi: 10.1161/CIRCULATIONAHA.106.178458
9. Chen Y, Liu Z, Li M, Yu Y, Jia Y, Ma G, et al. Reducing both radiation and contrast doses in coronary CT angiography in lean patients on a 16-cm wide-detector CT using 70 kVp and ASiR-V algorithm, in comparison with the conventional 100-kVp protocol. *Eur Radiol*. (2019) 29:3036–43. doi: 10.1007/s00330-018-5837-9
10. El Merhi F, Bou-Fakhredin R, El Ashkar B, Ghieh D, Ghosn Y, Saade C. State of the art of coronary computed tomography angiography. *Radiography*. (2020) 26:174–82. doi: 10.1016/j.radi.2019.10.001
11. Chen Y, Zhu Y, Xue H, Wang Y, Li Y, Zhang Z, et al. Third-generation dual-source CT for head and neck CT angiography with 70 kV tube voltage and 20–25 ml contrast medium in patients with body weight lower than 75 kg. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao*. (2017) 39:4–8. doi: 10.3881/j.issn.1000-503X.2017.01.002
12. Richards CE, Obaid DR. Low-dose radiation advances in coronary computed tomography angiography in the diagnosis of coronary artery disease. *Curr Cardiol Rev*. (2019) 15:304–15. doi: 10.2174/1573403X15666190222163737
13. Ippolito D, Riva L, Talei Franzesi CR, Cangiotti C, De Vito A, Di Gennaro F, et al. Diagnostic efficacy of model-based iterative reconstruction algorithm in an assessment of coronary artery in comparison with standard hybrid-Iterative reconstruction algorithm: dose reduction and image quality. *Radiol Med*. (2019) 124:350–9. doi: 10.1007/s11547-018-0964-6
14. Ippolito D, De Vito A, Franzesi CT, Riva L, Pecorelli A, Corso R, et al. Evaluation of image quality and radiation dose saving comparing knowledge model-based iterative reconstruction on 80-kV CT pulmonary angiography (CTPA) with hybrid iterative reconstruction on 100-kV CT. *Emerg Radiol*. (2019) 26:145–53. doi: 10.1007/s10140-018-1653-4
15. Park IK, Park J, Kim TH, Lee J, Han K, Oh C, et al. Non-inferior low-dose coronary computed tomography angiography image quality with knowledge-based iterative model reconstruction for overweight patients. *PLoS ONE*. (2018) 13:209243. doi: 10.1371/journal.pone.0209243
16. Schicchi N, Fogante M, Palumbo P, Agliata G, Esposto Pirani P, Di Cesare E, et al. The sub-millisievert era in CTCA: the technical basis of the new radiation dose approach. *Radiol Med*. (2020) 125:1024–39. doi: 10.1007/s11547-020-01280-1
17. Kosmala A, Petritsch B, Weng AM, Bley TA, Gassenmaier T. Radiation dose of coronary CT angiography with a third-generation dual-source CT in a "real-world" patient population. *Eur Radiol*. (2019) 29:4341–8. doi: 10.1007/s00330-018-5856-6
18. Abdullah KA, McEntee MF, Reed W, Kench PL. Radiation dose and diagnostic image quality associated with iterative reconstruction in coronary CT angiography: a systematic review. *J Med Imaging Radiat Oncol*. (2016) 60:459–68. doi: 10.1111/1754-9485.12473
19. Wang W, Zhao YE, Qi L, Li X, Zhou CS, Zhang LJ, et al. Prospectively ECG-triggered high-pitch coronary CT angiography at 70 kVp with 30mL contrast agent: an intraindividual comparison with sequential scanning at 120 kVp with 60mL contrast agent. *Eur J Radiol*. (2017) 90:97–105. doi: 10.1016/j.ejrad.2017.02.020
20. Tan SK, Yeong CH, Raja Aman RRA, Ng KH, Abdul Aziz YF, Chee KH, et al. Low tube voltage prospectively ECG-triggered coronary CT angiography: a systematic review of image quality and radiation dose. *Br J Radiol*. (2018) 91:874. doi: 10.1259/bjr.20170874

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer XP declared a shared affiliation with the authors XC and WT to the handling editor at the time of review.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 He, Chen, Hu, Sun and Tan. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Frontiers in Surgery

Explores and improves surgical practice and clinical patient management

A multidisciplinary journal which explores surgical practices - from fundamental principles to advances in microsurgery and minimally invasive techniques. It fosters innovation and improves the clinical management of patients.

Discover the latest Research Topics

See more →

Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact