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Co-use of medicines in surgery, 2nd edition

Edited by
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Co-use of medicines in surgery, 2nd edition

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ORIGINAL RESEARCH
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Application of Narrative Nursing Combined With Focused Solution Model to Anxiety and Depression in Patients With Lung Tumor During Perioperative Period

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Background: In the face of the dual pressure of disease and operation, patients with lung tumors in the perioperative period often have adverse psychological states such as anxiety and depression. There are many risk factors affecting the psychological state of patients in the perioperative period, and there is still a lack of effective nursing countermeasures in clinical practice.

Materials and Methods: We accessed our institutional database and retrospectively selected all patients with lung tumors who underwent surgical treatment between August 2018 and December 2018. Multivariate Logistic regression model was used to analyze the risk factors affecting the psychological state of patients during the perioperative period, and the HAD score, medication behavior, INR monitoring behavior and life behavior before and after narrative nursing combined with focused solution model nursing were compared with those of patients receiving conventional nursing plan.

Results: According to the inclusion and exclusion criteria, 148 cases of lung tumor patients undergoing surgical treatment were studied in this study. There were 45 cases without anxiety and depression and 103 cases with anxiety and depression in 148 patients. Income, medical environment, worry about work, family members' psychological state, family care, sleep quality, mental history, worry about postoperative pain, patients' knowledge of the diagnosis of the condition and the nature of the tumor were the single factors that affected the psychological state of patients with pulmonary tumor during perioperative period ($P < 0.05$). Multivariate analysis showed that income status, sleep quality, psychological status of family members, fear of postoperative pain and nature of tumor were the independent risk factors for psychological status of patients with lung tumor during perioperative period ($P < 0.05$). There was no difference in HAD score, medication behavior, INR monitoring behavior and life behavior score between the two groups when entering the group ($P > 0.05$). At the time of discharge, the HAD scores of the two groups were decreased, and those in the study group were lower than those in the control group ($P < 0.05$). At the time of discharge, medication behavior, INR monitoring behavior and life behavior of the two groups were increased, and the study group was higher than the control group ($P < 0.05$).

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Conclusion: Income status, sleep quality, fear of postoperative pain, Patient's knowledge of their condition and nature of tumor are the independent risk factors affecting the psychological state of patients with lung tumor during perioperative period. Narrative nursing combined with focused solution model can effectively improve the anxiety and depression status of patients with lung tumor during perioperative period and enhance their compliance behavior, which is worthy of promotion.

Keywords: focus resolution mode, narrative care, depression, anxiety, lung tumor

INTRODUCTION

Lung tumors, as one of the most common tumors in clinic. It originate from respiratory epithelial cells such as bronchi, bronchioles and alveoli, and can be classified into benign and malignant tumors, with malignant being more common (1). There are two types of benign tumors and malignant tumors, and malignant tumors are more common in clinical practice. Surgical resection is the first choice for radical treatment of lung tumors. Studies have shown that most patients with lung cancer in the perioperative period mostly have adverse psychological states of anxiety and depression, and a few of them even have suicidal thoughts (2). However, the psychological state of patients is often closely related to the quality of life, the clinical efficacy of patients who adopt a negative psychological response to clinical treatment is often unsatisfactory. So it is important to explore the influencing factors of anxiety and depression in patients with lung cancer during perioperative period and formulate relevant nursing countermeasures (3).

Narrative nursing is a new nursing mode innovatively developed on the basis of nursing theory. It can discover nursing problems by narrating with patients, which is more humanized than the traditional nursing model (4). Solution focused approach (SFA) is a psychological intervention method with the purpose of mining patients' own resources and capabilities, which can enhance patients' confidence in treatment and improve the clinical outcomes (5). In the past, it has not been reported that the two care modes were applied to disease care at the same time. To further improve the level of care for patients with lung cancer during the perioperative period in our hospital, we combined the two care modes and observed the care anxiety of patients, which is reported below.

MATERIALS AND METHODS

This study has been approved by the Ethics Committee of our hospital. All patients have informed and consented, and all the data have been confirmed.

We accessed our institutional database and retrospectively screened the case data of lung tumors who underwent surgery between August 2018 and December 2018. Inclusion criteria were as follows: (i) Patients with lung tumors confirmed by clinical, imaging, endoscopic and pathological examination; (ii) Primary school education or above; (iii) Patients with clear consciousness and no communication disorders. Exclusion criteria: (iv) Patients with severe heart, liver, kidney and nervous system diseases; (v) Patients with a history of mental illness or family history; (vi) Patients with a history of malignant tumor treatment.

The medical records of all patients were retrieved, and the baseline characteristics of all patients were collected. Including the patient's age, gender, marital status, income status, medical environment, worries about work, psychological state of family members, family care level, sleep quality, history of mental illness, worries about postoperative pain, patient's knowledge of their condition and nature of tumor. Amog them, the Pittsburghsleepqualityindex (PSQI) was used to assess sleep quality.

Perioperative Anxiety and Depression status of all patients was assessed by the Hospital Anxiety and Depression Scale (HAD) (6). HAD was composed of two sub-tables, anxiety and depression, each of which contained seven items, and each item was scored according to the Liker four-level scoring system, with the scoring range of each scale ranging from 0 to 21 points. Patients with HAD score < 8 points were considered as no-anxiety and depression, and patients with HAD score ≥ 8 points were considered as have anxiety and depression.

The investigator explained the purpose of the study to the surgical patients who had been included in the study. With the consent of the patients, the investigator himself/herself completed the questionnaire and general information questionnaire. Those who could not complete the questionnaire independently were filled in by the investigator through questions and answers.

The general information questionnaire was first filled out at the time of admission and the HAD scale was completed 1 day before surgery. All questionnaires were collected on the same day. According to the HAD evaluation results at the time of admission, the patients were divided into with anxiety and depression group and without anxiety and depression group.

All operations were performed according to the standard protocol. According to the differences of perioperative nursing methods, the patients were divided into a study group and a control group.

According to the doctor's advice, the nursing staff should guide the patient to train abdominal breathing, bed rest and defecation before operation. At the same time, the patients were given posture care, airway management, early rehabilitation exercise,

diet care, wound care, drainage tube care and health education after operation.

On this basis, patients in the study group were given narrative care combined with SFA. (i) Setting up a nursing group: With the head nurse of the department as the team leader, a nursing group consisting of one resident, one psychological consultant, two supervisor nurses and several responsible nurses was established. (ii) The basic data of the patients were analyzed within 1-2 d after admission, and one-on-one communication was conducted based on the basic data of patients. In the process of communication with patients, nurses should follow the principle of narrative nursing. First, the nurses should help patients to treat the problems brought by the disease rationally, guide patients to explore how the problem is formed and find the reasons behind the problem. Second, the occurrence of tumor is bound to cause a serious decline in the quality of life of patients, when we can use the positive guidance method, and patients with hypothetical reasoning. Discuss hypothetical questions with the patient, for example: How was life before the tumor? What is the effect of surgical treatment on? What is the negative effect of anxiety and depression on anticoagulation therapy? How to improve compliance behavior and so on. In the process of answering these questions, we can guide patients how to resolve anxiety and depression, form the habit of complying with the doctor, and actively cooperate with the treatment. At the same time, nurses can help patients to find an external witness to improve their treatment compliance when necessary, so that they can better receive treatment by building a sense of ceremony. Third, treatment documents are organized. According to the real feelings of patients, language, text and audio are used to help patients achieve relevant phased goals, and patients are helped to reshape their identity and identify with themselves according to their biased values and life goals. (iii) Construction goal: According to the clinical characteristics and psychological status of patients undergoing pulmonary tumor surgery, nursing team members can work with patients to construct feasible overall intervention goals, specifically HAD < 8 points, life behavior score ≥ 11 points, and total compliance behavior score ≥ 26 points. In addition, goals can be changed timely according to the specific behaviors of patients during implementation. (iv) The anxiety and depression degree and compliance behavior of patients were evaluated every 1 d, and compared with the scores before the start of nursing and the last test. The causes of changes in related indicators were analyzed, and the intervention plan was timely adjusted to guide the patients to make targeted improvements. The condition that the target value of patients reached the standard was evaluated weekly, and those who were satisfied with the evaluation results were given affirmation and praise. They constantly adjusted the potential of patients themselves and worked hard to achieve the ultimate intervention goal.

The HAD scale was used to assess the anxiety and depression states of the two groups. The compliance behavior of the two groups was assessed using the Compliance Behavior Scale, which included medication behavior, INR monitoring behavior and life behavior. Each item was scored using the Liker 4-level scoring system (7). The higher the score was, the better the compliance was. All observations were assessed at admission and discharge.

SPSS22.0 software was used for processing. The continuous variable data of experimental data were expressed as mean standard deviation ($\overline{x} \pm$ s)and adopted t-test. The classified variable data and descriptive analysis were expressed as (%) and adopted χ^2 test. Multivariate Logistic regression model was used to analyze the significant factors in single factor analysis. $\underline{P} < 0.05$ indicated the significant difference.

RESULTS

Finally, 148 patients with surgically treated lung tumors were included in the study according to the inclusion and exclusion criteria. The average HAD score of the 148 patients was (12.31 $\pm$ 3.56), including 45 cases without anxiety and depression, and 103 cases with anxiety and depression, accounting for 30.41 and 69.59%, respectively.

As shown in **Table 1**, age, gender, and marital status had no correlation with the perioperative psychological status of patients with lung cancer ($P > 0.05$). Income status, medical environment, worried about work, psychological state of family members, family care level, sleep quality, history of mental illness, worried about postoperative pain, patients' knowledge of the diagnosis of the condition and nature of tumor were the single factors that affected the psychological state of patients with lung tumor during perioperative period ($P < 0.05$).

The depression and anxiety status of patients were taken as dependent variables, and the factors with significant differences in **Table 1** were taken as independent variables to be included in the Logistic regression model. The assignments of the dependent variable and independent variable are shown in **Table 2**.

As shown in **Table 3**, income status, psychological status of family members, sleep quality, worried about postoperative pain and nature of tumor were the independent risk factors for psychological status of patients with pulmonary tumor during perioperative period ($P < 0.05$).

Of the 148 patients, 74 received traditional care (control group) and 74 received narrative care in combination with SFA (study group). In the control group, there were 23 cases without anxiety and depression and 51 cases with anxiety and depression. There were 22 cases without anxiety and depression and 52 cases with anxiety and depression in the study group. There was no significant difference in anxiety and depression between the two groups ($P > 0.05$).

As shown in **Table 4**, there was no difference in HAD score, medication behavior, INR monitoring behavior and life behavior score between the two groups at the time of admission ($P > 0.05$). At the time of discharge, the HAD scores of the two groups were decreased, and those in the study group were lower than those in the control group ($P < 0.05$). At the time of discharge, medication behavior, INR monitoring behavior and life behavior of the two groups were increased, and the study group was higher than the control group ($P < 0.05$).

TABLE 1 | Univariate analysis of psychological status of patients with pulmonary tumor during perioperative period.

Clinical pathological features		With anxiety and depression group ($n = 103$)	Without anxiety and depression group ($n = 45$)	t/χ^2 value	*P*-value
Age		49.31 ± 9.34	49.87 ± 9.71	0.332	0.741
Gender	Male	61(59.22)	25(55.56)	0.173	0.677
	Female	42(40.78)	20(44.44)		
Marital status	Married	69(66.99)	24(53.33)	5.287	0.071
	Unmarried	23(22.33)	13(28.89)		
	Widowed	11(10.68)	8(17.78)		
Income status	>10,000 yuan/month	29(28.16)	23(51.11)	9.868	0.007
	5,000∼10,000 yuan/month	19(18.45)	10(22.22)		
	<5,000 yuan/month	55(53.40)	12(26.67)		
Medical environment	Good	40(38.83)	35(77.78)	19.001	<0.001
	Poor	63(61.17)	10(22.22)		
Worried about work	No	32(31.07)	30(66.67)	16.304	<0.001
	Yes	71(68.93)	15(33.33)		
Psychological state of family members	Without anxiety and depression	21(20.39)	34(75.56)	41.341	<0.001
	Anxiety and depression	83(80.58)	11(24.44)		
Family concern	Good	34(33.01)	41(91.11)	42.296	<0.001
	Poor	69(66.99)	4(8.89)		
Sleep quality	Good	32(31.07)	32(71.11)	20.460	<0.001
	Poor	71(68.93)	13(28.89)		
History of mental illness	No	66(64.08)	42(93.33)	13.591	<0.001
	Yes	37(35.92)	3(6.67)		
Worried about postoperative pain	No	20(19.42)	32(71.11)	36.721	<0.001
	Yes	83(80.58)	13(28.89)		
Patient's knowledge of their condition	Clear	47(45.63)	37(82.22)	17.085	<0.001
	Fuzziness	56(54.37)	8(17.78)		
Tumor nature	Benign	43(41.75)	29(64.44)	6.458	0.011
	Malignant	60(58.25)	16(35.56)		

DISCUSSION

Anxiety, depression, fear and other abnormal emotions often occur to patients with lung tumors when they recognize their condition and the lung lobe needs to be removed during surgery (8). Studies have shown that between 25 and 70% of hospitalized patients have both anxiety and depression (9). In this study, HAD was used to assess the psychological state of patients with lung cancer during the perioperative period. The results showed that the proportion of anxiety and depression was 69.59%, which was basically in line with the previous literature (10).

Analysis of Factors Affecting Perioperative Patients' Psychological State

The logistics regression analysis was used to study the correlation between each independent variable and the occurrence of anxiety and depression in patients. Among them, income status, sleep quality, psychological status of family members, worried about postoperative pain and nature of tumor were the independent risk factors for psychological status of patients with pulmonary tumor during perioperative period ($P < 0.05$). There are many surgical options for lung tumors, and minimally invasive diagnostic techniques are being continually improved. Although various schemes have shown certain efficacy, the operation and treatment costs still impose certain pressure on patients. Especially for patients with a large gap between economic income and medical expenses, they may even be poor due to illness (11). This phenomenon also aggravates people's psychological endurance day by day, thus inducing patients' emotions to be in a negative state (12). Therefore, it is necessary to formulate treatment strategies according to the economic conditions of patients in clinical treatment, and it can help patients with low economic ability to seek social help, to reduce the impact of economic income on the psychological state of patients as much as possible.

A large number of studies have confirmed the correlation between sleep quality and mental health status (13). On the one hand, poor quality of time and sleep will lead to decreased body immunity and affect the curative effect of surgery (14).

TABLE 2 | Variable assignment table of multi-factor analysis of depression and anxiety of patients with pulmonary tumor during perioperative period.

Variable	The assignment
Dependent variable	
Anxiety and depression	No = 0, Yes = 1
Independent variables	
Income status	>10,000 yuan/month = 0, 5,000∼10,000 yuan/month = 1, <5,000 yuan/month = 2
Medical environment	Good = 0, Poor = 1
Worried about work	No = 0, Yes = 1
Psychological state of family members	Without anxiety and depression = 0, With anxiety and depression = 1
Family concern	No = 0, Yes = 1
Sleep quality	Good = 0, Poor = 1
History of mental illness	No = 0, Yes = 1
Worried about postoperative pain	No = 0, Yes = 1
Patient's knowledge of their condition	Clear = 0, Fuzziness = 1
Tumor nature	Benign = 0, Malignant = 1

TABLE 3 | Multivariate logistic regression analysis of of psychological status of patients with pulmonary tumor during perioperative period.

Factors	β	SE	Wald	*P*	OR(95%CI)
Income status	0.269	0.036	36.026	0.006	1.285∼10.349
Medical environment	0.264	0.989	37.169	0.461	0.615∼2.461
Worried about work	0.349	0.761	42.590	0.339	0.479∼1.582
Psychological state of family members	0.152	0.027	39.462	0.043	1.933∼11.597
Family concern	0.139	0.633	30.481	0.085	0.346∼1.274
Sleep quality	0.136	0.031	31.298	0.013	1.088∼9.315
History of mental illness	0.264	0.648	42.091	0.951	0.218∼1.979
Worried about postoperative pain	0.265	0.041	46.440	<0.001	1.798∼7.511
Patient's knowledge of their condition	0.281	0.711	32.899	1.563	0.634∼3.491
Tumor nature	0.165	0.036	20.592	<0.001	1.591∼6.949
Constant	−2.649	0.165	32.792	0.000	-

On the other hand, people with poor sleep quality tend to look at things in a negative attitude, which leads to dissatisfaction, disgust, depression and other negative emotional reactions. Therefore, sleep propaganda and education for patients should be strengthened in nursing work, and sedative drugs should be applied when necessary.

Acute trauma and internal organ damage caused by the operation itself and stimulation of drainage can lead to postoperative pain, which can cause severe physiological and psychological reactions and lead to a decline in the quality of life of the patient (15). Patients often have negative psychology for fear of postoperative pain, so targeted control of symptoms and maintaining comfort are the main nursing countermeasures (16).

Patients with lung tumors should not only face the pressure brought by tumors and surgery, but also face the psychological burden brought by a series of negative life events (17). In addition, the family members of patients with lung cancer should also be concerned about the impact. The anxiety and depression degree of family members will not only affect their physical and mental health, but also have a great negative effect on the patient's psychology, treatment and even future rehabilitation. Therefore, the psychological reactions of family members cannot be ignored in the process of clinical diagnosis and treatment. At the same time of nursing patients, psychological intervention should be carried out for their families.

Compared with benign tumors, patients with malignant tumors are under double mental pressure of cancer diagnosis and treatment during the treatment stage. Surgical resection of a wide range often affects the normal function of the body or the organ in which the tumor is located. Based on this, nursing staff should deeply understand the psychological changes of patients and assist doctors to patiently explain the necessity of the operation to save lives and prevent tumor recurrence before operation (18). In addition, patients with malignant tumors often need to receive adjuvant treatments such as radiotherapy and chemotherapy after operation, and their anxiety is often aggravated by their adjuvant treatments. Therefore, before carrying out various treatments, explanation should be carefully done so that patients can understand the role of treatment, brief steps, possible side effects and matters needing cooperation are links that cannot be ignored in psychological care for malignant tumors.

Narrative Nursing Combined With SFA Can Effectively Improve Anxiety and Depression in Patients With Pulmonary Tumor During Perioperative Period

The traditional perioperative care focuses on health education to patients and active prevention of postoperative complications, ignoring the stimulation and cultivation of patients' potential to participate in disease treatment and nursing. SFA is a clinical intervention model that fully respects individuals, and its characteristics are to guide individuals to fully mobilize their resources and potential, and take the initiative to participate in behavioral changes (19). The key of the SFA is to assist patients to construct constructive solutions, utilize their own resources and potential, and improve the puzzles and problems encountered in the current care (20). Some scholars believe that the implementation of the SFA is based on two aspects. One is to establish a specific and feasible goal based on the individual thinking mode, and the other is to use the exceptional question to explore the individual's experience in dealing with the problem and to seek various resources to achieve the goal. Narrative nursing therapy is a kind of treatment in postmodern psychology. At present, the specific definition of narrative nursing is still vague. Based on the views of many literatures, we have summarized the concept of narrative nursing as a nursing practice method in which nursing staff listen to the

TABLE 4 | Comparison of HAD scores and Compliance Behavior scores of patients with different nursing schemes before and after nursing.

Group	*n*	HAD		Medication behavior		INR monitoring behavior		Life behavior		Aggregate score	
		Before nursing	After nursing	Before nursing	After nursing	Before nursing	After nursing	Before nursing	After nursing	Before nursing	After nursing
Study group	74	12.96 ± 3.34	7.05 ± 2.16	6.39 ± 0.36	7.87 ± 0.65	6.41 ± 1.21	7.94 ± 1.35	8.69 ± 1.25	10.69 ± 1.63	21.49 ± 2.82	26.50 ± 3.63
control group	74	12.61 ± 3.45	8.94 ± 2.31	6.25 ± 0.41	7.13 ± 0.34	6.53 ± 1.25	7.42 ± 1.12	8.81 ± 1.32	9.67 ± 1.34	21.59 ± 2.98	24.22 ± 2.80
T		0.627	5.141	0.631	8.678	0.593	2.599	0.568	4.158	0.210	4.278
P		0.532	<0.001	0.529	<0.001	0.554	0.010	0.571	<0.001	0.834	<0.001

stories of patients, discover the key points of nursing and then implement nursing intervention on patients to help patients achieve the purpose of reconstructing life and diseases. Narrative nursing can externalize patients' bad emotions through effective communication and deconstruct their inner anxiety problems in empathy with patients on the basis of establishing good nurse-patient relationship (21–23). In this study, at the time of discharge, the HAD score of the study group was lower than that of the control group, and the medication behavior, INR monitoring behavior and life behavior were higher than those of the control group ($P < 0.05$). It indicated that narrative nursing combined with SFA could effectively improve the anxiety and depression status of patients with lung cancer during the perioperative period and enhance the treatment compliance of patients.

CONCLUSION

In summary, income status, sleep quality, fear of postoperative pain, Patient's knowledge of their condition and nature of tumor are the independent risk factors affecting the psychological state of patients with lung tumor during perioperative period. Narrative nursing combined with focused solution model can effectively improve the anxiety and depression status of patients with lung tumor during perioperative period and enhance their compliance behavior, 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 the Shanghai Chest Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LG is responsible for the design of the article. FJ is responsible for the evaluation and testing of the results. JF is responsible for data statistics and the writing of the paper. LJ is the supervisor of the entire study. All authors contributed to the article and approved the submitted version.

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Effect of Marital Status on Upper Digestive Tract Tumor Survival: Married Male Patients Exhibited a Better Prognosis

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Purpose: Marital status has been associated with the outcomes in several types of cancer, but less is known about upper digestive tract tumors (UDTTs). The study aims to explore the effect of marital status on the survival outcomes of UDTT.

Methods: We collected patient cases of UDTT using the Surveillance, Epidemiology, and End Results (SEER) database between 1975 and 2016. The univariate analyses of overall survival (OS) and cancer-specific survival (CSS) were performed using the Kaplan–Meier method. The multivariate survival analyses were performed using Cox proportional hazard model.

Results: A total of 282,189 patients were included, with 56.42, 16.30, 13.33, and 13.95% of patients married, never married, divorced or separated, and widowed, respectively. The significant differences were observed among married, never-married, divorced or separated, and widowed patients with regard to the year of diagnosis, sex, age, race, pathological type, anatomical site, the number of primary tumor, grade, rate of surgery performed, radiotherapy, chemotherapy ($p < 0.001$). The proportions of patients with 3-year and 5-year OS were 54.22 and 48.02% in the married group, 46.96 and 41.12% in the never-married group, 44.24 and 38.06% in the divorced or separated group, 34.59 and 27.57% in the widowed group, respectively ($p < 0.001$); the proportions of patients with 3-year and 5-year CSS were 70.76 and 68.13% in the married group, 62.44 and 59,93% in the never-married group, 63.13 and 60.53% in the divorced or separated group, 62.11 and 58.89% in the widowed group, respectively ($p < 0.001$); all these data indicated married patients exhibited favorable OS and CSS than never-married, divorced or separated, and widowed patients. Men in the married group showed better OS (*HR*, 1.16; 95%CI: 1.11–1.22) and CSS (*HR*, 0.96; 95%CI: 0.92–1.23) than those in the never-married group.

Conclusion: This study reveals that marital status is an independent prognostic factor for OS and CSS of patients with UDTT. Married male patients with UDTT trend to have a better prognosis.

Keywords: upper digestive tract tumors, marital status, SEER, prognostic factors, cancer-specific survival

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INTRODUCTION

Social supports are emerging and closely related to the cancer prognosis as the society develops attracting more attention (1, 2). Marital status as one of the most important social relationships has significant implications for human health and well-being. The numerous studies have identified significant differences in morbidity and prognosis of different diseases in different marital statuses (3–6). Aizer et al. used the Surveillance, Epidemiology, and End Results (SEER) database for analysis and found that unmarried patients have higher risks of cancer metastasis, under-treatment, and death compared to married patients in a sample size of nearly 1 million patients (7). Marital status has been increasingly considered as an independent factor in the prognostic assessment of many cancers (7–9).

The upper digestive tract tumors (UDTTs), accounted for 6.8% of new on-set cancers and 8.9% of cancer deaths worldwide in 2018, are the seventh most frequent cancer type and the seventh most common cause of death from cancer worldwide (10). The upper digestive tract (UDT), which includes oral cavity, larynx, and esophagus, is the passage through which food enters the body and is covered by squamous epithelium, and the most frequent pathological type of UDTT is squamous cell carcinoma (SCC) (11–13). Sociological behaviors and psychosocial factors such as smoking, drinking, HPV infection, and upset emotion contribute enormously to UDTT (14–18). Psychosocial factors are involved in the pathogenesis of mental disorders by acting *via* mechanisms involving epigenetics (19), and the impact of different marital statuses on sociological behavior and psychosocial factor is critical (20, 21). Marriage has been a protective factor in many previous studies of cancer associations (7, 8). However, as far as we are concerned, first, UDTT is closely related to many sociological factors, and whether marriage, as an important sociological factor, is related to UDTT has not been studied before. Second, on the research methods, many other tumor-related studies only discuss the relationship between marital status and overall survival (OS) rate, but the lack of research on relationship about marital status and cancer-specific survival (CSS) rate which is better at showing the relationship between the tumor and survival. Therefore, the aim of our study was to explore the effects of different marital statuses, which include married, never married, divorced or separated, widowed on the prognosis of patients with UDTTs according to the multiple stratified studies based on the SEER population-based database.

MATERIALS AND METHODS

Patient Selection and Data Collection

Patient cases of UDTT included between 1975 and 2016 were collected from the SEER database, which is the largest population-based cancer registry in the world and included 18 cancer registries as released on 2019 (22). UDT is comprised of three anatomical sites: (1) oral department consisting of lip (C000–C009), tongue (C019–C029), and floor of mouth (C040–C049); (2) pharyngeal department consisting of nasopharynx (C110–C119), tonsil (C090–C099), oropharynx (C100–C109), hypopharynx (C129–C130–139), and other oral cavity and pharynx (C140, C142–C148); (3) esophagus (C150–C159). Accordingly, three groups were classified based on the anatomical sites, oral, pharyngeal, and esophagus. Cases with different histological types were identified using the codes of International Classification of Oncology (ICD-O-3/WHO 2008) for tumor morphology (SCC = 8050–8084). Tumors of the salivary gland were excluded due to the differences in the type of epithelium, pathological type, and etiology. The flow chart is shown in **Figure 1**. Collected UDTT patients must have age more than 18 years, with demographic and clinical information that includes years of diagnosis, age, sex, race, marital status, anatomical site, pathological type, number of primary tumors, grade, stage, surgery, radiotherapy, chemotherapy, 3-year OS rate, 5-year OS, 3-year CSS rate, 5-year CSS, total OS rate, and total CSS rate. Grade was rated from I to IV based on the cancer cell differentiation. Stage was also rated from I to IV based on tumor metastasis. OS or CSS was defined as the date when the patient diagnosed with cancer to the date of the patient's death or cancer-specific death. When CSS calculated, deaths from other causes were treated as censored observations. It should be pointed out that, in many studies of UDTT and cancers, 45 and 75 are respectively regarded as the recognized age of a young patient and old patient (10, 23). Patients were age-stratified into <45 years, 45–60 years, 61–75 years, and >75 years. Marital status was classified as married, never married including those reported to cohabitate with an unmarried, domestic partner (same gender, opposite gender, or unregistered), divorced or separated, and widowed. Patients should be excluded if they had unknown parameters of stage, partnership status, treatment, or performance of sentinel lymph node biopsy.

Statistical Analysis

Categorical data are shown as percentage and analyzed by chi-square test. The OS and CSS of patients were plotted using the Kaplan–Meier method according to the different marital statuses and examined by log rank test. The survival is calculated as the number of months after the date of cancer diagnosis until the date of death in the SEER. Multivariate analysis was conducted to calculate OS rate and CSS rate with Cox proportional hazard ratios (HRs), respectively, and the nomograms were plotted to show the results of Cox regression. All statistical analyses were performed with R version 3.6.8 (R Core Team, Vienna, Austria), and the significance level was set as 0.05.

RESULTS

Patient Characteristics

A total of 282,189 eligible patients with UDTTs in the SEER database during a 42-year study period (1975–2016) were analyzed in this study. Their demographic and clinical information for all study population is shown in **Table 1**. The proportions were 56.42% (159,205/282,189) for married patients, 16.51% (46,600/282,189) for never-married patients, 13.33% (37,635/282,189) for divorced or separated patients, and 13.74% (38,749/282,189) for widowed patients. The highest proportion

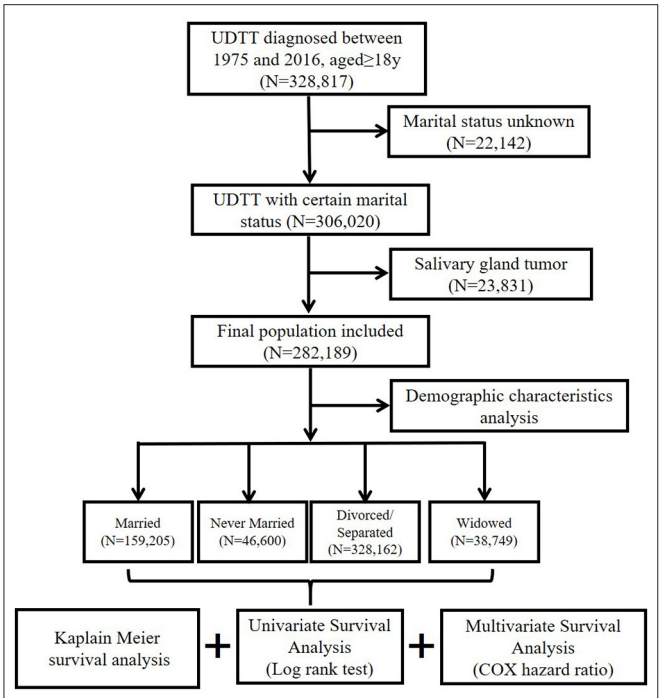

FIGURE 1 | Eligibility criteria for collection of patients with UDTTs.

of new diagnoses of UDTTs was found in the period of 2002–2016 (58.52%, 165,131/282,189), possibly due to the advances in diagnose of UDTTs. In each diagnosis period with a 14-year interval, married patients accounted for the majority ($p<0.001$). The proportion of never-married patients continued to increase, from 11.31% at the beginning to 18.48% at the end. The male patients accounted for 72.13% (203,557/282,189). With regard to age stratification, new diagnoses of UDTTs were found in age ranging from 45 to 75 years (73.92% in total). There were 82.57% of patients (232,998/282189) being white, 75.75% (213,746/282189) with SCC, 42.84% (120,901/282189) occurring in oral cavity, 69.22% (195,341/282189) with a primary lesion, 33.89% (95,637/282189) with grade II, and 19.63% (55,400/282189) with stage IV ($p < 0.001$).

Association Between Patient's Characteristics and Marital Status

Significant differences were observed among married, never-married, divorced or separated, and widowed patients with regard to the year of diagnosis, sex, age, race, pathological type, anatomical site, number of primary tumor, grade, rate of surgery performed, radiotherapy, and chemotherapy (**Table 1**, $p < 0.001$). In detail, a higher proportion of married patients and a lower proportion of never-married patients were found in the diagnosis period of 1975–1988 compared with other two periods ($p < 0.001$). A higher proportion of never-married patients and a lower proportion of widowed patients were found in the diagnosis period of 2003–2016 compared with other two periods ($p < 0.001$). Men had higher proportions in married (61.75 vs. 42.60%, $p < 0.001$) and never-married (17.41 vs. 14.19%, $p < 0.001$) patients but a lower proportion in widowed patients (7.5 vs. 29.89%, $p < 0.001$) when comparable to women. In each marital status, four age stratifications showed significant differences, so did race ($p < 0.001$). Higher proportions of SCC cases were noted in never-married (17.11 vs. 14.65%, $p < 0.001$) and divorced or separated (14.04 vs. 11.15%, $p < 0.001$) patients but a lower proportion of SCC cases were noted in married patients (55.14 vs. 60.42%, $p < 0.001$) than non-SCC cases. Most patients were diagnosed with grade IV in married group (62.34%), fewest patients with grade II in never-married group (14.29%), and fewest patients with grade IV in divorced or separated group (10.19%) and widowed group (10.89%). Concerning tumor stage, most stage I cases were found in married group (60.13%), most stage IV cases in never-married group (20.67%), and fewest stage IV cases in widowed group (9.17%). The proportion of patients undergoing surgery was higher than those not in married group (61.40 vs. 52.19%, $p < 0.001$), while the proportion of patients undergoing surgery was lower than those not in never-married (18.11 vs. 14.64%, $p < 0.001$), divorced or separated (14.39 vs. 12.09%, $p < 0.001$), and widowed (15.31 vs. 11.87%, $p < 0.001$) patients. More patients underwent radiotherapy and chemotherapy in married group (59.06 vs. 54.72%, $p < 0.001$), but fewer in widowed group (8.80 vs. 16.90%, $p < 0.001$).

Association Between Patient's Characteristics, Marital Status, and Survival Outcomes of Patients With UDTTs

The median survival time of all patients with UDTTs was 21 months, the median survival time was 26 months in the married group, 17 months in the never-married group, 17 months in the divorced or separated group, and 12 months in widowed group. As shown in **Figure 2**, the proportions of patients with 3-year and 5-year OS were 54.22 and 48.02% in the married group, 46.96 and 41.12% in the never-married group, 44.24 and 38.06% in the divorced or separated group, 34.59 and 27.57% in the widowed group, respectively ($p < 0.001$), which indicated that married patients exhibited favorable OS than never-married, divorced or separated, and widowed patients. Likewise, the proportions of patients with 3-year and 5-year CSS were 70.76 and 68.13% in the married group, 62.44 and 59.93% in the never-married group, 63.13 and 60.53% in the divorced or separated group, 62.11 and 58.89% in the widowed group, respectively ($p < 0.001$), which indicated that married patients exhibited favorable CSS than never-married, divorced or separated, and widowed patients. An early year of diagnosis (1975–1988), male, age older than 75 years, Black race, widowed, non-SCC, tumor in esophagus, number of primary tumors=1, tumor grade=III, stage IV, surgery not performed, and radiotherapy were considered as the significant risk factors ($p<0.001$) of OS and CSS rate. Furthermore, chemotherapy predicted better 3-year OS rate, but worse rates of 5-year OS, 3-year CSS, and 5-year CSS (**Table 2**).

TABLE 1 | Demographic characteristics for patient cases with UDTT by marital status.

Characteristic	Total *n* = 282,189	Married *n* = 159,205 (56.42%)	Never married *n* = 46,600 (16.51%)	Divorced/Separated *n* = 37,635 (13.33%)	Widowed *n* = 38,749 (13.74%)	*P* value
Years of diagnosis						
1975–1988	41,164 (14.59%)	24,064 (58.46%)	4,654 (11.31%)	5,453 (13.25%)	6,993 (16.98%)	<0.001
1989–2002	75,894 (26.89%)	42,472 (55.96%)	11,437 (15.07%)	9,645 (12.71%)	12,340 (16.26%)	
2003–2016	165,131 (58.52%)	92,669 (56.12%)	30,509 (18.48%)	22,537 (13.65%)	19,416 (11.75%)	
Sex						<0.001
Male	203,557 (72.13%)	125,706 (61.75%)	35,444 (17.41%)	27,162 (13.34%)	15,245 (7.5%)	
Female	78,632 (27.87%)	33,499 (42.60%)	11,156 (14.19)	10,473 (13.32%)	23,504 (29.89%)	
Age						<0.001
<45	16,736 (5.93%)	9,042 (54.03%)	5,828 (34.82%)	1,747 (10.44%)	119 (0.78%)	
45–60	94,113 (33.35%)	53,879 (57.25%)	20,986 (22.30%)	15,738 (16.72%)	3,510 (3.73%)	
61–75	114,489 (40.57%)	68,991 (60.30%)	15,053 (13.15%)	16,009 (13.98%)	14,436 (12.57%)	
>75	56,851 (20.15%)	27,293 (48.01%)	4,733 (8.33%)	4,141 (7.28%)	20,684 (36.38%)	
Race						<0.001
White	232,998 (82.57%)	136,386 (58.53%)	33,775 (14.50%)	30,494 (13.09%)	32,343 (13.88%)	
Black	30,466 (10.80%)	10,269 (33.71%)	10,172 (33.39%)	5,723 (18.78%)	4,302 (14.12%)	
Other*	18,725 (6.63%)	12,550 (7.88%)	2,653 (5.69%)	1,418 (3.76%)	2,104 (5.43%)	
Pathologic type						<0.001
SCC	213,746 (75.75%)	117,851 (55.14%)	36,571 (17.11%)	30,002 (14.04%)	29,322 (13.71%)	
Non-SCC	68,443 (24.25%)	41,354 (60.42%)	10,029 (14.65%)	7,633 (11.15%)	9,427 (13.78%)	
Site						<0.001
Oral carvity	120,901 (42.84%)	68,533 (56.69%)	19,433 (16.07%)	15,557 (12.87%)	17,378 (14.37%)	
Pharynx	74,844 (26.52%)	41,838 (55.90%)	13,980 (18.68%)	11,368 (15.19%)	7,558 (10.23%)	
Esophagus	86,444 (30.64%)	48,834 (56.50%)	13,187 (15.25%)	10,710 (12.40%)	13,713 (15.85%)	
Primary number						<0.001
1	195,341 (69.22%)	108,368 (55.48%)	34,921 (17.88%)	26,450 (13.54%)	25,602 (13.10%)	
≥2	86,848 (30.78%)	50,837 (58.54%)	11,679 (13.45%)	11,185 (12.88%)	13,147 (15.14%)	
Grade						<0.001
I	31,674 (11.22%)	18,515 (58.45%)	4,527 (14.29%)	3,619 (11.43%)	5,013 (15.83%)	
II	95,637 (33.89%)	52,512 (54.91%)	16,693 (17.45%)	13,475 (14.09%)	12,957 (13.55%)	
III	80,760 (28.62%)	47,166 (58.40%)	13,111 (16.23%)	10,739 (13.30%)	9,711 (12.07%)	
IV	7,053 (2.50%)	4,397 (62.34%)	1,169 (16.58%)	719 (10.19%)	768 (10.89%)	
Unknown	67,065 (23.77%)	36,615 (54.60%)	11,100 (16.55%)	9,083 (13.54%)	1,0267 (15.31%)	
Stage						<0.001
I	23,879 (8.46%)	14,358 (60.13%)	3,688 (15.44%)	2,681 (11.23%)	3,152 (13.20%)	
II	16,968 (6.01%)	9,793 (57.71%)	2,785 (16.41%)	2,160 (12.73%)	2,230 (13.15%)	
III	22,329 (7.91%)	12,962 (58.05%)	4,008 (17.95%)	3,065 (13.73%)	2,294 (10.27%)	
IV	55,400 (19.63%)	30,378 (54.83%)	11,452 (20.67%)	8,498 (15.33%)	5,072 (9.17%)	
Unknown	163,613 (57.98%)	91,714 (56.06%)	24,667 (15.07%)	21,231 (12.98%)	26,001 (15.89%)	
Surgery						<0.001
Not performed	152,557 (54.05%)	79,617 (52.19%)	27,622 (18.11%)	21,957 (14.39%)	23,361 (15.31%)	
Performed	129,632 (45.95%)	79,588 (61.40%)	18,978 (14.64%)	15,678 (12.09%)	15,388 (11.87%)	
Radiotherapy						<0.001
No/Unknown	122,149 (43.29%)	67,030 (54.88%)	20,161 (16.51%)	14,851 (12.16%)	20,107 (16.46%)	
Yes	160,040 (56.71%)	92,175 (57.59%)	26,439 (16.52%)	22,784 (14.24%)	18,642 (11.65%)	
Chemotherapy						<0.001
No/Unknown	171,855 (60.90%)	94,041 (54.72%)	26,925 (15.67%)	21,850 (12.71%)	29,039 (16.90%)	
Yes	110,334 (39.10%)	65,164 (59.06%)	19,675 (17.83%)	15,785 (14.31%)	9,710 (8.80%)	

**Including other (American Indian/AK Native, Asian/Pacific Islander) and unknowns.*

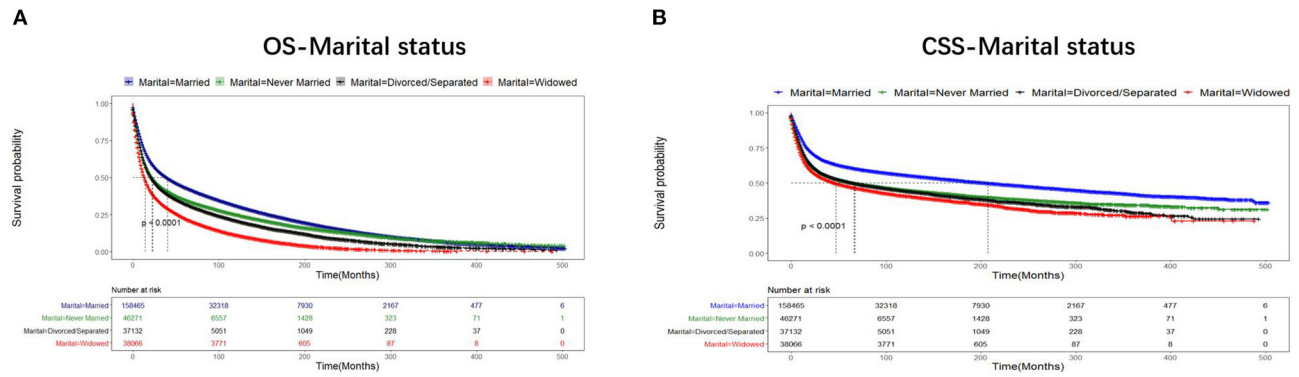

FIGURE 2 | Comparison of OS and CSS of the patients with UDTT in different marital statuses, 1975–2016 ($p < 0.001$). Censoring marks are indicated with small vertical lines. **(A)** OS- Marital status; **(B)** CSS- Marital status.

Marital Status as an Independent Factor Influencing Survival Outcomes of Patients With UDTTs

The variables that include sex, age, race, anatomical site, pathological type, grade, stage, surgery, radiotherapy, chemotherapy, and marital status were analyzed with Cox regression model for their correlations with the prognosis of patients with UDTTs. All variables were found to be independent prognostic factors of OS of patients with UDTTs (**Figure 3**, **Table 3**): sex (male: *HR*, 1.08; 95%CI: 1.06–1.10), age (45–60 years: *HR*, 1.32; 95%CI: 1.26–1.39; 61–75 years: *HR*, 1.74; 95%CI: 1.66–1.82; > 75 years: *HR*, 2.72; 95%CI: 2.58–2.85), race (Black: *HR*, 1.35; 95%CI: 1.32–1.39; other: *HR*, 0.97; 95%CI: 0.94–1.01), anatomical site (pharynx: *HR*, 0.82; 95%CI: 0.80–0.84; esophagus: *HR*, 3.00; 95%CI: 2.92–3.08), pathological type (NSCC: *HR*, 0.97; 95%CI: 0.94–0.99), grade (II: *HR*, 1.18; 95%CI: 1.14–1.21; III: *HR*, 1.18; 95%CI: 1.14–1.22; IV: *HR*, 1.08; 95%CI: 1.02–1.15;), stage (II: *HR*, 1.58; 95%CI: 1.53–1.63; III: *HR*, 2.25; 95%CI: 2.18–2.32; IV: *HR*, 3.25; 95%CI: 3.16–3.35;), surgery (performed: *HR*, 0.45; 95%CI: 0.44–0.46), radiotherapy (Yes: *HR*, 0.66; 95%CI: 0.65–0.67), chemotherapy (yes: *HR*, 0.57; 95%CI: 0.56–0.59), and marital status (never married: *HR*,1.36; 95%CI: 1.33–1.39; divorced/separated: *HR*, 1.35; 95%CI: 1.32–1.39; widowed: HR, 1.38; 95%CI: 1.34–1.42). Only in race, other race showed no significant difference (p=0.134), and other variables are significantly different. Likewise, all variables were found to be the independent prognostic factors of CSS of patients with UDTTs: sex (male: *HR*, 1.05; 95%CI: 1.02–1.07), age (45–60 years: *HR*, 1.11; 95%CI: 1.06–1.18; 61–75 years: *HR*, 1.74; 95%CI: 1.08–1.21; > 75 years: *HR*, 1.40; 95%CI: 1.32–1.48), race (Black: *HR*, 1.36; 95%CI: 1.31–1.41; other: *HR*, 1.10; 95%CI: 1.05–1.15), anatomical site (pharynx: *HR*, 0.78; 95%CI: 0.76–0.81; esophagus: *HR*, 3.91; 95%CI: 3.77–4.04), pathological type (NSCC: *HR*, 1.10; 95%CI: 1.06–1.13), grade (II: *HR*, 1.20; 95%CI: 1.15–1.26; III: *HR*, 1.24; 95%CI: 1.19–1.30; IV: *HR*, 1.13; 95%CI: 1.05–1.23), stage (II: *HR*, 1.97; 95%CI: 1.87–2.06; III: *HR*, 3.26; 95%CI: 3.11–3.41; IV: *HR*, 5.35; 95%CI: 5.13–5.59;), surgery (performed: *HR*, 0.43; 95%CI: 0.42–0.44), radiotherapy (Yes: *HR*, 0.74; 95%CI: 0.72–0.76), chemotherapy (yes: *HR*, 0.56; 95%CI: 0.55–0.58), and marital status (never married: *HR*,1.41; 95%CI: 1.37–1.45; divorced or separated: *HR*, 1.33; 95%CI: 1.28–1.37; widowed: *HR*, 1.32; 95%CI: 1.32–1.43;).

Stratified Analysis of Marital Status

Furthermore, we studied the effect of sex, age, race, anatomic site, pathological type, grade, stage, surgery, radiotherapy, chemotherapy, and marital status on OS and CSS of patients with UDTTs by COX proportional hazard regression model (**Figure 4**). Men had poor OS and CSS than women in never married and divorced or separated by comparing the HR in OS (never married: *HR*, 1.40; 95%CI: 1.37–1.44; divorced or separated: *HR*, 1.39; 95%CI: 1.35–1.43) and CSS (never married: *HR*, 1.45; 95%CI: 1.41–1.50; divorced/separated: *HR*, 1.39; 95%CI: 1.34–1.44). Compared with marital status, older women were more risk in never married (**Figure 4**). So, we made subgroup analysis according to married and never married (**Figure 5**). Regarding the OS patients with UDTTs, men in the married group showed better OS than those in the never-married group (*HR*, 1.16; 95%CI: 1.11–1.22). Regarding the CSS patients with UDTTs, men in the married group showed better CSS than those in the never-married group (*HR*, 0.96; 95%CI: 0.92–1.23). Notably, compared with the unmarried group, whether for OS or CSS, age is a greater risk factor for the married group. These data showed married male patients owed better survival outcome.

DISCUSSION

As far as we are concerned, few researches have focused on the heterogeneity of patients with UDTT in different marital statuses with stratified comparisons. UDTT, as a type of tumor with a higher incidence and a poor prognosis (24), is closely related to psychological and behavioral factors (14, 15), and the marital relationship has a significant impact on it through psychological and behavioral differences (20, 21). Our study indicated that married patients had better OS/CSS rate of UDTT, while widowed patients were had worse OS/CSS rate. This similar survival difference was also observed in each gender, stage, and treatments.

TABLE 2 | Univariate survival analyses of patients with UDTT according to various clinicopathological variables.

Variables	n	OS-3 years	OS-5 years	Log rank $\chi 2$ test	*P*	CSS- 3 years	CSS- 5 years	Log rank $\chi 2$ test	*P*
Years of diagnosis				1808.118	<0.001			1347.515	<0.001
1975–1988	41,164	40.13%	32.27%			60.48%	57.47%		
1989–2002	75,894	43.02%	35.30%			63.29%	60.06%		
2003–2016	165,131	53.77%	48.80%			70.64%	68.52%		
Sex				116.401	<0.001			289.070	<0.001
Male	203,557	48.31%	42.18%			66.28%	63.65%		
Female	78,632	50.39%	44.26%			69.51%	67.19%		
Age				18879.218	<0.001			3304.258	<0.001
<45	16,736	69.39%	65.22%			74.61%	71.75%		
45–60	94,113	57.32%	51.88%			68.21%	65.19%		
61–75	114,489	46.98%	40.46%			66.67%	64.16%		
>75	56,851	32.76%	25.69%			63.32%	62.56%		
Race				4463.418	<0.001			4107.093	<0.001
White	232,998	50.33%	44.04%			68.74%	66.26%		
Black	30,466	33.16%	27.95%			53.88%	51.35%		
Other*	18,725	56.56%	50.95%			69.41%	65.99%		
Marital status				8234.502	<0.001			3963.207	<0.001
Married	159,205	54.22%	48.05%			70.76%	68.13%		
Never married	46,600	46.96%	41.12%			62.44%	59.93%		
Divorced/Sepratated	37,635	44.24%	38.06%			63.13%	60.53%		
Widowed	38,749	34.59%	27.57%			62.11%	59.89%		
Pathological type			10013.912	<0.001			12162.172	<0.001	
SCC	213,746	52.98%	46.29%			71.37%	68.78%		
Non-SCC	68,443	36.11%	31.73%			54.10%	51.67%		
Site				57625.713	<0.001			54541.736	<0.001
Oral carvity	120,901	62.90%	55.54%			79.89%	77.47%		
Pharynx	74,844	56.83%	50.16%			72.94%	69.79%		
Esophagus	86,444	22.42%	18.50%			44.42%	42.21%		
Primaries number				1797.913	<0.001			35763.428	<0.001
1	195,341	46.47%	41.41%			54.86%	51.87%		
≥2	86,848	54.35%	45.81%			94.89%	94.03%		
Grade				4939.578	<0.001			5681.069	<0.001
I	31,674	64.03%	56.60%			80.27%	78.26%		
II	95,637	48.56%	42.03%			67.98%	65.29%		
III	80,760	41.65%	36.31%			59.84%	57.18%		
IV	7,053	51.30%	45.65%			65.86%	62.25%		
Unknown	67,065	50.68%	38.97%			68.85%	66.47%		
Stage				6301.868	<0.001			7478.189	<0.001
I	23,879	70.63%	64.06%			87.55%	85.77%		
II	16,968	56.02%	49.01%			75.84%	72.90%		
III	22,329	49.71%	44.35%			66.77%	64.04%		
IV	55,400	43.50%	39.54%			59.43%	57.32%		
Unknown	163,613	46.49%	39.88%			65.99%	63.25%		
Surgery				38200.422	<0.001			32165.19	<0.001
Not performed	152,557	34.54%	29.86%			57.62%	55.44%		
Performed	129,632	65.77%	57.94%			80.55%	77.65%		
Radiotherapy				211.477	<0.001			196.963	<0.001
No/Unknown	122,149	49.17%	43.40%			70.13%	68.43%		
Yes	160,040	48.68%	42.27%			64.93%	61.73%		
Chemotherapy				110.581	<0.001			1,731.93	<0.001
No/Unknown	171,855	50.34%	43.77%			70.67%	68.42%		
Yes	110,334	51.29%	41.19%			61.75%	58.73%		

**Including other (American Indian/AK Native, Asian/Pacific Islander) and unknowns.*

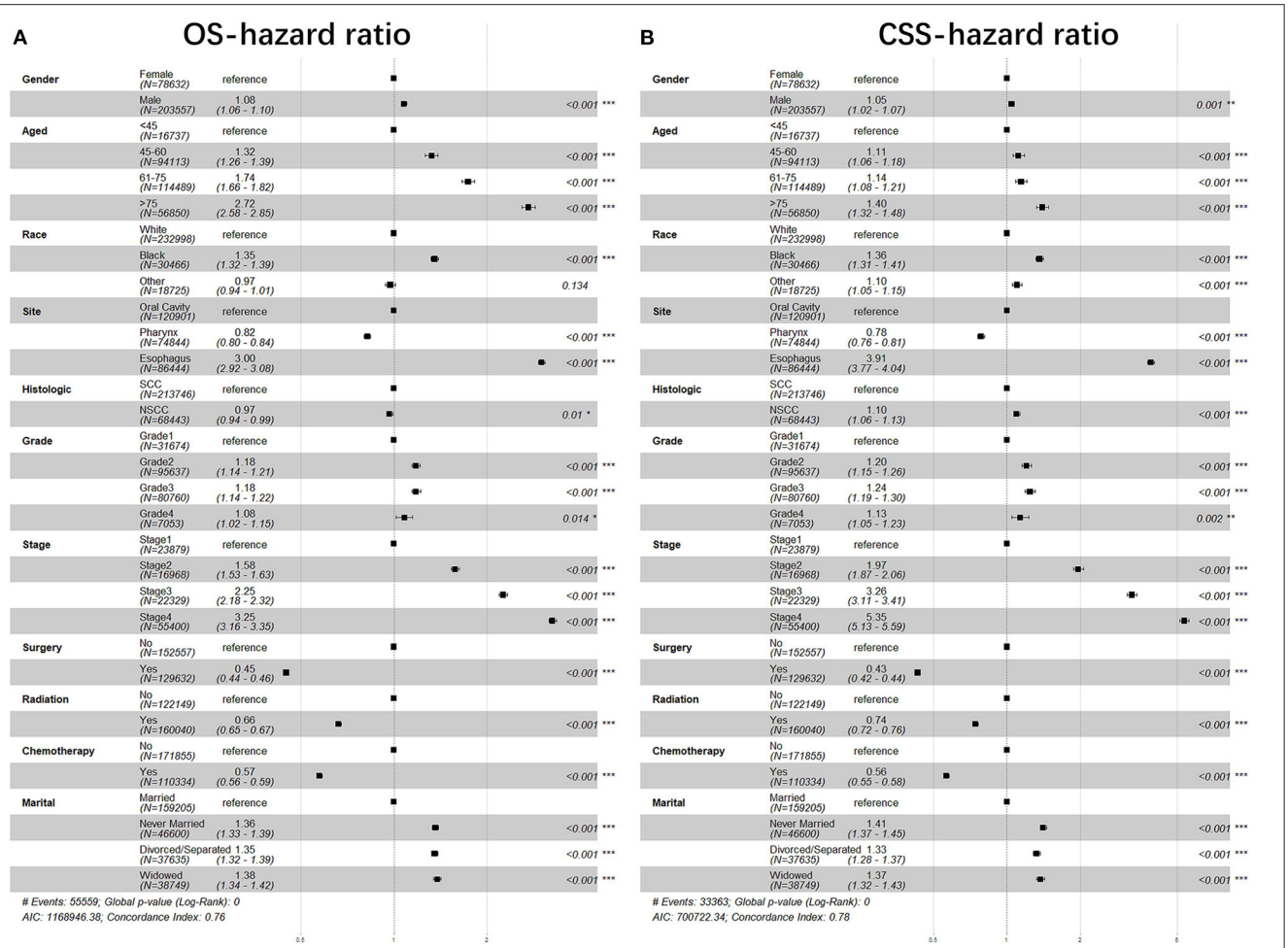

FIGURE 3 | The forest plot of HR (95% CI) for OS and CSS of the patients with UDTT. HR, hazard ratio; CI, confidence interval. **(A)** OS- hazard ratio; **(B)** CSS- hazard ratio.

In our study, the never-married group had gradually increased from 1975 to 2016, which is consistent with the declining marriage rate in the United States (25). At the same time, the proportion of male patients was significantly higher than that of female patients, which may be due to the fact that UDTT is related to smoking, drinking, and other living habits. The 3-year and 5-year survival rates gradually improved as the time of diagnosis approached, which indicates that with the advancement of medicine, both diagnosis and treatment of UDTT have made significant progress. Both 3-year and 5-year OS and CSS were significantly lower for men than for women. The 3-year and 5-year survival rates for Blacks were also significantly lower than Whites and other races. For the 3-year and 5-year survival rates, being married is an obvious protective factor.

Most studies suggested that unmarried patients have worse survival rates due to delayed diagnosis and under-treatment (3, 7, 26, 27). Hinyard et al. found that the probability of late-stage diagnosis among unmarried female patients was 1.18-folds higher than married female patients (28). Hershman et al. stated that unmarried subjects tended to postpone the start of adjuvant chemotherapeutic treatment after receiving the surgeries of breast carcinoma, which led to higher mortality (29). Our study found something similarly in Cox multivariate regression analysis, and we found that never-married and divorced patients in OS and CSS had greater risks for men than women, and increased age was riskier for women. From the site of UDTT, the prognosis of esophageal cancer in men was worse than that in women. Women can benefit more from the surgery. In the further stratified comparison of married and never-married status, it was found that men can benefit more from marriage than women, thus avoiding premature death caused by UDTT. The never-married group received more benefits in treatment than the married group.

There are several studies that have emphasized the importance of marriage to the patients with cancer. On the one hand, it is analyzed by psychological differences. Unmarried patients more likely display greater stress and depression when diagnosed with cancer, which can change immune function and cause tumor progression (30, 31). Meanwhile, unmarried patients lack the support and care from their spouses, so they often

TABLE 3 | Multivariate Cox analyses of prognostic factors of UDTT.

Variables	OS- Hazard Ratio	95% CI	*P*	CSS- Hazard Ratio	95% CI	*P*
Sex			<0.001			<0.001
Female	1.00	Reference		1.00	Reference	
Male	1.08	1.06–1.10		1.05	1.02–1.07	
Age			<0.001			<0.001
<45	1.00	Reference		1.00	Reference	
45–60	1.32	1.26–1.39		1.11	1.06–1.18	
61–75	1.74	1.66–1.82		1.14	1.08–1.21	
>75	2.72	2.58–2.85		1.40	1.32–1.48	
Race			<0.001			<0.001
White	1.00	Reference		1.00	Reference	
Black	1.35	1.32–1.39		1.36	1.31–1.41	
Other	0.97	0.94–1.01		1.10	1.05–1.15	
Site			<0.001			<0.001
Oral carvity	1.00	Reference		1.00	Reference	
Pharynx	0.82	0.80–0.84		0.78	0.76–0.81	
Esophagus	3.00	2.92–3.08		3.91	3.77–4.04	
Pathological type			<0.001			<0.001
SCC	1.00	Reference		1.00	Reference	
NSCC	0.97	0.94–0.99		1.10	1.06–1.13	
Grade			<0.001			<0.001
I	1.00	Reference		1.00	Reference	
II	1.18	1.14–1.21		1.20	1.15–1.26	
III	1.18	1.14–1.22		1.24	1.19–1.30	
IV	1.08	1.02–1.15		1.13	1.05–1.23	
Stage			<0.001			<0.001
I	1.00	Reference		1.00	Reference	
II	1.58	1.53–1.63		1.97	1.87–2.06	
III	2.25	2.18–2.32		3.26	3.11–3.41	
IV	3.25	3.16–3.35		5.35	5.13–5.59	
Surgery			<0.001			<0.001
Not performed	1.00	Reference		1.00	Reference	
Performed	0.45	0.44–0.46		0.43	0.42–0.44	
Radiotherapy			<0.001			<0.001
No/Unknown	1.00	Reference		1.00	Reference	
Yes	0.66	0.65–0.67		0.74	0.72–0.76	
Chemotherapy			<0.001			0.48
No/Unknown	1.00	Reference		1.00	Reference	
Yes	0.57	0.56–0.59		0.56	0.55–0.58	
Marital status			<0.001			<0.001
Married	1.00	Reference		1.00	Reference	
Never married	1.36	1.33–1.39		1.41	1.37–1.45	
Divorced/Sepratated	1.35	1.32–1.39		1.33	1.28–1.37	
Widowed	1.38	1.34–1.42		1.37	1.32–1.43	

[*] *Including other (American Indian/AK Native, Asian/Pacific Islander) and unknowns.*

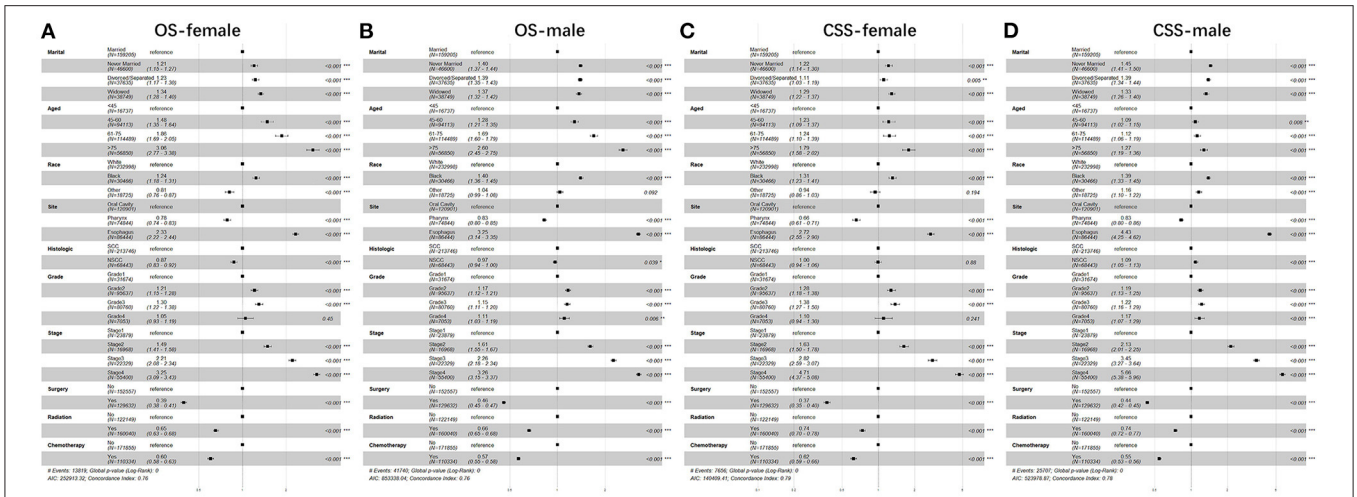

FIGURE 4 | The forest plot of HR (95% CI) for OS and CSS of the patients with UDTT in each gender. HR, hazard ratio; CI confidence interval; **(A)** OS of female; **(B)** OS of male; **(C)** CSS of female; **(D)** CSS of male.

FIGURE 5 | The forest plot of HR (95% CI) for OS and CSS of the patients with UDTT in subgroups of married and never married. HR, hazard ratio; CI confidence interval; **(A)** OS of married; **(B)** OS of never married; **(C)** CSS of married; **(D)** CSS of never married.

suffer from distressed psychological state and indulge in bad habits, just like smoking and excessive drinking, which lead to an exacerbation of tumor and poor treatment outcomes (32–34). Widowhood is a serious emotion stress, which means that social support and material support are reduced that could lead the patients to pay less attention to health and causing more non-definitive treatment even when symptoms are present (27). On the other hand, the lack of marriage has a corresponding effect on the hormones and mediators of the patient's body. The lack of social support and chronic stress may promote the secretion of cortisol (35, 36). Other studies have shown that increased psychological stress by pass through the hypothalamic-pituitary-adrenal axis to decrease the immune response and promote development of tumor. Furthermore, the release of glucocorticoids and catecholamines is regulated, which further directly influences the tumor microenvironment (37, 38), and has been implicated in cancer survival (39, 40). In contrast, it has been suggested that mates tend to encourage screening and compliance to treatment and therefore could improve treatment outcomes (4, 7).

Our study was based on a big database and involved a huge population and could give light on the impact of marital status on the prognosis in patients with UDTT. However, there are still some limitations. First, the SEER database only records marital status of patient at the time of diagnosis, not dynamically, so changes in marital status as the tumor progresses may affect the outcome of a different marital status on survival outcomes. Second, SEER database lacks corresponding records of marital quality, because disharmony and depression in marriage may negatively affect the prognosis (41). Third, a considerable proportion of patients may not have a legal marriage, but live in de facto same or opposite sex or partnerships (4). It was not

until June 2015, the United States officially legalized same-sex marriage (42), and the SEER does not record it, so it is impossible to know whether there is a difference in the prognosis of tumors between same-sex and heterosexual marriages. Finally, SEER also has limited the information on adverse habits such as smoking and drinking.

In summary, our study has revealed that marital status is an independent prognostic factor of OS and CSS rates in patients with UDTTs. Compared with other marital status groups, married patients gained significantly better outcome, irrespective of different variables we studied. The never-married group performed significantly worse in OS and CSS, while men with UDTTs benefited more from marriage than women. Men with UDTTs who were never married had at higher risk than women. Thus, married status plays a significant role as a protective factor in patients with UDTTs, especially for men. Therefore, the marital status of the patients is recommended for predicting the prognosis as a clinical routine during the treatment of UDTTs, and never-married men with UDTTs also need more attention.

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.

ETHICAL STATEMENT

The SEER belongs to public databases. The patients involved in the database have obtained ethical approval. Users can download relevant data for free for research and publish relevant articles. Our study is based on open-source data, so there are no ethical issues and other conflict of interests.

AUTHOR CONTRIBUTIONS

MFQ as the first author and corresponding author conceived the study, wrote the initial draft, and edited the final version. JKP prepared the experimental resources and the software. QHS and HX performed data analysis and interpretation, and contributed to charts. QMC as a corresponding author assisted in manuscript revision. All authors contributed significantly to the initiation and design of the study and manuscript approval.

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Application of Bevacizumab Combined With Chemotherapy in Patients With Colorectal Cancer and Its Effects on Brain-Gut Peptides, Intestinal Flora, and Oxidative Stress

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Objective: To investigate the efficacy of bevacizumab combined with chemotherapy in the treatment of colorectal cancer (CRC) and to analyze the effects on brain peptides, intestinal flora, and oxidative stress in CRC patients.

Methods: Eighty two patients with CRC who were admitted to our hospital from March 2018 to June 2021 were selected as the research subjects and divided into the control group ($n = 41$) and the observation group ($n = 41$). The control group was treated with XELOX chemotherapy, and the observation group was additionally treated with bevacizumab, which was repeated every 3 weeks for a total of two treatments. The therapeutic effects of the two groups were evaluated after treatment. The brain-gut peptide index, intestinal flora index and oxidative stress index were detected, and the adverse reactions of the two groups were recorded.

Results: In the control group, ER was 36.59% (15/41) and DCR was 73.17% (30/41). In the observation group, ER was 63.41% (26/41) and DCR was 90.24% (37/41). ER and DCR in the observation group were higher than those in the control group ($P < 0.05$). After treatment, the levels of motilin and gastrin in the observation group were lower than those in the control group, and ghrelin was higher than that in the control group ($P < 0.05$). After treatment, the levels of Bifidobacterium, Lactobacilli and Enterococcus in the observation group were higher than those in the control group, and the level of *Escherichia coli* was lower than that in the control group ($P < 0.05$). After treatment, the SOD level of the observation group was lower than that of the control group, and the MDA level was higher than that of the control group.

Conclusion: Bevacizumab combined with chemotherapy has good efficacy in the treatment of colorectal cancer patients, which can effectively improve the gastrointestinal motility of patients, regulate the intestinal flora of the body, rebuild the microecological

balance, effectively reduce the oxidative stress response of patients, and reduce the incidence of adverse reactions.

Keywords: colorectal cancer, bevacizumab, chemotherapy, brain-gut peptides, intestinal flora, oxidative stress

INTRODUCTION

Colorectal cancer (CRC) is one of the common malignant tumors, ranking the third in the incidence of malignant tumors and the sixth in the mortality rate. The incidence rate of CRC shows a rising trend year by year. Moreover, about one quarter of patients with colorectal cancer are in the advanced stage at the time of their initial diagnosis (1, 2). Surgery is the main treatment, and combined chemotherapy and radiotherapy are the classical treatment modes for colorectal cancer. Although improved chemotherapy regimens and the combination of molecular targeted drugs have increased the survival time of patients, the prognosis of advanced colorectal cancer, especially the right colorectal cancer, is still poor (3, 4). Therefore, exploring effective treatment of CRC is extremely important for improving the survival rate of tumor patients. In recent years, with the deepening of research on the molecular mechanism of tumors, targeted drugs targeting specific tumor molecular markers and signaling pathways have gradually emerged, some of which have been applied in clinical practice, among which the most representative targeted drugs include cetuximab, bevacizumab, and panizumab (5, 6). Vascular endothelial growth factor (VEGF) can specifically bind to the corresponding receptor and act on vascular endothelial cells, and is also an important growth factor to promote angiogenesis. Studies have shown that the inhibition of tumor growth can be achieved by down-regulating the expression of VEGF (7, 8). Bevacizumab can delay tumor growth by specifically binding to VEGF and inhibiting vascular endothelial cell generation and angiogenesis. At present, bevacizumab has been approved for the treatment of advanced CRC, breast cancer and many other advanced malignant tumors (9, 10). The purpose of this study was to investigate the efficacy of bevacizumab combined with chemotherapy in the treatment of CRC and to analyze the effects on brain peptides, intestinal flora and oxidative stress in CRC patients.

MATERIALS AND METHODS

Patients

A total of 82 patients with CRC who were admitted to our hospital from March 2018 to June 2021 were selected as the research subjects. Tumor sites: colon cancer 45 cases, rectal cancer 37 cases. Clinical stages included T3 stage (58 cases) and T4 stage (24 cases). Inclusion criteria: All the patients met the diagnostic criteria of CRC through pathological and cytological examination; Patients who have not received other chemotherapy within 1 month before this treatment; Patients who are not allergic to the current therapeutic drugs; The patient's survival is expected to be more than 3 months; At least 1 target lesion measurable by imaging. Exclusion criteria: Patients with abnormal liver and kidney function; Cardiac insufficiency; Contraindications to chemotherapy; Poor adherence or refusal to participate in the investigator. All the patients were divided into two groups, 41 cases in each group. There was no significant difference in general data between the two groups ($P > 0.05$). As shown in **Table 1**.

Treatment Methods

The control group was treated with XELOX chemotherapy: On the first day, oxaliplatin (Qilu Pharmaceutical Hainan Co., LTD.) 130 mg/m^2 was given by intravenous infusion. Capecitabine (Shanghai Roche Pharmaceuticals Co., LTD.) 1,000 mg/m^2 was administered orally twice daily for 14 consecutive days. Three weeks is one cycle. On the basis of the control group, bevacizumab was additionally used in the observation group: bevacizumab (Roche Diagnostics GmbH) was given by intravenous infusion at 7.5 mg/kg. The treatment was repeated every 3 weeks and the curative effect was observed after 2 cycles.

Observation Indicators

Efficacy Evaluation

The efficacy of patients after treatment is evaluated according to the efficacy evaluation criteria of solid tumors (11), which can be divided into complete response (CR), partial response (PR), disease stability (SD), and disease progression (PD). The effective rate (ER) = (CR + PR) cases/total cases ×100%, and the disease control rate (DCR) = (CR + PR + SD) cases/total cases × 100%.

Detection of Brain-Gut Peptide Indicators

Five milliliter of fasting venous blood in the morning of the patients was drawn before and after treatment, and the serum levels of motilin, gastrin and ghrelin of the patients were detected by radioimmunoassay. The relevant kits were purchased from Shanghai Yuanxin Biotechnology Co., Ltd.

Detection of Intestinal Flora Indicators

Anaerobes: *Bifidobacterium* and *Lactobacilli*; Aerobic bacteria: *Escherichia coli* and *Enterococcus*. Patients' fresh feces (0.1 g) were collected before and after treatment and diluted with normal saline at a ratio of times and mixed evenly, and inoculated into different media. The anaerobes were cultured by air extraction and ventilation for 72 h and then counted. The aerobic bacteria were cultured at 37°C for 48 h and then counted. They were identified by ALB semi-automatic microbial assay system.

Detection of Oxidative Stress Indicators

Serum superoxide dismutase (SOD) level was determined by xanthine oxidase colorimetric method, and serum malondialdehyde level was determined by thiobarbituric acid colorimetric method. The relevant kits were purchased from Shenzhen Jingmei Biological Technology Co., Ltd.

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

Group	Gender		Age (years)	Tumor site		Clinical stages		Tumor diameter (cm)
	Male	Female		Carcinoma of colon	Rectal cancer	T3	T4	
Control group ($n = 41$)	26	15	49.38 ± 8.76	25	16	31	10	3.49 ± 0.58
Observation group ($n = 41$)	22	19	49.66 ± 8.43	20	21	27	14	3.54 ± 0.61
t/χ^2	0.804		0.147	1.231		0.943		0.380
P	0.369		0.883	0.267		0.332		0.705

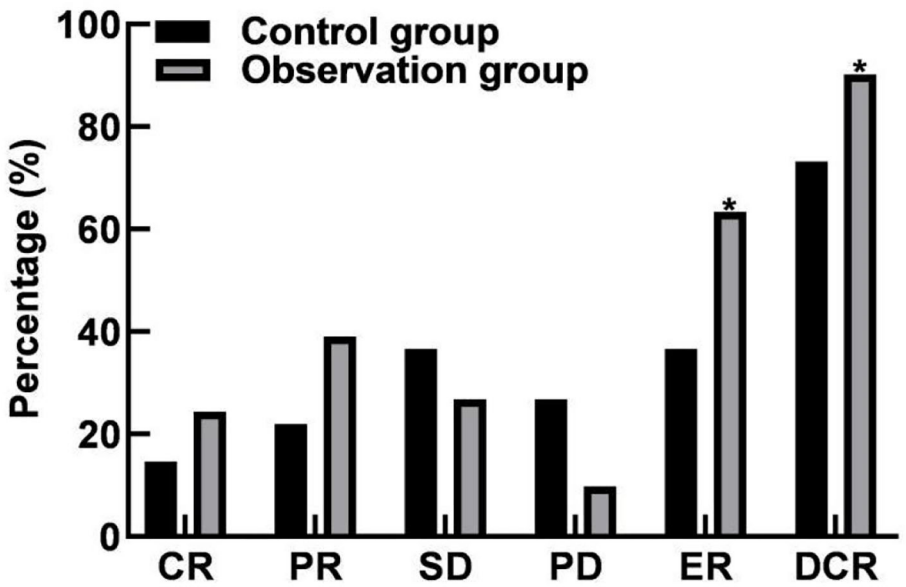

FIGURE 1 | Comparison of efficacy between the two groups. Compared with the control group, $^*P < 0.05$.

Adverse Reactions

The adverse reactions such as thrombocytopenia, nausea and vomiting, hypertension, and rash in the two groups were recorded during the treatment.

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 ±s). The difference is statistically significant when $P < 0.05$.

RESULTS

Comparison of Efficacy Between the Two Groups

In the control group, ER was 36.59% (15/41) and DCR was 73.17% (30/41). In the observation group, ER was 63.41% (26/41) and DCR was 90.24% (37/41). ER and DCR were significantly different between the two groups ($P < 0.05$). As shown in **Figure 1**.

Comparison of Brain-Gut Peptide Indicators Between the Two Groups

The levels of motilin, gastrin and ghrelin in control group were (168.45 ± 22.16) pg/mL, (206.18 ± 23.63) pg/mL, and (34.12 ± 4.63) pg/mL, respectively. Observation group were (149.58 ± 18.63) pg/mL, (185.65 ± 20.49) pg/mL, (36.94 ± 5.01) pg/mL, respectively. There were significant differences in motilin, gastrin and ghrelin levels between the two groups after treatment ($P < 0.05$). As shown in **Figure 2**.

Comparison of Intestinal Flora Indicators Between the Two Groups

After treatment, the levels of bifidobacterium, Lactobacillus and enterococcus in control group were (8.35 ± 0.79) CFU/g, (6.85 ± 0.52) CFU/g, (9.12 ± 0.76) CFU/g, and (7.51 ± 0.63) CFU/g, respectively. Observation group were (9.41 ± 0.83) CFU/g, (7.61 ± 0.58) CFU/g, (8.45 ± 0.59) CFU/g, (8.32 ± 0.59) CFU/g, respectively. There were significant differences in the levels of bifidobacteria, lactobacillus, *Escherichia coli*, and enterococcus between the two groups after treatment ($P<0.05$). As shown in **Figure 3**.

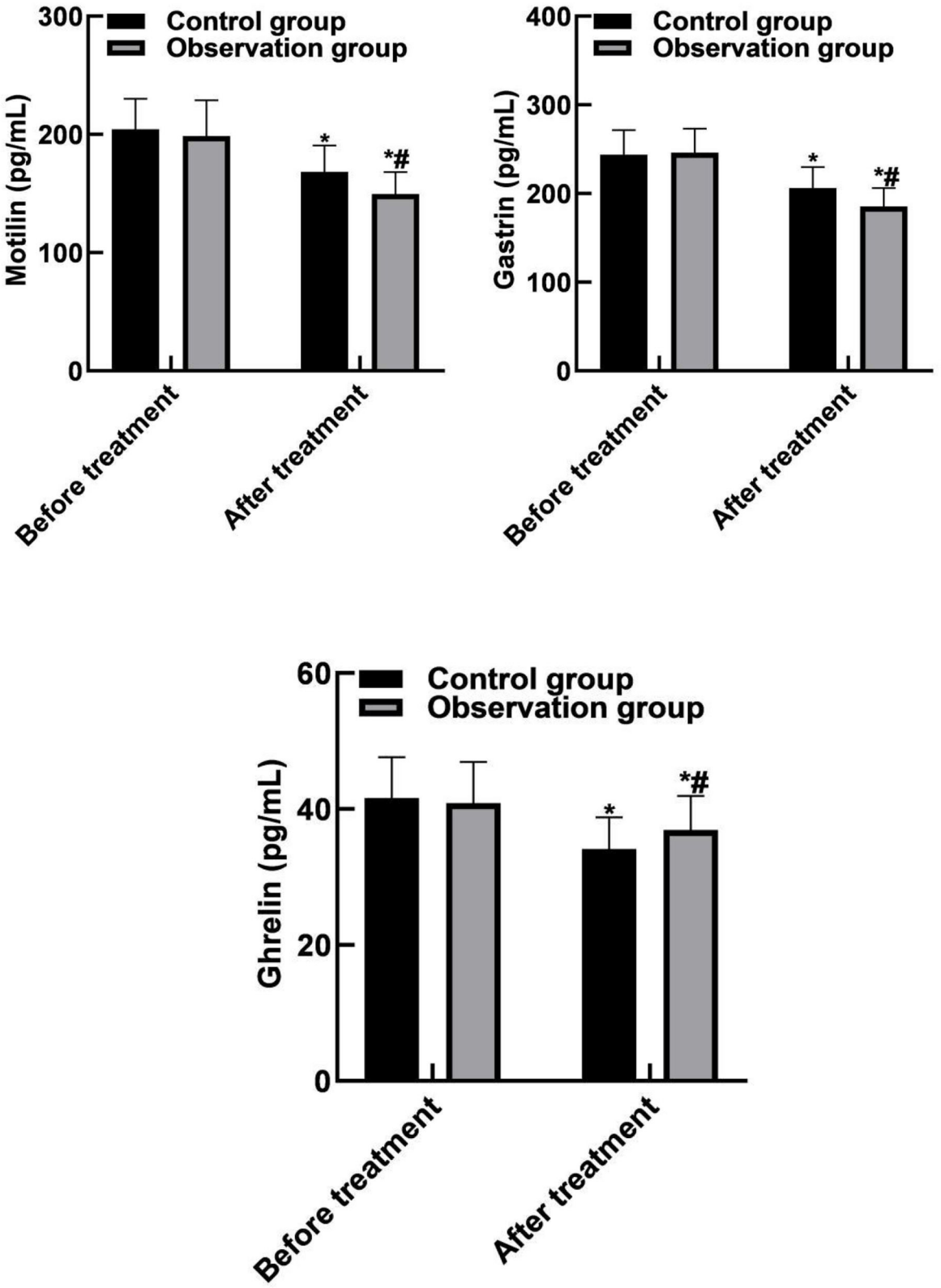

FIGURE 2 | Comparison of brain-gut peptide indicators between the two groups. Compared with before treatment, $^{*}P < 0.05$. Compared with the control group, $^{\#}P < 0.05$.

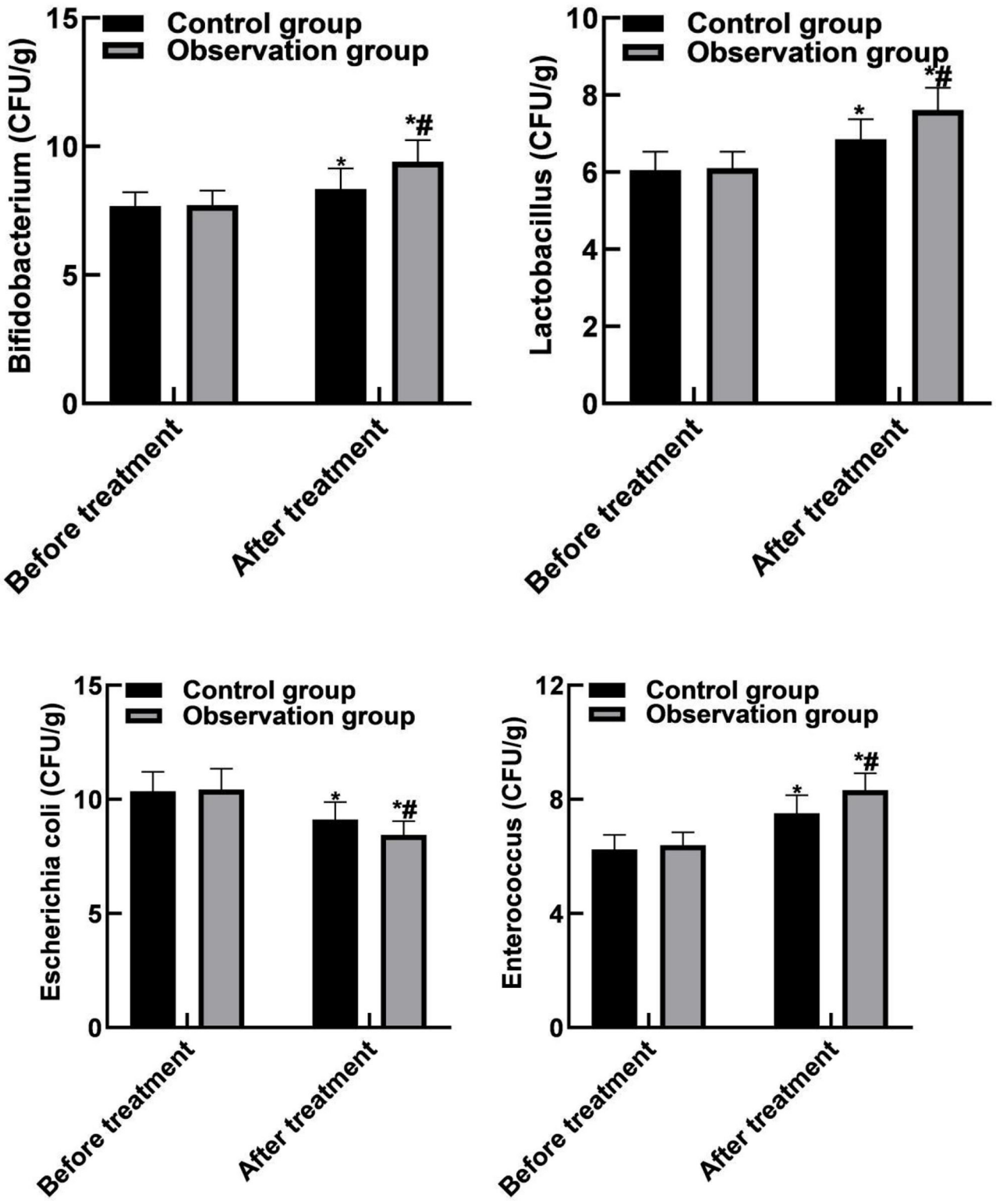

FIGURE 3 | Comparison of intestinal flora indicators between the two groups. Compared with before treatment, $^{*}P < 0.05$. Compared with the control group, $^{\#}P < 0.05$.

Comparison of Oxidative Stress Indicators Between the Two Groups

SOD and MDA levels in the control group were (81.05 ± 6.91) NU/mL and (4.35 ± 1.24) nmol/mL, respectively. The observation group were (76.83 ± 6.32) NU/mL and (5.56 ± 1.38) nmol/mL, respectively. SOD and MDA levels were significantly different between the two groups after treatment ($P < 0.05$). As shown in **Figure 4**.

Comparison of Adverse Reactions Between the Two Groups

The incidence of adverse reactions was 41.46% (17/41) in the control group and 34.15% (14/41) in the observation group. There was no significant difference in the total incidence of adverse reactions between the two groups ($P > 0.05$). As shown in **Figure 5**.

DISCUSSION

Colorectal cancer is a common malignant tumor in the gastrointestinal tract. It has a high incidence and mortality in the elderly, which are mostly related to the high-fat diet, large intestinal adenoma and related genetic factors (12, 13). The main clinical symptoms of CRC are hematochezia, increased stool frequency, internal urgency and then severity, which have seriously affected the life and health of patients as well as the quality of daily life (14, 15). Patients with early colorectal cancer have no specific symptoms, so they can be easily ignored to delay the optimal treatment timing. With the progression of the disease, symptoms such as abdominal pain, anemia, abdominal mass and hematochezia will gradually appear. Most patients have progressed to the intermediate and advanced stage when they are diagnosed, and the cancer cells metastasize to a distance, so their lives can only be prolonged by chemotherapy (16, 17). At present, the oxaliplatin-based combination regimen of XELOX and FOLFOX is mainly used for patients with advanced colorectal cancer who miss the opportunity of surgery. Compared with the latter, the XELOX regimen has less toxic and side effects and is widely used in clinical practice. Relevant clinical findings show that oxaliplatin chemotherapy has a significant clinical effect, which can remove more than 25% of cancer cells and surrounding lesions in patients (18, 19). However, oxaliplatin chemotherapy also has some shortcomings. Due to many adverse reactions after chemotherapy, especially liver function damage and fatigue, the follow-up recovery time of patients is prolonged, and thus the normal life of patients is affected (20, 21). Therefore, this result will increase the suffering of the patient and the recurrence rate after treatment, seriously affecting the patient's mood and aggravating the deterioration of the disease. Capecitabine, as a new fluorouracil drug, has the characteristics of selective and specific targeting. After drug administration, capecitabine is converted into an intermediate 5-deoxy−5-fluorocytidine in the liver, and catalyzes

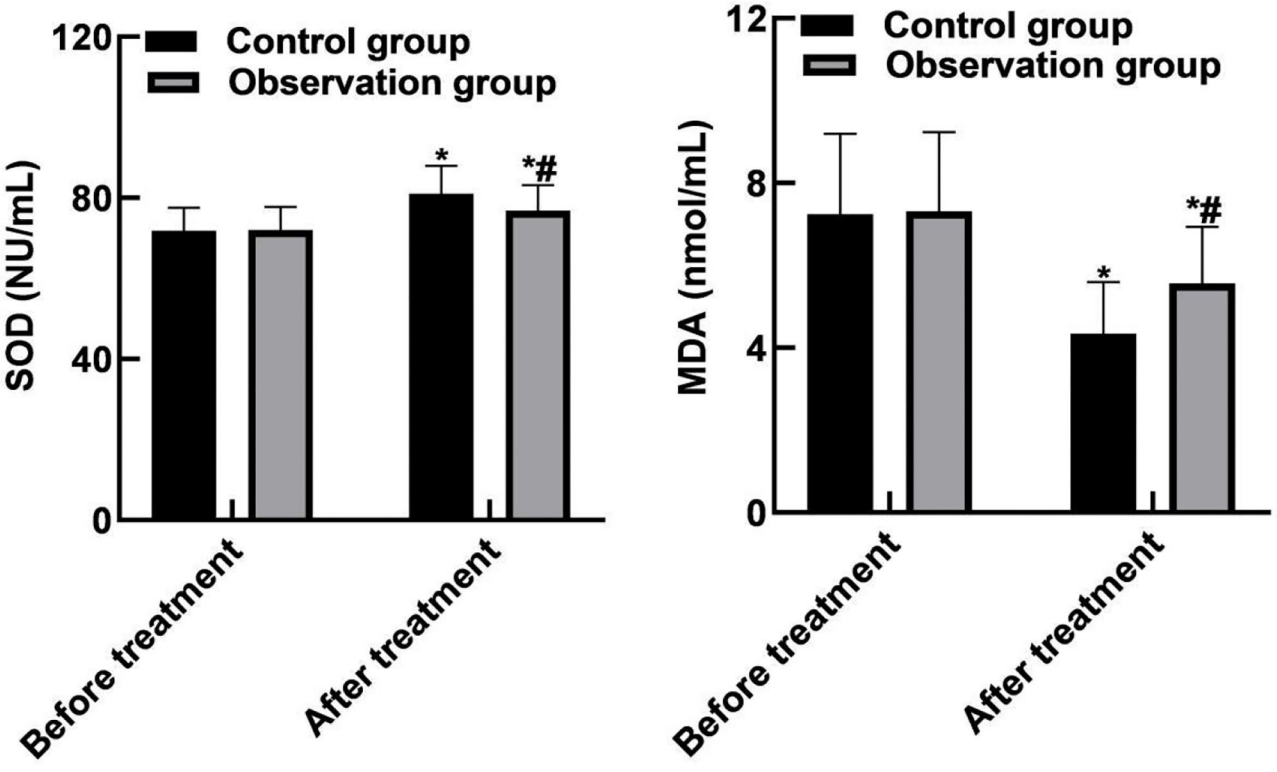

FIGURE 4 | Comparison of oxidative stress indicators between the two groups. Compared with before treatment, $^{*}P < 0.05$. Compared with the control group, $^{\#}P < 0.05$.

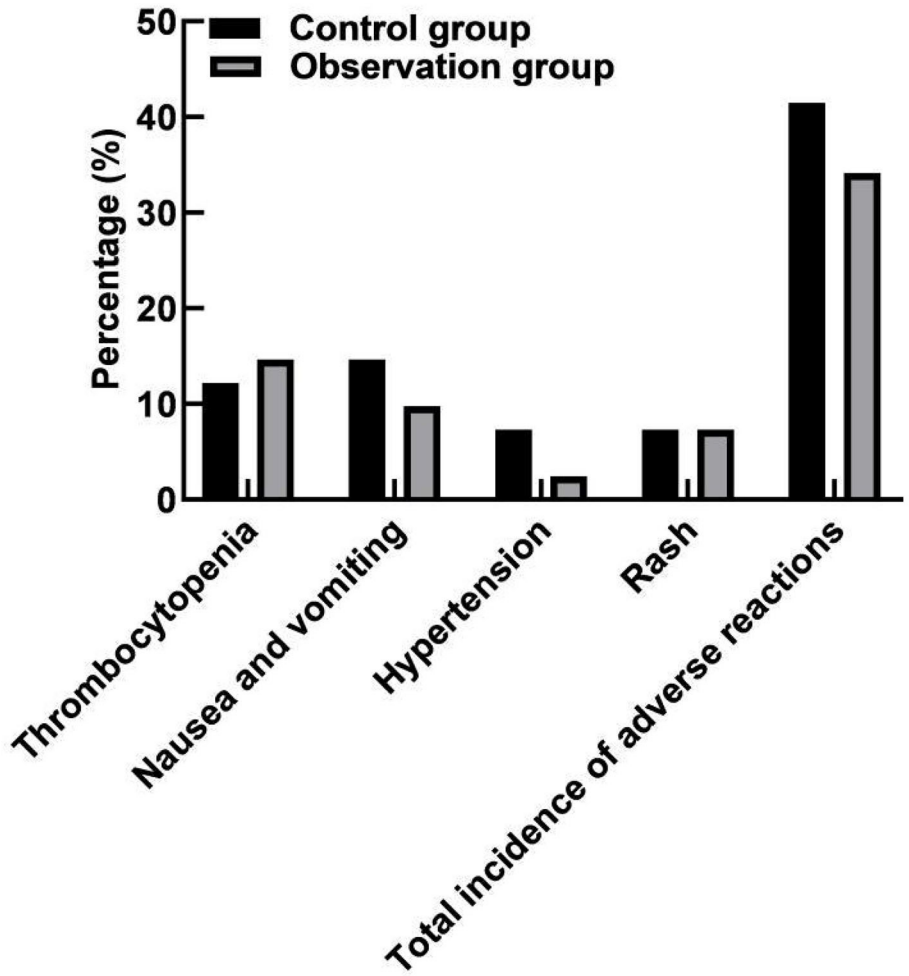

FIGURE 5 | Comparison of adverse reactions between the two groups.

the formation of fluorouracil in lesion tissues to directly act on cancer cells. The capecitabine has the characteristics of rapid absorption, strong pertinence and high safety. Bevacizumab, as a monoclonal antibody drug, can directly act on vascular endothelial growth factor to inhibit endothelial cell proliferation and angiogenesis, so as to achieve the purpose of inhibiting the growth of lesions.

Angiogenesis is one of the ten major features of tumors, and angiogenesis in tumors can provide the nutrients needed for tumor growth, so as to maintain the continuous proliferation of tumors. In the angiogenesis process, there are many angiogenic factors involved, among which VRGF belongs to endothelial cell-specific factor and is one of the most potent angiogenic factors (22, 23). VEGF mainly binds to VEGFR2 and activates the downstream signaling pathway, ultimately leading to the formation of new blood vessels. The main functions of VEGF: (1) Specifically enhance the mitosis of vascular endothelial cells, stimulate the proliferation of vascular endothelial cells and promote neovascularization; (2) Improve the permeability of micro blood vessels, and provide nutrients for the growth of tumor cells and the establishment of capillary network through the extravasation of nutrients such as plasma macromolecules. There is often a relatively high expression of VEGF in colorectal cancer patients, and relevant studies have also shown that high expression of VEGF in tumor tissue or blood often indicates a poor prognosis (24, 25). At present, the treatment targeting VEGF/VEGFR has become an important means of tumor treatment. The mechanism is mainly through competitive binding with endogenous VEGF, and inhibiting or reducing the binding of VEGF to vascular endothelial cell surface receptors, thereby inhibiting endothelial cell proliferation and angiogenesis, and finally playing a role in inhibiting tumor growth (26, 27).

The results of this study showed that the ER and DCR values in the observation group were higher than those in the control group, indicating that bevacizumab combined with chemotherapy could effectively improve the treatment effect. The reason is analyzed that bevacizumab can affect the proliferation of endothelial cells and inhibit the formation of tumor neovascularization. It is an antibody drug approved in the world for inhibiting the growth of blood vessels. Bevacizumab

takes vascular endothelial growth factor as a target, reduces neovascularization, promotes the degradation of the existing tumor blood vessels, blocks oxygen, blood and other nutrients for tumor growth, inhibits endothelial cell mitosis, leads the surviving tumor blood vessels to tend to be normal, limits the growth of tumors, and has obvious effects on the treatment of various metastatic cancers. Gastrointestinal movement is jointly regulated by a variety of mechanisms such as vegetative nervous system, myogenic electrical activity and body fluid. Brain-gut peptides are biologically active enzymes with hormone-like effects, and they participate in the motility regulation of digestive organs together with the nervous system. Motilin is mainly secreted by M cells of duodenum and jejunum, and its main effect is to induce transitional motor complex waves during digestion and accelerate the emptying of the gastrointestinal tract. Gastrin is secreted by G cells in gastric antrum and duodenum, which can stimulate the secretion of gastric acid and pepsin, and promote the gastrointestinal motility and the growth of gastric mucosa (28, 29). Ghrelin is mainly secreted by the stomach and has the effects of promoting growth hormone, stimulating appetite, increasing body weight, and regulating energy metabolism. The results of this study showed that after treatment, the levels of motilin and gastrin in the observation group were lower than those in the control group, and ghrelin was higher than that in the control group. It is suggested that bevacizumab combined with chemotherapy can improve gastrointestinal motility.

In human intestinal bacteria, obligate anaerobic bacteria such as bifidobacterium, lactobacillus, and bacteroides account for about 99% of that total intestinal bacteria, and facultative anaerobe such as Escherichia coli and Enterococcus account for about 1%, constituting a complex intestinal micro-ecological system. Bifidobacterium and Lactobacillus belong to beneficial bacteria, while Escherichia coli and Enterococcus belong to harmful bacteria. The coordination effect of intestinal beneficial bacteria can promote intestinal peristalsis and mucus flow, resist the adhesion of harmful bacteria to epithelial cells, and then form the intestinal mucosal barrier function, and regulate the intestinal mucosal immune system (30, 31). The results of this study showed that after treatment, the levels of Bifidobacterium, Lactobacilli and Enterococcus in the observation group were higher than those in the control group, and the level of Escherichia coli was lower than that in the control group. These results indicated that bevacizumab combined with chemotherapy could significantly improve the intestinal flora of patients and rebuild the intestinal microecological balance. Besides, the results of this study showed that after treatment, the SOD level of the observation group was lower than that of the control group, and the MDA level was higher than that of the control group. These results indicated that bevacizumab combined with chemotherapy can reduce the stress response of patients.

The toxic and side effects of chemotherapy drugs will lead to bone marrow suppression, gastrointestinal and skin abnormal reactions in patients, while bevacizumab can also lead to internal bleeding in target organs, gastrointestinal perforation and other adverse reactions. There was no statistical difference in the incidence of adverse reactions between the two groups in this study. In clinical treatment, attention should be paid to adverse reactions in patients, and preventive measures should be formulated in advance to improve the quality of life of patients.

CONCLUSION

Bevacizumab combined with chemotherapy has good efficacy in the treatment of CRC patients, which can improve the gastrointestinal motility of patients, regulate the intestinal flora of the body, rebuild the microecological balance, effectively reduce the oxidative stress response of patients, and reduce the incidence of adverse reactions.

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 Nankai University Affiliated Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors of the 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 article. All authors contributed to the article and approved the submitted version.

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Clinical Study on the Treatment of Female Stress Urinary Incontinence With Modified Buzhong Yiqi Decoction

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Purpose: To study the clinical application value of Modified Buzhong Yiqi Decoction in the treatment of female stress urinary incontinence (SUI).

Methods: A total of 103 female patients with SUI were included in this study, 13 were lost to follow-up, and the final number of studies was 90. General information about the patients, including age, years of menopause, body mass index (BMI), reproductive history, chronic respiratory disease, hypertension, and diabetes, were recorded. All the patients were treated with Modified Buzhong Yiqi Decoction alone for 4 weeks. The Patient Global Impression of Improvement (PGI-I), the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICI-QSF) and 72-h voiding diary were used to evaluate the patients' subjective symptoms and urinary incontinence degree before treatment, 1 month after treatment and 1 year after treatment, the efficacy and efficacy-related factors of Modified Buzhong Yiqi Decoction in the treatment of female SUI were analyzed.

Results: One month after Modified Buzhong Yiqi Decoction treatment, compared with before treatment, the PGI-I questionnaire was very much better (68.89%), much better (8.89%), a little better (12.33%), no change (8.89%), the ICI-QSF score decreased ($P < 0.05$), and 72-h urine leakage frequency decreased ($P < 0.05$); One year after treatment compared with before treatment, the PGI-I questionnaire was very much better (40.00%), much better (17.78%), a little better (12.22%), no change (30.00%), the ICI-QSF score decreased ($P < 0.05$), and 72-h urine leakage frequency decreased ($P < 0.05$); and 1 year after treatment compared with 1 month after treatment, the ratio of very much better at 1 year after treatment was significantly decreased ($P < 0.05$), the score of the ICI-QSF was significantly increased ($P < 0.05$), and 72-h urine leakage frequency was significantly increased ($P < 0.05$). The correlation analysis showed that the efficacy at 1 month after treatment was negatively correlated with the severity of SUI and chronic respiratory diseases, but was not significantly correlated with age, menopause status, BMI, number of pregnancies, and number of births. The efficacy at 1 year after treatment was negatively correlated with the severity of SUI, chronic respiratory disease, age, and number of births and was positively correlated with BMI, but not significantly correlated with menopause status and number of pregnancies.

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Conclusion: Modified Buzhong Yiqi Decoction can effectively treat SUI in women. The efficacy is related to the severity of SUI and chronic abdominal hypertension, but the long-term efficacy decreases.

Keywords: Modified Buzhong Yiqi Decoction, female, stress urinary incontinence, efficacy, correlation

INTRODUCTION

Stress urinary incontinence (SUI) is a disorder of voiding dysfunction due to anatomical defects in the supporting tissues of the urethra (1). Its clinical manifestations are involuntary urine flow when abdominal pressure increases such as coughing, sneezing, laughing, and exertion, but there is no enuresis in normal state, which affects the quality of life of more than 200 million people in the world (2). The disease is common in adult women and is the most common type of urinary incontinence. The prevalence of SUI in Chinese women has been reported to be as high as 18.9%, while the prevalence in older women over 60 years of age rises to about 30% (3). The incidence of SUI is showing a gradual increase with the advent of an aging population. The International Consultation on Incontinence (ICI) and the United Kingdom's National Institute for Health and Clinical Excellence (NICE) recommended nonsurgical treatment as the preferred treatment for SUI in women (3, 4).

At present, the study on the treatment of female SUI by traditional Chinese medicine (TCM) is limited to short-term clinical efficacy reports. So far, there is no clinical short-term and long-term efficacy observation and related drug pharmacological mechanism study. Chinese medicine believes that the operation of the spleen is mainly based on the rise and the rise is to maintain the normal position of the body's internal organs. "Su Wen Linglan Secret Canon" says: "The bladder is the official of the state capital, the body fluid is stored, and after the body fluid is vaporized by the yang of the lower coke, it can go out through the waterway." The Kidney Qi controls stool and urination. If the Kidney Qi is insufficient and the Kidney Yang is deficient, the transformation of the Qi of the bladder is not smooth and symptoms such as clear and long urination last drops and urinary incontinence will be seen. Therefore, the clinical differentiation of SUI is not simply based on spleen deficiency, but mainly based on spleen and kidney deficiency and the principle of treatment is to invigorate the middle and ascend the sag and invigorate the kidney and solidify the astringency. In this study, the modified formula was prepared on the basis of Buzhong Yiqi Decoction and the Patient Global Impression of Improvement (PGI-I), the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICI-QSF), and 72-h urination diary were used. The short-term therapeutic effect of 1 month after treatment of Modified Buzhong Yiqi Decoction and the long-term therapeutic effect of 1 year after treatment were observed, to evaluate the feasibility and influencing factors of clinical application of this prescription in the treatment of female SUI. The report is as follows.

MATERIALS AND METHODS

Study Object

This study was a prospective self-controlled study. A total of 103 female patients with SUI who were treated with Modified Buzhong Yiqi Decoction in the Pelvic Floor Disease Diagnosis and Treatment Center of the Obstetrics and Gynecology Hospital Affiliated to Zhejiang University School of Medicine from January 2012 to January 2015 were included.

Western Medicine Diagnostic Criteria

It met the diagnostic criteria of the International Urogynecological Association (IUGA) for SUI in women (5). It is mainly manifested in the involuntary flow of urine from the urethral opening when the patient has a sudden increase in abdominal pressure. Urodynamic studies revealed abnormal results on uroflow rate, bladder manometry during filling, and stress leaky point pressure.

Traditional Chinese Medicine Syndrome Differentiation

According to the theory of traditional Chinese medicine and related literatures, this study divided SUI into three syndrome types: Spleen-deficiency and Qi-trapping type, Kidney-Qi deficiency type, and Spleen-Kidney Yang deficiency type.

Stress Urinary Incontinence Severity Rating

All the patients were graded according to the Ingelman–Sundberg scale (6): Mild: Urinary incontinence occurred when coughing and sneezing, no needed to use a urine pad. Moderate: Urinary incontinence occurred during daily activities such as running, jumping, and brisk walking and required the use of urine pads. Severe: Urinary incontinence occurs with light activity and changes in the supine position.

Inclusion Criteria

It meets the diagnostic criteria for SUI. Be 18 years of age or older. Patients voluntarily accepted the treatment with Modified Buzhong Yiqi Decoction and subsequent clinical observation and signed the informed consent form. The patient was never referred for this. Urinary incontinence medication should be discontinued for more than 3 months.

Exclusion Criteria

It includes residual urine $>$ 30 ml and maximum urinary flow rate $<$ 20 ml/s. Other types of urinary incontinence, such as neurogenic bladder, psychogenic incontinence, and impulsive incontinence, are also present. Urethral sphincter

atresia insufficiency, ectopic ureter, etc., requiring surgical treatment. Patients with urinary stones, infections, lower urinary tract obstruction, and renal disease. Patients with history of surgical treatment for urinary incontinence or history of pelvic floor surgery. Genital prolapse $\geq 2^{\circ}$. Combined with serious medical diseases such as cardiovascular and cerebrovascular, hematopoietic system, liver, and kidney. Reluctance to accept clinical observers. Those who did not adhere to the medication as prescribed and could not judge the curative effect. Those who could not meet the follow-up conditions.

Medication Method

All the patients were treated with Modified Buzhong Yiqi Decoction orally. The main ingredients of Modified Buzhong Yiqi Decoction: 15 g of *Astragalus*, 15 g of fried *Atractylodes*, 6 g of tangerine peel, 6 g of *Cimicifuga*, 9 g of Bupleurum, 15 g of ginseng, 3 g of Licorice, 12 g of *Angelica*, 15 g of Alpiniae Oxyphyllae Fructus, 9 g of *Mantidis ootheca*, 15 g of Cortex Eucommiae, 6 g of *Lindera aggregata*, and 15 g of *Rosa laevigata* Michx. There were slight additions and subtractions through dialectics. Oral, 1 dose per day, warmly divided into two decoctions, each decoction was about 200 ml. Decoction in the morning and evening, 4 weeks as a course of treatment. The medicines were provided by the Chinese Medicine Pharmacy of the Obstetrics and Gynecology Hospital Affiliated to Zhejiang University School of Medicine, China, and each patient was treated for one course of treatment.

Data Collection

In this study, a special person was responsible for recording the general conditions of the patients, including age, menopause, year of menopause, body mass index, reproductive history, whether there was a history of chronic increased abdominal pressure such as chronic respiratory disease, whether there was a history of common medical diseases in the elderly such as hypertension and diabetes mellitus; and follow-up was performed during and after taking the medicine for up to 1 year. Before treatment, 1 month after treatment and 1 year after treatment, the PGI-I was used to evaluate the patients' subjective symptoms and the ICI-QSF and 72-h urination diary were used to evaluate the degree of urinary incontinence. The ICI-QSF questionnaire included a total of 7 questions and each question had a score of 0 to 3. The higher the score, the greater the impact of urinary incontinence on the quality of life. The urination diary was used to continuously record urination for 72 h, including each urination time, urine volume, water drinking time, water consumption, accompanying symptoms, and urinary incontinence time, etc. In this study, a total of 103 female patients with SUI were treated with Modified Buzhong Yiqi Decoction, 13 patients with SUI were lost to follow-up, and 90 patients with SUI were finally studied.

Data Analysis

Measurement data were described by mean ± SD, including age, height, weight, BMI, frequency of urinary leakage, and the ICI-QSF. The enumeration data were described by percentage, including age composition ratio, menopause or not and its years, reproductive history, chronic respiratory diseases, hypertension, and diabetes. Data analysis was performed using the statistical software SPSS version 11.0 (SPSS, Chicago, Illinois, USA). The ICI-QSF questionnaire score results and the number of urine leakage before and after treatment were analyzed by the *t*-test and the correlation between the treatment effect and various clinical characteristics was analyzed by bivariate correlation. A two-sided test with $P < 0.05$ was considered as statistically significant.

RESULTS

Basic Information of Patients With Stress Urinary Incontinence

All the 103 patients with SUI completed 28-day treatment as required, of which 13 patients with SUI were lost to follow-up within 1 year after treatment, with a loss-to-follow-up rate of 12.62%. Lost telephone contact was the reason for the loss to follow-up. Data were analyzed using per-protocol (PP) analysis and those who were lost to follow-up were not included in the analysis. Among 90 patients who were followed-up to 1 year after treatment, age 50.04 ± 13.58 (years old), height 1.60 ± 0.05 (m), weight 60.25 ± 11.83 (kg), and BMI 23.46 ± 4.52 (kg/m^2) were also included. The basic information of 90 patients with SUI was shown in **Table 1**.

TABLE 1 | Basic information of patients with stress urinary incontinence (SUI) (n = 90).

Items	Distributed	Number of people (ratio of the total)
Age	<40 years old	19 (21.11%)
	40–50 years old	30 (33.33%)
	51–60 years old	22 (24.45%)
	>60 years old	19 (21.11%)
Menopause	1–5 years	17 (18.89%)
	6–10 years	7 (7.78%)
	>10 years	16 (17.78%)
Number of pregnancies	1 time	14 (15.56%)
	2 time	32 (35.56%)
	3 time	18 (20.00%)
	>3 time	26 (28.90%)
Number of births	1 time	49 (54.45%)
	2 time	30 (33.33%)
	3 time	7 (7.78%)
	>3 time	4 (4.44%)
Vaginal delivery		85 (94.44%)
Cesarean section		5 (5.56%)
Chronic abdominal hypertension disease	Chronic respiratory diseases	14 (15.56%)
Medical comorbidities	Hypertension	13 (14.44%)
	Diabetes	3 (3.33%)

TABLE 2 | The Patient Global Impression of Improvement (PGI-I) at 1 month and 1 year after treatment with Modified Buzhong Yiqi Decoction ($n = 90$).

Choose a number that best described the condition of the patient's urethra after treatment compared to before the patient started treatment.			
Sequence	**Description**	**1 month after treatment**	**1 year after treatment**
1	Very much better	62 (68.89)	36 (40.00)
2	Much better	8 (8.89)	16 (17.78)
3	A little better	12 (12.33)	11 (12.22)
4	No change	8 (8.89)	27 (30.00)
5	A little worse	0 (0.00)	0 (0.00)
6	Much worse	0 (0.00)	0 (0.00)
7	Very much worse	0 (0.00)	0 (0.00)

Comparison of the Patient Global Impression of Improvement at 1 Month and 1 Year After Treatment With Modified Buzhong Yiqi Decoction

According to the PGI-I questionnaire, **Table 2** and **Figure 1** show that, compared with before treatment, the subjective symptoms of urinary incontinence were significantly improved after the treatment of Modified Buzhong Yiqi Decoction for 1 month and 1 year ($P < 0.05$); Compared to 1 month after treatment, there was a tendency for subjective symptoms of urinary incontinence to return 1 year after treatment: The self-reported no change and very much better 1 month after treatment were 8.89 and 68.89%, respectively, and the self-reported no change and very much better 1 year after treatment were 30.00 and 40.00%, respectively, and there was a statistical difference between the two ($P < 0.05$).

Comparison of the International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form Score and 72-H Urine Leakage Frequency at 1 Month and 1 Year After Treatment With Modified Buzhong Yiqi Decoction

Table 3 and **Figure 2** show that the ICI-QSF score before treatment with Modified Buzhong Yiqi Decoction was 12.08 ± 5.10, the ICI-QSF score at 1 month after treatment was 2.82 ± 4.53, and the ICI-QSF score at 1 year after treatment was 4.90 ± 6.21. The latter two were significantly lower than those before treatment ($P < 0.05$), but the ICI-QSF score at 1 year after treatment was significantly higher than that at 1 month after treatment ($P < 0.05$). **Table 3** and **Figure 3** show that 72-h urine leakage frequency before treatment with Modified Buzhong Yiqi Decoction was 6.72 ± 6.61, 72-h urine leakage frequency at 1 month after treatment was 1.32 ± 3.72, and 72-h urine leakage frequency in 1 year after treatment was 3.00 ± 6.16, the latter two were also significantly lower than those before treatment ($P < 0.05$), and 72-h urine leakage frequency at 1 year after treatment was significantly higher than that at 1 month after treatment ($P < 0.05$).

Analysis of the Related Factors of Curative Effect of Modified Buzhong Yiqi Decoction in the Treatment of Female Stress Urinary Incontinence

Using the PGI-I to evaluate the treatment effect, after statistical analysis of correlation, **Table 4** shows that, 1 month after treatment, the curative effect was negatively correlated with SUI severity and chronic respiratory disease ($P < 0.05$), but had no significant correlation with age, menopause situation, BMI, number of pregnancies, and number of births ($P > 0.05$). 1 year after treatment, the curative effect was negatively correlated with SUI severity, chronic respiratory disease, age, and number of births ($P < 0.05$) and was positively correlated with BMI ($P < 0.05$), but had no significant correlation with menopause situation and number of pregnancies ($P > 0.05$).

Safety of Modified Buzhong Yiqi Decoction in the Treatment of Female Stress Urinary Incontinence

There were no adverse reactions during and 1 year after taking the drug, including 19 elderly patients > 60 years old and 16 patients with hypertension or diabetes and no aggravation of primary underlying diseases such as hypertension and diabetes was found.

DISCUSSION

Urinary incontinence can lead to inconvenience in movement, inability to perform housework, affect normal social and sexual life, etc., resulting in the isolation of patients from society and family and a series of depression or psychological disorders (7). According to a community survey of women over the age of 40 years in the United Kingdom, the prevalence of urinary incontinence in the region was 34%, but only 25% of patients visited a doctor. A survey in Germany showed that 43% of patients concealed a history of urinary incontinence and even 25% of patients had a history of more than 5 years. Thus, urinary incontinence is not only a health problem, but also a social problem. SUI is the most common type of urinary incontinence, accounting for about 50% of urinary incontinence and its economic burden on families and society cannot be ignored (8, 9). At present, the treatment methods of SUI mainly include drug therapy, surgery, physical therapy, and so on. Among them, surgical treatment has many adverse reactions and although drugs and physical therapy have few adverse reactions, the cure rate is still unsatisfactory (10).There is still a need to find better ways to treat SUI.

The understanding of urinary incontinence in Chinese medicine has a long history; water and fluid are controlled in the spleen; if the Spleen Qi does not rise, urinary incontinence is seen; however, its origin is in the kidney. If the Kidney Qi is insufficient and the Kidney Yang is deficient, urinary incontinence can also be seen. Therefore, to identify its etiology and pathogenesis, it must

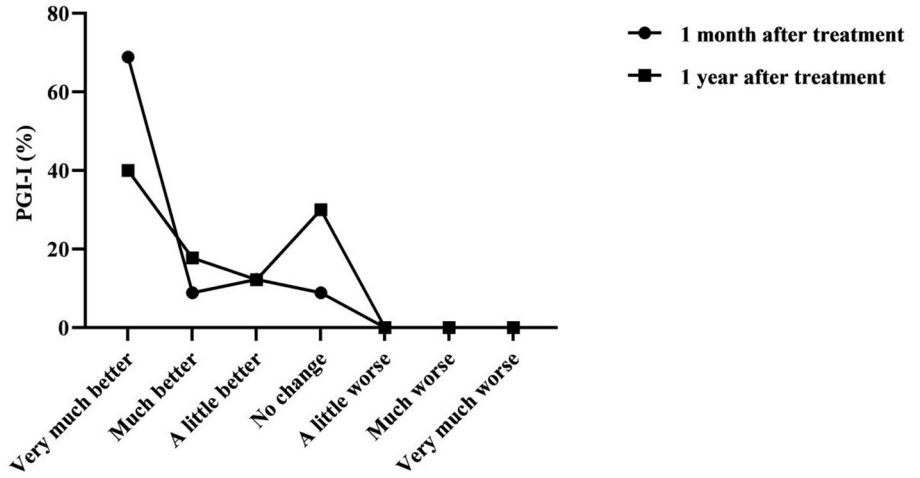

FIGURE 1 | The Patient Global Impression of Improvement (PGI-I) at 1 month and 1 year after treatment with Modified Buzhong Yiqi Decoction ($n = 90$).

TABLE 3 | The International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICI-QSF) score and 72-h urine leakage frequency at 1 month and 1 year after treatment with Modified Buzhong Yiqi Decoction ($n = 90$).

	Before treatment	1 month after treatment	1 year after treatment
ICI-QSF (scores)	12.08 ± 5.10	2.82 ± 4.53*	4.90 ± 6.21*#
Frequency of urine leakage (times)	6.72 ± 6.61	1.32 ± 3.72*	3.00 ± 6.16*#

**was a significant difference compared with before treatment, $P < 0.05$; # was a significant difference compared with 1 month after treatment, $P < 0.05$.*

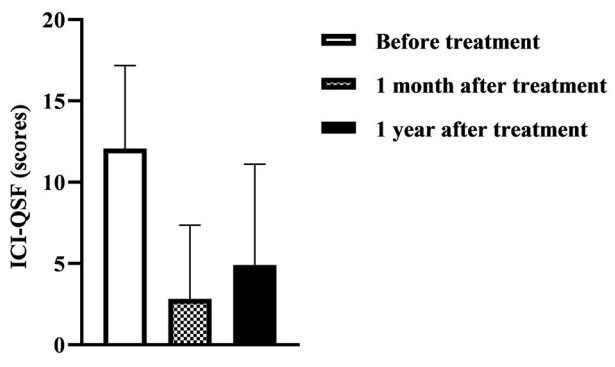

FIGURE 2 | The International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICI-QSF) score at 1 month and 1 year after treatment with Modified Buzhong Yiqi Decoction ($n = 90$).

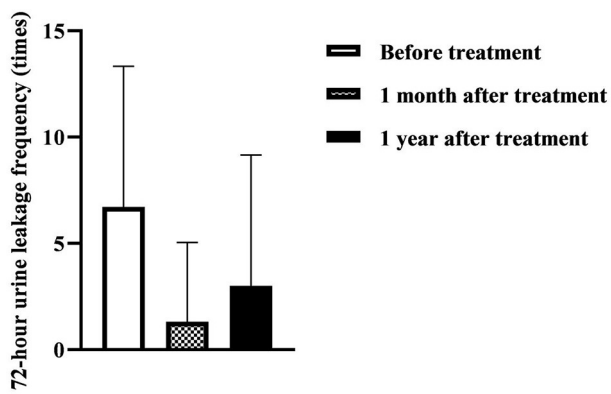

FIGURE 3 | 72-h urine leakage frequency at 1 month and 1 year after treatment with Modified Buzhong Yiqi Decoction ($n = 90$).

be that the Spleen Qi does not rise, the Qi transformation has no power, the Kidney Qi is insufficient, the bladder is out of restraint, and the opening and closing are abnormal. Urinary incontinence mostly occurs in elderly patients. Traditional Chinese medicine believes that when a person reaches the age of 49 years, the Ren pulse is deficient, the Taichong pulse is less weak, and the Kidney Qi is weak. Simple application of Buzhong Yiqi Decoction cannot improve the symptoms of urinary incontinence caused by kidney deficiency. Therefore, in this study, on the basis of Buzhong Yiqi Decoction, the medicine for nourishing Kidney Qi is added, the treatment is to nourish the middle and ascend the sag, invigorate the kidney, solidify astringency, and after a 1-year follow-up study, in order to evaluate the clinical application value of Modified Buzhong Yiqi Decoction in the treatment of female SUI.

Compared with before treatment, 1 month after treatment with Modified Buzhong Yiqi Decoction, the subjective symptoms of the patients were significantly different ($P < 0.05$), the ICI-QSF score was decreased ($P < 0.05$), and 72-h urine leakage frequency was decreased ($P < 0.05$). It is indicated that by invigorating the middle and ascending the sag and invigorating the kidney and solidifying the astringency, the Modified Buzhong Yiqi decoction can effectively improve the symptoms of female SUI. One year after treatment, compared with before treatment,

TABLE 4 | Analysis of related factors of curative effect of Modified Buzhong Yiqi Decoction after 1 month and 1 year of treatment.

Factor	1 month after treatment		1 year after treatment	
	Spearman correlation coefficient	*P* value	Spearman correlation coefficient	*P* value
Age	−0.136	0.314	−0.446	<0.001
Menopause	0.197	0.141	0.222	0.1
Year of menopause	−0.157	0.243	−0.188	0.165
BMI	−0.007	0.96	0.568	<0.001
Number of pregnancies	−0.006	0.962	−0.086	0.530
Number of births	−0.02	0.884	−0.215	0.023
SUI severity	−0.51	<0.001	−0.478	<0.001
Chronic respiratory diseases	−0.392	0.003	−0.38	0.004

there were still significant differences in patients; subjective symptoms ($P < 0.05$), the ICI-QSF score still decreased ($P < 0.05$), and 72-h urine leakage frequency still decreased ($P < 0.05$). It shows that Modified Buzhong Yiqi Decoction is still effective for female SUI 1 year after treatment compared with before treatment. However, 1 year after treatment compared with 1 month after treatment, the rate of very much better at 1 year after treatment was significantly lower ($P < 0.05$), the ICI-QSF score was significantly higher ($P < 0.05$), and 72-h urine leakage frequency was significantly increased ($P < 0.05$). It shows that the improvement of SUI symptoms and quality of life with Modified Buzhong Yiqi Decoction cannot be permanent and the efficacy decreases with time. In addition, we found that the short-term (1 month) and long-term (1 year) efficacy of Modified Buzhong Yiqi Decoction for severe SUI were relatively poor. Based on this, we speculate that Modified Buzhong Yiqi Decoction is suitable for mild-to-moderate female SUI and patients with recurrent disease need to increase the course of treatment to consolidate the curative effect. Among the cases, 2 patients had SUI symptoms after repregnancy and the statistics were judged as no change, but they were still cured after using Modified Buzhong Yiqi Decoction again.

In the formula of Modified Buzhong Yiqi Decoction, *Astragalus* enters the spleen and lung meridians, can invigorate the middle and benefit qi, raise yang and ascend sag, and can solidify the surface and stop sweating, so it is reused as the king (11). Ginseng is great for nourishing vitality, fried *Atractylodes* nourishes Qi and spleen, Licorice nourishes the middle and invigorating Qi, and helps *Astragalus* to nourish Qi and strengthen the spleen, all of which are ministerial medicines (12, 13) and the patient's qi deficiency for a long time often damages the blood. Therefore, it is compatible with *Angelica* to nourish blood and nutrition; tangerine peel can adjust Qi and regulate Qi and stomach, so that various medicines can be replenished without stagnation; *Cimicifuga* and *Bupleurum* can help to raise yang and ascend sag, which can help the monarch medicine to ascend the Qi in depression; Alpiniae Oxyphyllae Fructus, *Mantidis ootheca*, and *Lindera aggregata* warm the spleen and kidney; Cortex Eucommiae nourishes the liver and kidney; *Rosa laevigata* Michx shrinks urine and solidifies sperm. The above flavors are used as adjuvants and are basically suitable for various syndromes of SUI (14–16). Licorice reconciles various medicines and is also used as messenger medicine. This formula combines tonification with Qi circulation, tonifying but not accumulating stagnation, and tonification with elevation, raising yang and lifting traps, which is especially suitable for Spleen and Stomach Qi deficiency and lower detachment (17).

This study found that chronic respiratory diseases were negatively correlated with the efficacy of Modified Buzhong Yiqi Decoction at 1 month and 1 year after treatment. It shows that if the patient is complicated with chronic respiratory system diseases, the short-term and long-term efficacy will be poor, suggesting that active treatment of chronic abdominal pressure diseases such as chronic abdominal hypertension disease should be carried out while traditional Chinese medicine is used to treat female SUI. This study also found that with the increase of age and the number of births, the long-term efficacy of Modified Buzhong Yiqi Decoction in the treatment of SUI was worse. It is well known that urethral support tissue damage and degeneration caused by pregnancy and childbirth and menopause and aging are important causes of SUI in women. Prolificity can cause repetitive, stale damage to the supporting tissues of the urethra. Aging can cause irreversible degenerative changes in the supporting tissues of the urethra. Therefore, the efficacy of drug intervention in such patients is relatively reduced. However, we did not find a correlation between menopause and the efficacy of Modified Buzhong Yiqi Decoction in the treatment of SUI, which may be related to the fact that the average age of the population included in this study was 50 years old and it was mainly perimenopausal and postmenopausal women. In addition, we found that BMI was positively correlated with the efficacy of Modified Buzhong Yiqi Decoction in the treatment of SUI. BMI is a high risk factor for SUI and people with high BMI are prone to spleen deficiency (18–20). From this, we speculate that Modified Buzhong Yiqi Decoction has the effect of invigorating the spleen and the spleen is healthy and normal, the water transport and transformation will be normal, so it is suitable for patients with SUI with obesity.

Stress urinary incontinence is more common in middle-aged and elderly women and elderly patients often have medical diseases such as hypertension and diabetes and their drug tolerance decreases (21). For example, Western medicine α1-adrenoceptor agonists tend to constrict vascular smooth muscle and affect hypertensive patients (22). Tricyclic antidepressants have uncertain efficacy and many side effects, including nausea and vomiting (40% or more of patients), dry mouth, constipation, dizziness, insomnia, somnolence, and fatigue (23). Therefore, there is no recognized effective and safe anti-SUI western medicine. In this study, there were 19 elderly patients over 60 years old and 16 patients with hypertension or diabetes. There were no adverse reactions during the medication and during the follow-up and no exacerbation of hypertension and/or diabetes

was found. It shows that the safety of Modified Buzhong Yiqi Decoction is good and it is suitable for clinical promotion.

CONCLUSION

Modified Buzhong Yiqi Decoction can effectively treat SUI in women. The efficacy is related to the severity of SUI and chronic abdominal hypertension, but the long-term efficacy decreases.

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 Review Committee of the Obstetrics and Gynecology Hospital Affiliated to Zhejiang University School of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC and JS are the mainly responsible for the writing of the article. QZ is mainly responsible for research design. FZ is mainly responsible for data analysis. LJ and XM are responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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Alleviation of Myocardial Inflammation in Diabetic Rats by Flavonoid Extract of Helichrysum Arenarium and Its Effect on Damaged Myocardial Cells Induced by High Glucose

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Objective: To investigate the effects of helichrysum arenarium flavonoid extract on high glucose damaged cardiomyocytes and the alleviation of myocardial inflammation in diabetic rats.

Methods: The study was divided into two parts, the first part was a cellular experiment in which a high-glucose cardiomyocyte injury model (H9C2) was established using a high-glucose culture medium, divided into low (group N1, 6.25 μg/mL), medium (group N2, 12.5 μg/mL), high dose group (group N3, 25 μg/mL) of helichrysum arenarium intervention and a model control group. The levels of enzyme activities [creatine kinase (CK) and lactate dehydrogenase (LDH)] in each group of H9c2 cells were measured by Enzyme-linked immunosorbent assay (ELISA), the expression levels of apoptotic proteins (Bax and Bcl-2) by western blot (WB), and the expression levels of inflammatory factors [tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6)] by RT-qPCR. The second part is animal experiments, after establishing the diabetic rat model, we used helichrysum arenarium flavonoid extract to intervene SD rats, divided into helichrysum arenarium intervention low (group S1, 250 mg/kg), medium (group S2, 500 mg/kg), high dose group (group S3, 1 g/kg), SD rat model group. Hematoxylin-eosin (HE) staining was used to observe myocardial tissue lesions, and Real Time Quantitative PCR (RT-qPCR) method was used to detect inflammatory (TNF-α, IL-1β, and IL-6) infiltration in myocardial tissue.

Results: Cellular experiments: The activity levels of enzymes such as CK and LDH and the levels of inflammatory factors such as TNF-α, IL-1β, and IL-6 in damaged cardiac myocytes were significantly decreased after helichrysum arenarium intervention; the expression levels of Bax protein were significantly down-regulated and the expression levels of Bcl-2 protein expression were significantly up-regulated. Animal experiment: HE staining showed that the model group had widened intercellular spaces, interstitial edema and obvious inflammatory cell infiltration in cardiac muscle tissue. After the intervention of helichrysum arenarium, the collagen fibers of rat myocardial cells were significantly

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reduced and cell degeneration was alleviated. Animal experiment: HE staining showed that the model group had widened intercellular spaces, interstitial edema and obvious inflammatory cell infiltration in cardiac muscle tissue. After the intervention of helichrysum arenarium, the collagen fibers of rat myocardial cells were significantly reduced and cell degeneration was alleviated; the levels of TNF-α, IL-1β, IL-6 and other inflammatory factors in myocardial tissues were significantly decreased.

Conclusion: The helichrysum arenarium flavonoid extract can reduce the degree of damage of H9C2 cells induced by high glucose and decrease the cellular inflammatory response, and its mechanism of action may be achieved by regulating the apoptotic factors Bax and Bcl-2. In addition, the extract of helichrysum arenarium can reduce the histopathological damage of myocardium in diabetic rats, decrease the inflammatory response in the tissue, and achieve the effect of myocardial protection.

Keywords: myocardial inflammation, diabetic, flavonoid extract of helichrysum arenarium, myocardial cells, high-glucose

INTRODUCTION

With the change of people's lifestyle and diet structure, the progress of population aging and the increase of obesity rate, the global incidence of diabetes mellitus (DM) is surging at an alarming rate, and the prevention and treatment of DM has become a worldwide problem (1, 2). DM and its complications pose a serious threat to human health, especially cardiovascular complications, and an epidemiological follow-up survey (3) of DM patients found that the number of deaths due to cardiovascular diseases in the DM population was much higher than in the non-DM population. This phenomenon may be due to the fact that diabetes increases the incidence of cardiovascular disease by promoting cardiovascular atherosclerosis, and that the "glucotoxicity" and "lipotoxicity" of diabetes affects the function and normal physiological state of cardiomyocytes, eventually leading to heart failure and death (4, 5).

Diabetic cardiomyopathy (DCM) is a widespread focal myocardial necrosis caused by myocardial metabolic disorders and cardiac microangiopathy due to diabetes mellitus, and its pathological changes are mainly characterized by cardiomyocyte hypertrophy, myocardial fibrosis and myocardial collagen formation (6, 7). The specific mechanism of how DCM occurs is not clear, and many domestic and foreign scholars (8–10) believe that it may be due to the involvement of increased oxidative stress, abnormal myocardial energy metabolism, and activation of inflammatory pathways, causing apoptosis, necrosis, fibrosis, and other changes in myocardial cells, which ultimately lead to structural and functional changes in the myocardium.

At present, the treatment methods of DCM include traditional Chinese medicine treatment and western medicine treatment. Traditional western medicine treatment for DCM mainly uses hypoglycemic agents, insulin and insulin-producing agents, and β-blockers, all of which have unavoidable adverse effects and are prone to drug dependence (11, 12). Single herbs such as Milkvetch Root and Dan-Shen Root and herbal compounds such as Shengmai Powder and Decoction GuiQi, which are commonly used in Chinese medicine treatment, also have limitations due to the uncertainty of dosing and onset of action (13). While some herbs and their extracts have been reported as potential therapeutic agents for DCM in recent years, they have not yet entered the market in the form of highly effective drugs and need to be further studied in depth.

Helichrysum arenarium is a folkloric medicinal herb of Xinjiang with complex chemical composition, mainly divided into flavonoids, total saponins and phenolic acids. Reports by MORIKAWA (14), Kramberger (15) showed that helichrysum arenarium extract has hypoglycemic effect and in addition MORIKAWA found that its extract inhibited dipeptidyl peptidase-activity. In order to investigate more deeply the hypoglycemic effect of helichrysum arenarium extract, this study combined with the pharmacology of helichrysum arenarium network to improve DCM as an entry point, and to investigate the protective effect of helichrysum arenarium on high glucose-induced damaged cardiomyocytes and the alleviation of myocardial inflammation in diabetic rats.

MATERIALS AND METHODS

Materials

Main Drugs, Reagents and Instruments

Helichrysum Arenarium was collected in April 2020 in the Altai region of Xinjiang, Streptozotocin (STZ) dry powder, RIPA lysis buffer, Paraformaldehyde solution (Sigma, USA); carbon dioxide thermostat culture (Thermo, USA); 96-well cell culture plate, DMEM/F-12 culture solution (GIBCO, USA); fetal bovine serum (Hyclone); fluorescent quantitative PCR Mix, reverse transcription kit, trizol reagents (Invitrogen, USA); pathology microtome (Leica, Germany), enzyme-labeled instrument (Bio-Tek, Germany); and fetal bovine serum (Hyclone). Rabbit Anti-Mouse TNF-α Antibody, Rabbit Anti-Mouse IL-1β Antibody, Rabbit Anti-Mouse IL-6 Antibody, Rabbit Anti-Mouse GAPDH Antibody (Bio-Tek, Beijing, China); Bax antibody, Bcl-2 antibody (Bio-Tek, Wuhan, China); CK ELISA kit, LDH ELISA kit (Yanjin Biological Company, Shanghai, China); Bicinchonic

acid disodium salt (BCA) protein quantification kit (Bolf, Wuhan, China); blood glucose meter (Yi Cheng, Beijing, China).

Cell Grouping and Manipulation

Using trypsin digestion method, log phase H9c2 cells (purchased from the cell bank of Chinese Academy of Sciences) were made into cell suspensions, and each well was inoculated into 96-well plates at 5×10^4, and 6 replicate wells were set up for each group, and incubated in a cell incubator (37°C, 5% CO_2), and the cells were handled appropriately according to the grouping scheme after being attached to the wall. According to the purpose of the experiment, the cells were divided into four groups: model control group (HG group, high glucose stimulation at a concentration of 33.3 mmol/L for 48 h), low dose group (N1 group, high sugar concentration and treatment as model control, with 6.25 μg/mL of helichrysum arenarium extract added after handling), medium dose group (N2 group, high sugar concentration and treatment as model control, with 12.5 μg/mL of helichrysum arenarium extract added after handling), and high dose group (N3 group, high sugar concentration and treatment as model control, with 25 μg/mL of extracts of helichrysum arenarium was added after handling).

Animal Grouping and Handling

Healthy male SD rats weighing 180∼200 g were selected and randomly divided into four groups, including low (S1 group, 250 mg/kg), medium (S2 group, 500 mg/kg), and high dose groups (S3 group, 1 g/kg) of helichrysum arenarium intervention and 4 groups of SD rat model (DCM group) after adaptive feeding for 1 week, 10 animals in each group. The DM model was constructed by intraperitoneal injection of STZ (30 mg/kg) in rats, and the DM modeling was considered successful for rats with blood glucose values higher than 16.7 mmol/L for 3 consecutive days. From day 4, rats in S1, S2, and S3 groups were given the corresponding concentrations of helichrysum arenarium extract by gavage for 8 weeks, while rats in DCM group were given the same volume of saline by gavage, and the drug doses were determined according to the pre-test and previous literature (16, 17). Body weight, blood glucose, blood lipids and fasting insulin were measured after 10 weeks of successful model establishment.

Methods

Enzyme-Linked Immunosorbent Assay

The content of CK and LDH was determined according to the instructions of Shanghai Research and Technology Co. The steps were as follows: standard addition—sample addition—liquid preparation—washing—enzyme addition—incubation—washing—color development—termination of the reaction—determination of absorbance. The assay should be carried out within 15 min of the addition of the termination solution.

Protein Blotting (WB)

The cells were lysed using RIPA and quantified by disodium bis(quinolinic acid) (BCA) protein quantification kit at a uniform concentration of 100 μg. 20 μg was applied to each well, electrophoresis was performed, the membrane was transferred, 5% skimmed milk powder was closed at room temperature for 1.5 h, the membrane was washed with phosphate buffer saline (PBS-T), primary antibody (1:500), overnight at 4°C, rinsed, secondary antibody (1:5,000) at room temperature for 2 h, rinsed, and then luminescence developed in an electrochemiluminescence (ECL) imaging system. Glyceraldehyde-3phosphate dehydrogenase (GAPDH) was used as an internal reference, and the results were scanned in grayscale for semi-quantitative analysis.

TABLE 1 | Target gene names and PCR primers.

Name of gene		Primer sequences
TNF-α	Forward	5'-GCTGCACTTTGGAGTGATCG-3'
	Reverse	5'-GAGGGTTTGCTACAACATGGG-3'
IL-1β	Forward	5'-AGAAG- TACCTGAGCTCGCCA-3'
	Reverse	5'-CTG- GAAGGAGCACTTCATCTGT-3'
IL-6	Forward	5'-ACTCACCTCTTCAGAACGAATTG-3'
	Reverse	5'-CCATCTTTGGAAGGTTCAGGTTG-3'
GAPDH	Forward	5'-AGAAGGCTGGGGCTCATTTG-3'
	Reverse	5'-AGGGGCCATCCACAGTCTTC-3'

Fluorescent Quantitative PCR (qRT-PCR)

Total mRNA was extracted from each group of H9c2 cells and rat myocardial tissue using TRIzol, and the total mRNA was reverse transcribed into cDNA and PCR amplified according to the instructions. PCR primers were designed as in **Table 1** reverse transcription and qRT-PCR reactions were performed strictly according to the kit instructions. The relative expression of target genes was expressed as $2^{-\Delta\Delta Ct}$.

Hoechst (HE) Staining

Myocardial tissues (about 2 mm thick) were taken from rats, and myocardial tissues were fixed in 4% paraformaldehyde solution after washing with ice-cold saline, and then de-watered and paraffin-embedded after 48 h. The sections were stained according to HE staining kit, and the morphological and structural changes of myocardial cells were observed under the light microscope.

Blood Glucose and Lipid Testing

Blood glucose (GLU) level was measured by blood glucose meter; serum total cholesterol (TC) and triacylglycerol (TG) were measured by automatic biochemical analyzer, all operations were performed with reference to the kit instructions, and the relevant kits were provided by Beijing Ovia Biotechnology Co.

Statistical Treatment

SPSS 21.0 software was used for statistical analysis. Statistical indicators were tested for normality and chi-square test, and each statistical data was expressed as mean ± standard deviation (Mean ± SD); one-way ANOVA was used for the analysis of multi-group measurement data, and the difference between two groups was analyzed by *t*-test. $p < 0.05$ indicated statistical differences. GraphPad Prism 8.0 software was used for statistical calculations and graphing.

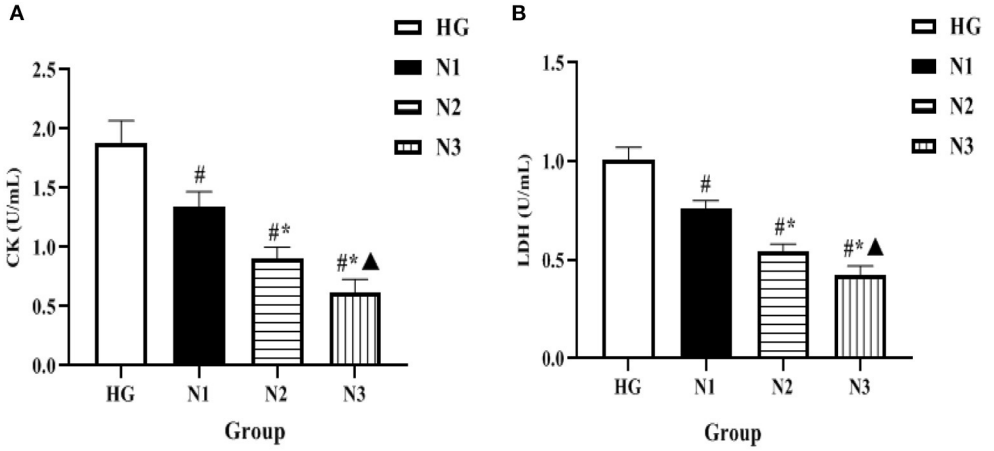

FIGURE 1 | Comparison of enzyme activity levels in H9c2 cells in each group. In the above figure, **(A)** the comparison of CK levels in the four groups of H9c2 cells, and **(B)** the comparison of LDH levels in the four groups. Compared with HG group, $^{\#}P < 0.05$; compared with N1 group, $^{*}P < 0.05$; compared with N2 group, $^{\blacktriangle}P < 0.05$.

RESULTS

Comparison of Enzyme Activity Levels in H9c2 Cells in Each Group

The levels of intracellular enzymes such as CK and LDH were significantly lower in the N1, N2, and N3 groups when compared with the HG group ($P < 0.05$ or $P \leq 0.01$), among which the lowest level of intracellular enzyme activity was found in the helichrysum arenarium 25 μg/mL group (N3), as shown in **Figure 1**. Suggesting that the flavonoid extract of helichrysum arenarium can inhibit the extent of high glucose-induced damage in damaged myocardial cells.

Apoptotic Protein Expression Levels in H9c2 Cells in Each Group

Compared with the HG group, the expression of apoptosis-related factors BAX was down-regulated and Bcl-2 was up-regulated in the N1, N2, and N3 groups, and the differences were statistically significant ($P < 0.05$ or $P \leq 0.01$), and the most significant in the helichrysum arenarium 25 μg/mL group, as shown in **Figure 2**. It is suggested that helichrysum arenarium can inhibit the apoptosis of damaged cardiomyocytes induced by high glucose, and the inhibition of the above-mentioned apoptosis-related analysis increased with the increase of the dose of helichrysum arenarium. The effect of apoptosis-related analysis increased with increasing dose of helichrysum arenarium.

Expression Levels of Inflammatory Factors in H9c2 Cells in Each Group

The expression levels of mRNA of inflammatory factors such as IL-6, IL-1β, and TNF-α in the cells of each group were detected by qRT-PCR, and the changes were as follows: compared with the HG group, the mRNA levels of inflammatory factors such as IL-6, IL-1β, and TNF-α in the cells of the N2 and N3 groups were significantly lower ($P < 0.05$), and the mRNA levels of inflammatory factors such as IL-6, IL-1β, and TNF-α in the cells of the N3 group were lower than those of the N2 group ($P < 0.05$), as shown in **Figure 3**. Suggesting that helichrysum arenarium can inhibit the inflammatory response in damaged cardiomyocytes induced by high glucose in a dose-dependent manner.

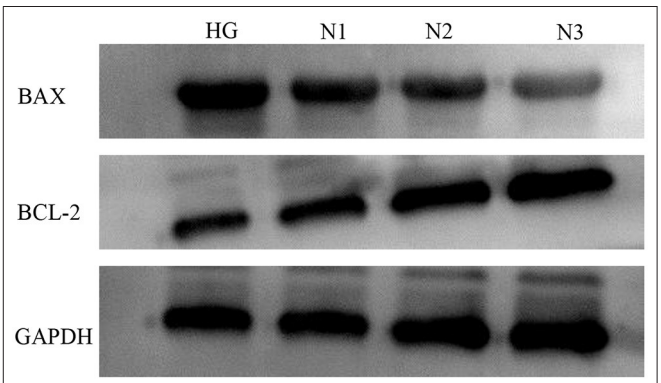

FIGURE 2 | Apoptotic protein expression levels in H9c2 cells in each group. The electrophoresis of apoptosis-related proteins in each group.

Body Weight, Blood Glucose, and Lipid Levels of Rats in Each Group

After 10 weeks of continuous administration, the body weight of rats in S1, S2, and S3 groups gradually increased compared with the DCM group, with the most significant increase in the S3 group ($P < 0.05$ for the S3 group compared with the DCM group). Compared with the DCM group, the GLU level of S1 and S2 groups decreased, but it was not statistically significant, while the high dose of helichrysum arenarium could reduce the GLU levels in rats with DM ($P < 0.05$). At 10 weeks, the TC and

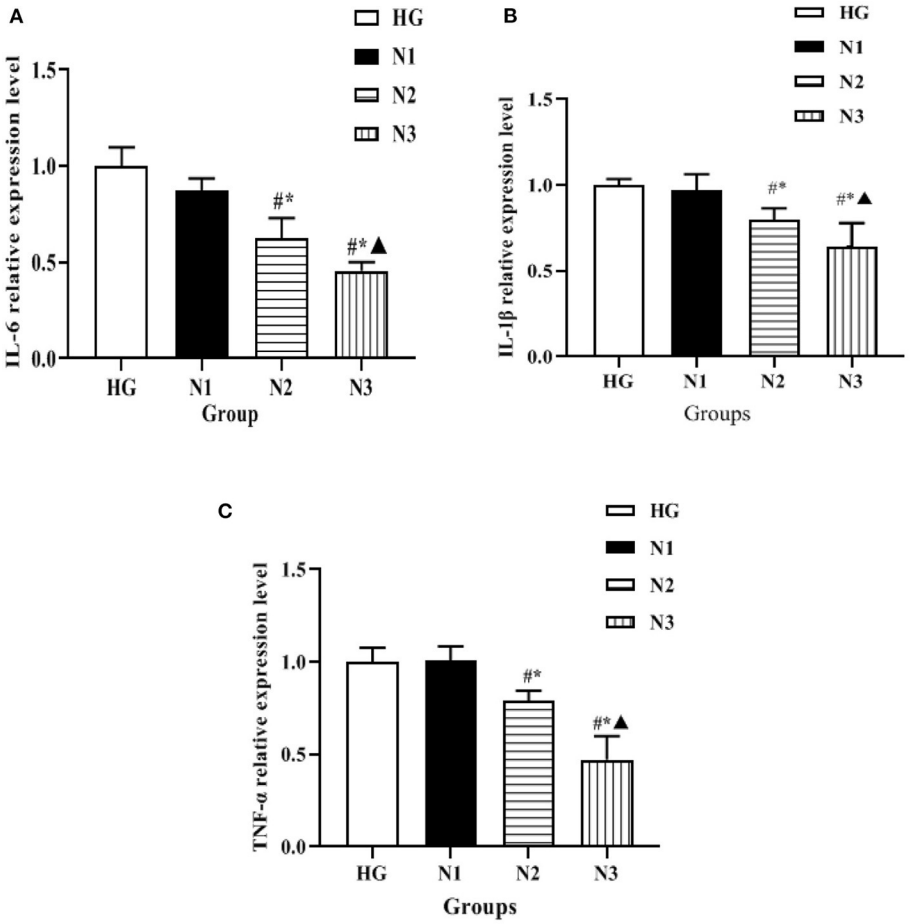

FIGURE 3 | Expression levels of inflammatory factors in H9c2 cells in each group. In the above figure, **(A)** the comparison of IL-6 expression levels in the four groups of H9c2 cells, **(B)** the comparison of IL-1β expression levels in the four groups of H9c2 cells, and **(C)** the comparison of TNF-α expression levels in the four groups of H9c2 cells. Compared with HG group, $^{\#}P < 0.05$; compared with N1 group, $^{*}P < 0.05$; compared with N2 group, $^{\blacktriangle}P < 0.05$.

TG levels of rats in S2 and S3 groups were significantly lower than those in DCM group ($P < 0.05$), as shown in **Figure 4**. This suggests that helichrysum arenarium can improve lipid metabolism in rats with diabetic myocarditis.

Histomorphological Changes of Myocardium in Each Group of Rats (HE, ×400)

In DCM group, myocardial fibers of mice were disordered, with uneven texture, cellular hypertrophy and deformation, increased cellular gaps, and inflammatory infiltration was seen around them. In comparison with DCM group, myocardial fibers and cells of rats were improved in S2 and S3 groups, and myocardial fibers and myocytes of S3 group were more neatly arranged and fibers were intact, and the improvement was most obvious. See **Figure 5.**

Expression Levels of Inflammatory Factors in Myocardial Tissue of Rats in Each Group

The expression levels of mRNA of inflammatory factors such as IL-6, IL-1β, and TNF-α in myocardial tissues of DM rat model were detected by qRT-PCR in each group, and the changes were as follows: compared with DCM group, the mRNA levels of inflammatory factors such as IL-6, IL-1β, and TNF-α in myocardial tissues of rats in S2 and S3 groups were significantly lower ($P < 0.05$); the mRNA levels of inflammatory factors such as IL-6, IL-1β, and TNF-α in myocardial tissues of rats in S3 group were lower than those in S2 group ($P < 0.05$) (see **Figure 6**). It was suggested that helichrysum arenarium could inhibit the myocardial inflammatory response in DM rat model and showed a dose-dependent effect.

DISCUSSION

The incidence of DM is increasing, and the incidence of DM-related complications is also gradually increasing due to the long-term hyperglycemic environment, irrational use of hypoglycemic drugs, and poor glycemic control after drug therapy, among which DCM is the most common (18, 19). DCM is defined as myocardial disease that occurs in patients with DM, can be excluded as being caused by other diseases, and is the leading cause of death (20). Therefore, along with aggressive glycemic control, efforts to find drugs to prevent and mitigate myocardial and vascular

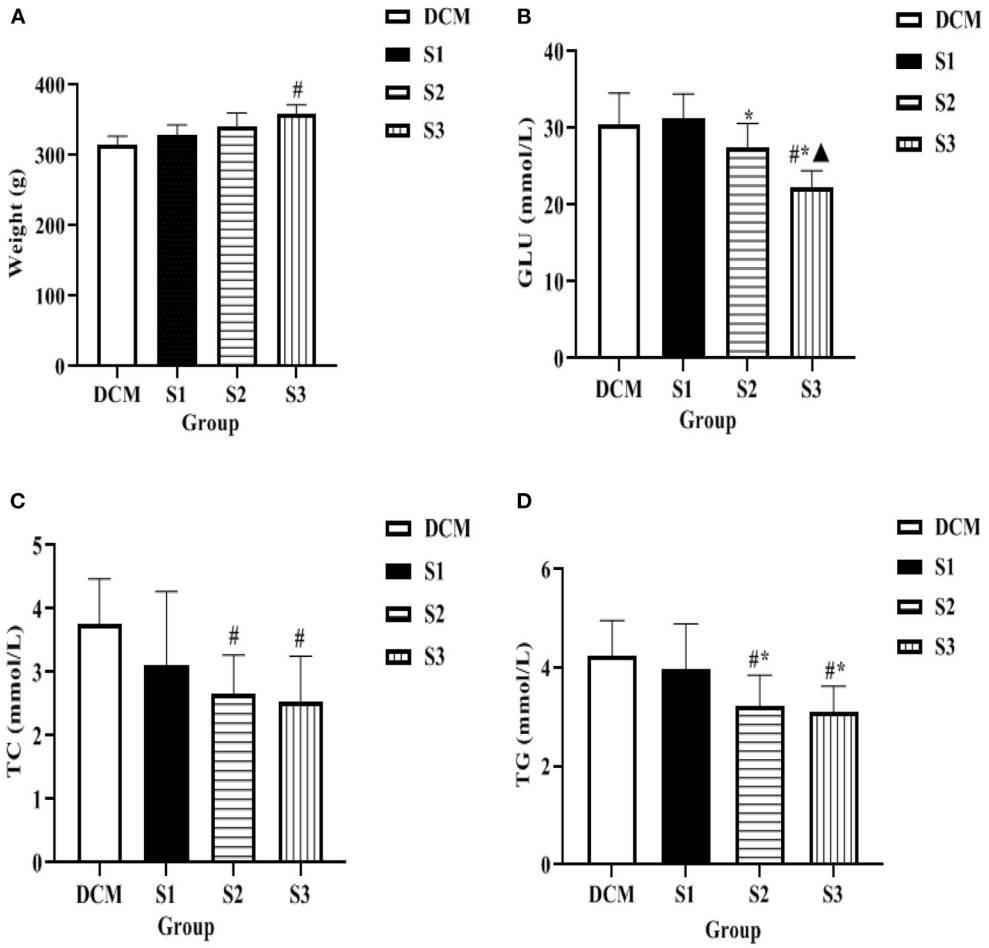

FIGURE 4 | Body weight, blood glucose and lipid levels of rats in each group **(A)** is the comparison of body weight of four groups of rats, **(B)** is the comparison of GLU level of four groups of rats, **(C)** is the comparison of TC level of four groups of rats, **(D)** is the comparison of TG level of four groups of rats. Compared with the DCM group, $^{\#}P < 0.05$; compared with the S1 group, $^{*}P < 0.05$; compared with the S2 group, $^{\blacktriangle}P < 0.05$.

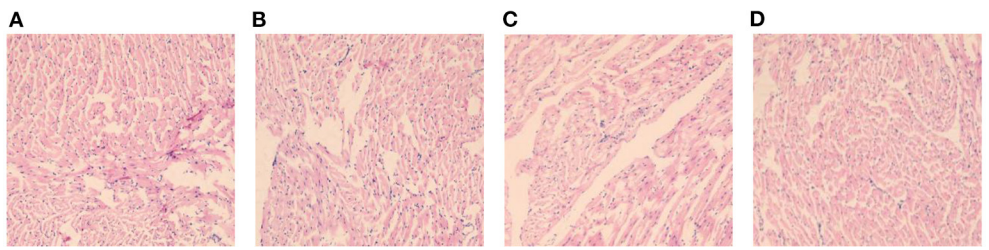

FIGURE 5 | Histomorphological changes of myocardium in each group of rats (HE, ×400). **(A)** is the DCM group, **(B)** is the S1 group, **(C)** is the S2 group, and **(D)** is the S3 group.

injury are particularly important to reduce cardiovascular events. Helichrysum arenarium has been shown to have hypoglycemic effects and potential targets for the treatment of type 2 diabetes mellitus (T2DM) have been reported in the literature (21, 22) in tissues such as liver, muscle, pancreas, and brain, and these targets provide new ideas for the study of the pharmacological mechanism of T2DM in helichrysum arenarium.

In this study, the H9c2 cardiomyoblast cell line was treated with high glucose environment to simulate a model of damaged cardiomyocytes. It was found that helichrysum arenarium could reduce the leakage of CK and LDH in cardiomyocytes induced

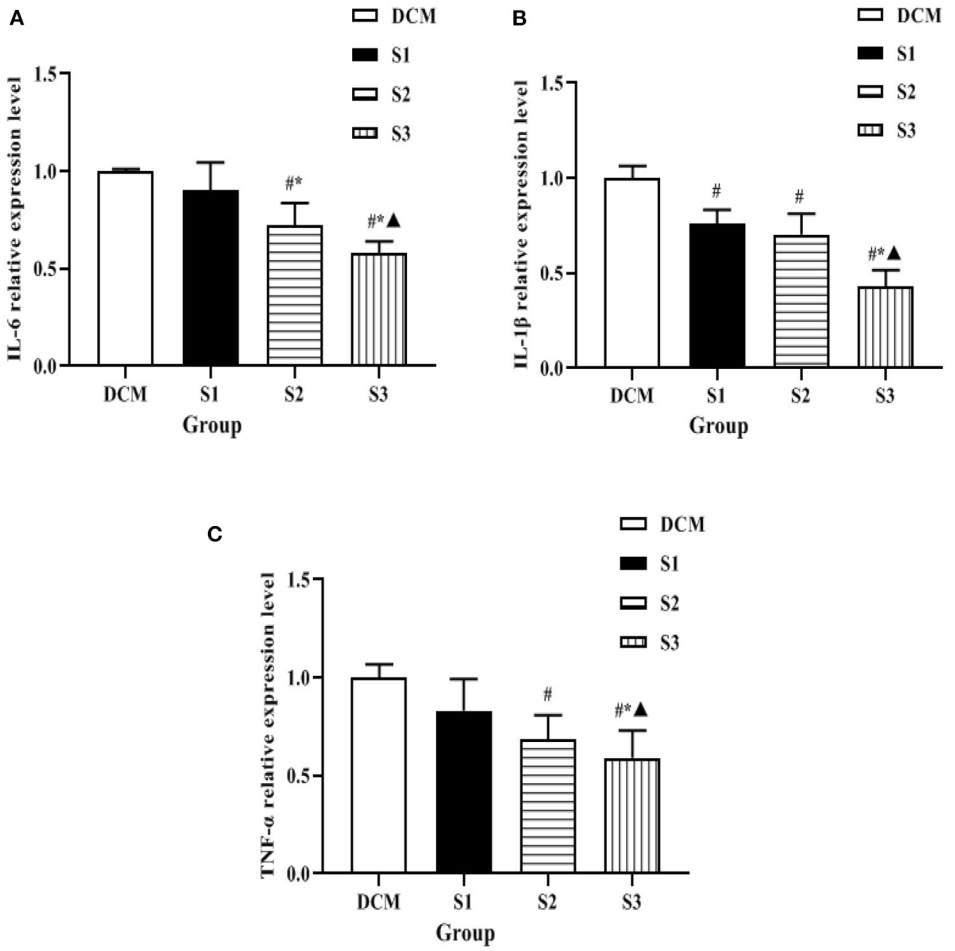

FIGURE 6 | Expression levels of inflammatory factors in myocardial tissue of rats in each group. **(A)** is the comparison of IL-6 expression levels among the four groups, **(B)** is the comparison of IL-1β expression levels among the four groups, and **(C)** is the comparison of TNF-α expression levels among the four groups. Compared with the DCM group, $^{\#}P < 0.05$; compared with the S1 group, $^{*}P < 0.05$; compared with the S2 group, $^{\blacktriangle}P < 0.05$.

by high glucose, and could inhibit apoptosis of damaged cardiomyocytes induced by high glucose, and the inhibitory effect was enhanced with increasing dose of helichrysum arenarium. Active enzymes such as CK and LDH present in cardiomyocytes cannot cross the cardiomyocyte membrane under normal conditions; however, when the cells are damaged, the permeability of the cell membrane increases and CK and LDH leak out of the cells. Therefore, the level of pericellular CK and LDH can reflect the degree of cardiomyocyte damage (23, 24). The Bcl-2 family is a gene family closely related to apoptosis, and the protein products of this family are functionally divided into proteins with apoptosis-promoting effects, such as Bax, and proteins with apoptosis-inhibiting effects, such as Bcl-2. Under normal physiological conditions, there is a dynamic balance between pro-apoptotic and anti-apoptotic proteins, and when the body or cell is subjected to noxious stimuli, the disruption of this balance leads to increased apoptosis (25, 26). In this study, cells cultured under high glucose environment showed a significant increase in CK and LDH content, up-regulation of intracellular BAX expression and down-regulation of Bck-2 expression over time. However, helichrysum arenarium was able to reduce CK and LDH leakage induced by high glucose, and BAX expression was down-regulated and Bck-2 expression was increased, which indicates that it has a certain ameliorative effect on myocardial injury induced by high glucose and can inhibit apoptosis of damaged myocardial cells.

The DM model was established by intraperitoneal injection of STZ, and the body weight, blood glucose and lipid levels of rats were detected after 10 weeks, and HE staining of myocardial tissues of rats was taken for pathological section. The results showed that the levels of GLU, TC and TG in S3 group were significantly lower than those in DCM group at 10 weeks. In the DCM group. HE staining in the DCM group showed that the cardiomyocytes were hypertrophied and disordered, and the intercellular space was widened. Compared with the DCM group, the structure of the cardiomyocytes in the S1, S2, and S3 groups was destroyed and the arrangement disorder was alleviated, and the S3 group improved more pronounced. Thus,

it can be seen that helichrysum arenarium may improve the lipid metabolism of diabetic rats and reduce the accumulation of lipids in the myocardium, thus reducing the damage of lipids and their metabolites to the myocardium.

In recent years, with the in-depth study of clinical medicine, it was found that the subclinical inflammatory response plays an important role in the development and progression of DCM, and the inflammatory response is accompanied by the release of a large number of cytokines and acute phase proteins, such as IL-6, IL-1β, and TNF-α (27–29). The present experiment revealed that IL-6, IL-1β, and TNF-α were significantly increased in the myocardial tissue of H9c2 cells and DM rats exposed to high glucose environment, indicating that during the course of diabetic cardiomyopathy, an inflammatory response occurs in the myocardium, and this inflammatory response promotes the secretion of myocardial inflammatory factors and eventually myocardial inflammatory injury. The extract has been found to be effective in reducing the neutral fat content in the stem cells of hyperlipidemic rats and has lipid-lowering effects, in addition to its anti-atherosclerotic effects, but there are few reports on the role of helichrysum arenarium in the inflammatory response (30). In this study, we found that the expression levels of inflammatory factors such as IL-6, IL-1β, and TNF-α in the myocardial tissues of H9c2 cells and DCM rats were all decreased to different degrees, and the decrease was the most in the high-dose group. Combined with the above results, we speculate that Wax chrysanthemum may produce anti-inflammatory myocardial injury effects by reducing the expression levels of inflammatory factors such as IL-6, IL-1β, and TNF-α.

From the above analysis we are able to conclude that the helichrysum arenarium flavonoid extract can reduce the degree of damage of H9C2 cells induced by high glucose and decrease the cellular inflammatory response, and its mechanism of action may be achieved by regulating the apoptotic factors Bax and Bcl-2. In addition, the extract of helichrysum arenarium can reduce the histopathological damage of myocardium in diabetic rats, decrease the inflammatory response in the tissue, and achieve the effect of myocardial protection.

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 the Animal Ethics Committee of XinJiang Medical University.

AUTHOR CONTRIBUTIONS

HL and WL made equal contributions, intellectually, and physically. Both authors contributed to the article and approved the submitted version.

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The Impact of Triangle Hierarchical Management on Self-Management Behavior and Quality of Survival in Parkinson's Patients

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Objective: To investigate the effect of Triangle tiered and graded management on the self-management behavior and quality of survival of Parkinson's Disease (PD) patients.

Methods: Eighty ambulatory PD patients admitted to the neurology outpatient clinic of our hospital from June 2020 to January 2021 were selected for the study. Eighty patients were divided into 40 cases each in the test group and the control group using the random number table method. Patients in the control group were given conventional treatment and care, while in the test group, Triangle hierarchical management was applied on the basis of the control group. Non-motor symptoms [assessed by the Montreal Cognitive Inventory (MoCA), the Scale for Outcomes in PD for Autonomic Symptoms disability Scale (SCOPA-DS) and the Nocturnal Scale (SCOPA-NS)], motor symptoms [assessed by the Functional Gait Assessment (FGA), the Modified Ashworth Scale, and the Unified Parkinson's Disease Rating Scale (UPDRS-III)], quality of life (assessed by Barthel Index), medication adherence (self-administered medication adherence questionnaire), quality of survival (assessed by the 39-item Parkinson's Disease Quality of Survival Questionnaire, PDQ-39), and self-management effectiveness (assessed by the Chronic Disease Self-Efficacy Scale, symptom management and disease co-management) were compared between the two groups before and after the intervention. The two groups were also observed for satisfaction with care.

Results: After the intervention, the MoCA score, FGA score, Barthel Index, Medication adherence and all scores of self-management effectiveness were significantly higher in the test group than in the control group ($P < 0.05$); the SCOPA-DS score, SCOPA-NS score, Ashworth score, UPDRS-III score and PDQ-39 score were significantly lower than in the control group ($P < 0.05$). Satisfaction with nursing care was significantly higher in the test group than in the control group ($P < 0.05$).

Conclusion: The application of Triangle's tiered and graded management to the home care of ambulatory PD patients was effective in improving their non-motor and motor symptoms, their ability to perform daily activities, medication adherence and self-management effectiveness, and their overall survival outcome.

Keywords: Parkinson's, Triangle, tiered management, self-management behavior, quality of survival

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PREFACE

With the accelerated aging of the population, Parkinson's disease (PD) has become the second most serious progressive neurodegenerative disease after dementia that affects the elderly worldwide (1, 2). The motor and non-motor symptoms of PD can cause a range of functional impairments of varying severity, seriously jeopardizing patients' physical and mental health and quality of life, and increasing the incidence of accidental risk and mortality (3). PD is not yet completely curable, so clinical treatment is primarily aimed at slowing the disease process, improving functional impairment, reducing the risk of complications and improving survival. However, the complexity of pharmacological regimens and fear of side effects have led to a decline in compliance, while the prolonged, irreversible, slow-onset nature of the disease and the lack of family support have severely undermined patients' self-confidence, resulting in a majority of patients being unable to sustain functional rehabilitation and thus exacerbating the disease's progression (4, 5). Therefore, it has become a major concern for the community to improve the effectiveness of pharmacological and rehabilitative treatments to improve the clinical outcome of PD patients.

Recent studies (6–8) have shown that as the concept and content of nursing services continue to develop, the nursing management model, as an effective complement to medical services, can effectively enhance the treatment and rehabilitation of patients with various chronic diseases. It has a positive effect on improving patients' prognosis, preventing disease recurrence, improving quality of life and reducing the burden on patients and their families. The Triangle Chronic Disease Tiered Management Model was developed by Kaiser Permanente, a large managed care organization in California, and has been used since 2002 to manage the care of patients with chronic diseases (9, 10). The model divides patients into high-risk, moderate-risk, and stable tiers, and then provides specialized medical care proportional to the needs of each tier, creating a pyramidal tiered management model that is more economical and The model is a pyramidal hierarchical management model that treats patients more economically and effectively (11). This study refers to the Triangle Chronic Disease Stratified Management Model (12) and combines it with the Hoehn-Yahr classification of PD (13) to construct stratified and graded management criteria that are consistent with ambulatory PD patients. Ambulatory PD patients were classified as high-risk patients, moderate-risk patients and stable patients for management at three levels, and three levels of care were provided for case care, self-management and disease management. The aim is to improve treatment adherence, self-management and quality of survival for PD patients.

MATERIALS AND METHODS

Study Population

Eighty ambulatory PD patients admitted to the neurology outpatient clinic of our hospital from June 2020 to January 2021 were selected for the study.

TABLE 1 | Stratified and graded management criteria for ambulatory PD patients.

Criteria for patient stratification	Grading management standards
Smooth stratum Grade 1: Unilateral limb disease. Grade 1.5:unilateral limb combined with trunk (axial) symptoms.	Tertiary follow-up care requirements: (1) Outpatient follow-up once every 3 months; (2) Telephone or other follow-up once every month; (3) Daily exercise training, no more than 45 min each time, 3 times/day; (4) Population health education: mainly conventional education (e.g., through books, videos, audio-visual materials, etc.), encouraging patients to participate in group activities; encouraging patients to present themselves and participate in the education of other patients, giving them the opportunity to serve as role models opportunities. (5) Follow-up: telephone follow-up.
Intermediate risk stratum Grade 2: bilateral limb symptoms but no balance disturbance. Grade 2.5: Mild bilateral symptoms with recovery from backward pull test. Grade 3: Mild to moderate bilateral symptoms, unable to recover from pull-back test, unstable posture, slower turning, many functional limitations but patient is able to care for himself/herself.	Secondary follow-up care requirements: (1) Outpatient follow-up once every 2 months; (2) Telephone or other means of follow-up once every half month; (3) Daily exercise training of no more than 40 min each time, two times/day; (4) Point follow-up care: health education is based on group education, for patients who cannot participate in group education, individual education can be adopted. (5) Follow-up methods: telephone follow-up, outpatient follow-up, WeChat, WeChat platform, etc.
High risk stratum Grade 4: Severely disabled, able to stand and walk without assistance. Grade 5: Wheelchair-bound or bedridden, totally dependent on others for assistance.	Primary follow-up care requirements: (1) Outpatient follow-up once every 1 month; (2) Telephone or other follow-up once every 7 days; (3) Daily exercise training not exceeding 20 min each time, 2 times/day; (4) Case follow-up care: according to the patient's condition, individualized care plans are formulated and individualized, targeted health education is implemented. (5) Follow-up methods: telephone follow-up, outpatient follow-up, home follow-up, WeChat, WeChat platform, etc.

Inclusion and Exclusion Criteria

Inclusion criteria: (i) patients who met the new clinical diagnostic criteria for PD established by the International Movement Disorders Society (MDS) in 2015 (14); (ii) patients aged 18–70 years old; (iv) patients who were in the stable stage of the disease, were mentally alert, had no language communication impairment and had the ability to understand; (v) patients and family members who gave informed consent and voluntarily participate in this study.

Exclusion criteria: (i) Patients who did not agree to participate in the study. (ii) Patients who were not in their right mind, had difficulty in verbal communication and had cognitive impairment. (iii) Patients without the ability to understand. (iv) Patients who died midway or withdrew from the intervention trial. (v) Patients with severe depression and severe anxiety.

TABLE 2 | Comparison of baseline information between the two groups (%, $\bar{x} \pm s$).

Items		Control group ($n = 40$)	Test group ($n = 40$)	t or χ^2 value	*P*-value
Gender	Male	19 (47.50)	17 (42.50)	0.202	0.653
	Female	21 (52.50)	23 (57.50)		
Mean age (years)	64.21 ± 8.74	65.20 ± 8.17	0.523	0.602	
Duration of illness (years)	5.23 ± 2.46	4.87 ± 1.69	0.763	0.448	
Personal monthly income (yuan)	0∼999	5 (12.50)	7 (17.50)	1.189	0.756
	1,000–2,999	17 (42.50)	19 (47.50)		
	3,000–4,999	10 (25.00)	9 (22.50)		
	>5,000	8 (20.00)	5 (12.50)		
Marital status	Unmarried	3 (7.50)	5 (12.50)	1.900	0.387
	Married	29 (72.50)	31 (77.50)		
	Widowed or divorced	8 (20.00)	4 (10.00)		
Hoehn-Yahr grading	1–2	7 (17.50)	9 (22.50)	1.293	0.524
	2.5–3	30 (75.00)	27 (67.50)		
	4–5	3 (7.50)	4 (10.00)		

Sample Size Calculation

The sample size was estimated based on the formula for the sample size required for comparison of the means of two samples, based on a two-sided $\alpha = 0.05$, $1–\beta = 0.90$ and assuming $\delta/\sigma = 0.80$, and the sample size was derived from the attached table as 34 cases per group. However, considering the possible sample attrition during the study, the sample size was expanded by 20% from the original one, and the final sample size was determined to be 40 cases per group, with a total of 80 cases. A random number table was used to divide the 80 patients into a test group and a control group of 40 patients each. Patients in the control group were given conventional treatment and care, while the test group was managed by Triangle stratification on the basis of the control group, and both groups were intervened and followed up for 12 months.

Intervention Methods

The baseline survey included general information on gender, age, marital status, duration of illness, financial income and severity of illness, the Parkinson's Disease Rating Scale Part III (UPDRS-III), the Medication Adherence Scale, the 39-item Parkinson's Disease Quality of Life Questionnaire (PDQ-39) and the Chronic Disease Self-Efficacy Scale.

Control group: Patients were given the usual medication, diet, sleep, rehabilitation exercise instruction and psychological care. The duration of intervention was 12 months, with monthly telephone follow-ups and monthly outpatient follow-ups in the 3rd, 6th and 12th months.

Test group: The Triangle stratification and grading management model was used to stratify ambulatory PD patients in the following ways. i. At the time of consultation, patients were classified into a smooth stratum (Hoehn-Yahr classification of 1 to 1.5), an intermediate risk stratum (Hoehn-Yahr classification of 2 to 3) and a high risk stratum (Hoehn-Yahr classification of 4 to 5) according to the baseline findings and with reference to Triangle stratification and Hoehn-Yahr classification criteria for PD. Establish follow-up files for ambulatory PD patients at each tier. The files report the patient's general information, contact information, clinical manifestations and examination results, etc. The files for the smooth, medium-risk and high-risk tiers are marked in green, orange and red, respectively. The follow-up methods we adopt are telephone follow-up, outpatient follow-up, home follow-up, WeChat and WeChat platform, etc. The graded management criteria for patients are specified in **Table 1**. iii. Tier flow: Patients are reassessed once after the intervention in 1, 3, 6, and 12 months according to the tier criteria to determine the number of tier flow instances, as well as file reorganization and management into the new tier criteria.

Evaluation Indicators

Non-motor symptoms: The Montreal Cognitive Inventory (MoCA), the Scale for Outcomes in PD for Autonomic Symptoms disability Scale (SCOPA-DS) and the Nocturnal Scale (SCOPA-NS) were used to assess the pre and post intervention. The MoCA scale consists of 8 dimensions with a total score of 30, with higher scores indicating better cognitive function. scores range from 0 to 15 for the SCOPA-NS and from 0 to 18 for the SCOPA-DS, with lower scores indicating better sleep.

Motor symptoms: Functional Gait Assessment (FGA), modified Ashworth Scale, Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) were assessed before and after the intervention. The FGA assessed the patient's functional gait from items 1–10 of the FGA, and each item was scored on a 4-point scale from 0 to 3 out of 30, with higher scores indicated better balance and walking ability. A modified version of Ashworth was used to assess the patient's muscle tone, and scores from 0 to 4 were assigned from normal muscle tone to stiffness during movement of the affected area. UPDRS-III included 14 items with a total score of 0 to 70, with higher scores indicated poorer motor function.

Ability to perform activities of daily living: A comprehensive evaluation using the Barthel Index rating of 10 items such as eating, grooming, continence control and bed and chair transfer,

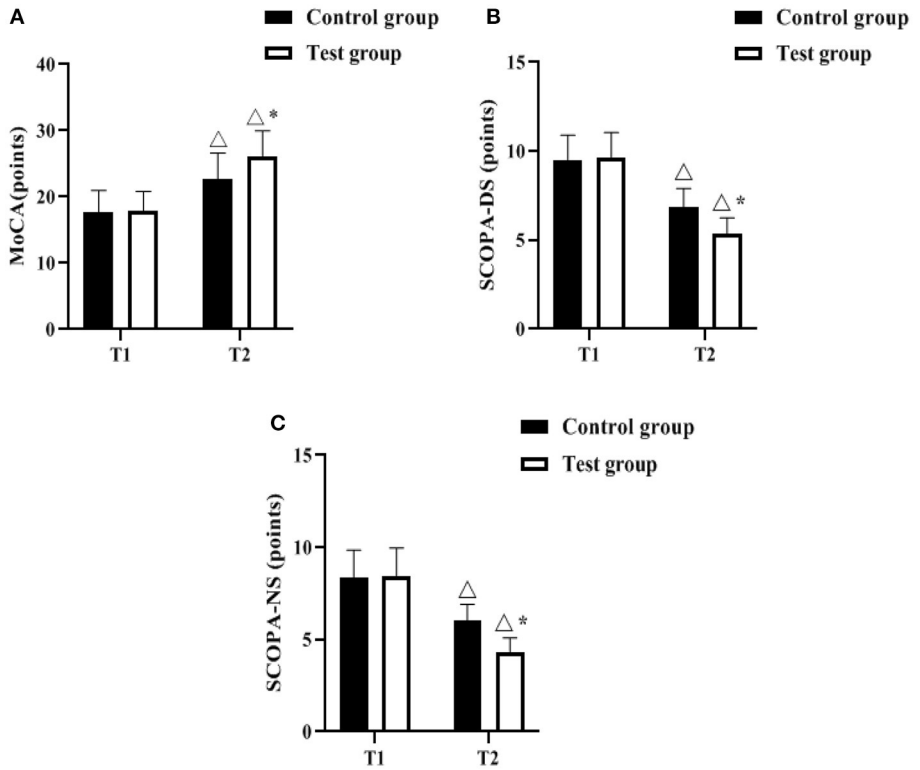

FIGURE 1 | Comparison of non-motor symptoms (n, $\bar{x}\pm$ s). **(A–C)** indicate the MoCA, SCOPA-DS, and SCOPA-NS scales, respectively. Icon Δ indicates the difference between T2 period and T1 period between the same groups, $P < 0.05$. Icon * indicates the difference between the two groups in T2 period, $P < 0.05$.

each with a score of 10, for a total score of 100. A higher score indicates that the patient needs less help and is less dependent.

Medication adherence: A self-made PD medication questionnaire was used to evaluate the medication compliance of the two groups of patients, and the internal consistency of the questionnaire was 0.813. The total score of the questionnaire was 100 points, with a score of 86–100 indicated complete compliance, 70–85 indicated partial compliance, and ≤69 indicated non-compliance.

Quality of survival: The 39-item Parkinson's Disease Quality of Survival Questionnaire (PDQ-39) was used to assess the quality of survival. The scale consists of 39 items in 8 dimensions, each with five health levels (0 to 4), and the sum of the scores for each item was converted to a percentage, with higher total scores indicating lower quality of survival.

Self-management efficacy: The Chronic Disease Self-Efficacy Scale was used to assess the patient's self-management efficacy, which consists of 6 items in 2 dimensions, namely symptom management self-efficacy and disease co-management self-efficacy. The scale is rated on a scale of 1∼10, with higher scores indicating higher self-management efficacy, in which the total score <4 points is regarded as low level; 4 ∼ 7.9 points are regarded as medium level; ≥8 points are regarded as high level.

Nursing satisfaction: The nursing satisfaction questionnaire for ambulatory Parkinson's disease patients developed by the nursing department of our hospital was used to investigate the satisfaction of the two groups of patients with nursing services, which were divided into extremely satisfied, generally satisfied and unsatisfied, and the satisfaction rate = extremely satisfied rate + general satisfaction rate.

Statistical Methods

SPSS 22. 0 software was used for data analysis. The statistical data were expressed as percentages using the χ^2 test, and the measurement data were expressed as $\bar{x}\pm$s using the t test. The difference was considered statistically significant at $P < 0.05$

RESULTS

Comparison of Baseline Information Between the Two Groups

The differences in gender, mean age, duration of disease, monthly personal income, marital status and Hoehn-Yahr classification among the different groups of ambulatory PD patients were not statistically significant ($p > 0.05$) and subsequent comparisons could be made. As shown in **Table 2**.

Comparison of Non-motor Symptoms

The MoCA, SCOPA-DS and SCOPA-NS scales were used to assess the degree of non-motor symptoms of the patients before and after the management intervention. As shown in

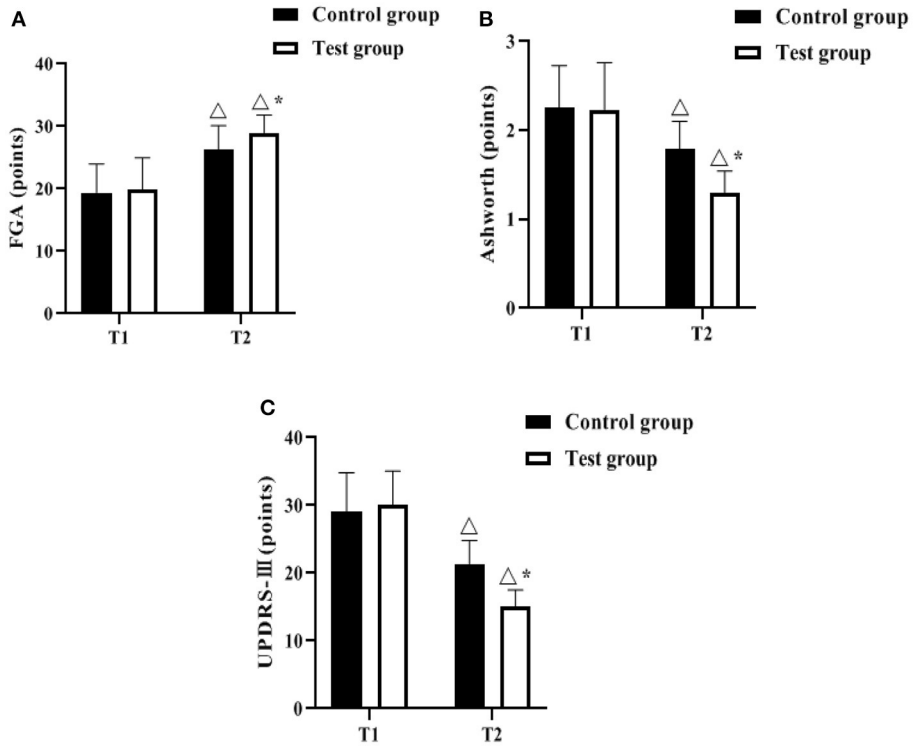

FIGURE 2 | Comparison of movement symptoms (n, $\bar{x} \pm$ s). **(A–C)** indicate the FGA, Ashworth and UPDRS-III scales, respectively. Icon Δ indicates the difference between T2 period and T1 period between the same groups, $P < 0.05$. Icon * indicates the difference between the two groups in T2 period, $P < 0.05$.

Figures 1A–C, the differences in the scores of MoCA, SCOPA-DS, and SCOPA-NS between the control group and the test group before the intervention (T1) were not statistically significant ($P > 0.05$). 12 months after the Triangle stratified management intervention (T2), MoCA scores increased in both groups compared to T1, and were higher in the test group ($P < 0.05$); SCOPA- DS and SCOPA-NS scores decreased in both groups compared to T1, and were lower in the test group ($P < 0.05$).

Comparison of Movement Symptoms

The FGA, Ashworth and UPDRS-III scales were used to assess the degree of motor symptoms of the patients before and after the management intervention. As shown in **Figures 2A–C**, there was no difference between the control group and the test group in comparing the scores of FGA, Ashworth, and UPDRS-III at T1 ($P > 0.05$). The FGA scores of both groups increased at T2 compared with T1, and were higher in the test group ($P < 0.05$); the Ashworth and UPDRS-III scores of both groups decreased compared with T1, and were lower in the test group ($P < 0.05$).

Comparison of Barthel Index, Medication Adherence, PDQ-39 Scores

The Barthel Index, Medication adherence and PDQ-39 scales were used to assess the ability to perform daily activities, medication compliance and quality of life before and after the management intervention, respectively. As shown in **Figures 3A–C**, there was no difference in Barthel index, medication adherence, and PDQ-39 scores at T1 between the control and experimental groups ($P > 0.05$). The Barthel Index and Medication adherence scores increased in both groups at T2 compared to T1, with the test group having a higher score ($p < 0.05$); the PDQ-39 scores decreased in both groups compared to T1, with the test group having a lower score ($p < 0.05$).

Comparison of Self-Management Effectiveness Scores

The Chronic Disease Self-Efficacy Scale was used to assess the patients' self-management effectiveness before and after the management intervention. As shown in **Figures 4A,B**, there was no difference in symptom management and disease co-management scores between the control and test groups at T1 ($P > 0.05$). The symptom management and disease commonality management scores increased in both groups at T2 compared to T1, and were higher in the test group ($p < 0.05$).

Nursing Satisfaction

A hospital-made questionnaire was used to assess patients' satisfaction with nursing management. In the control group, the number of patients in the three levels of "extremely satisfied," "generally satisfied" and "dissatisfied" were 22, 11, and 7, respectively, with a satisfaction rate of 82.50% (33/40). In the test group, there were 29, 10 and 1 cases of "extremely satisfied," "moderately satisfied" and "dissatisfied", respectively, with a satisfaction rate of 97.50% (39/40). As shown in **Figure 5**.

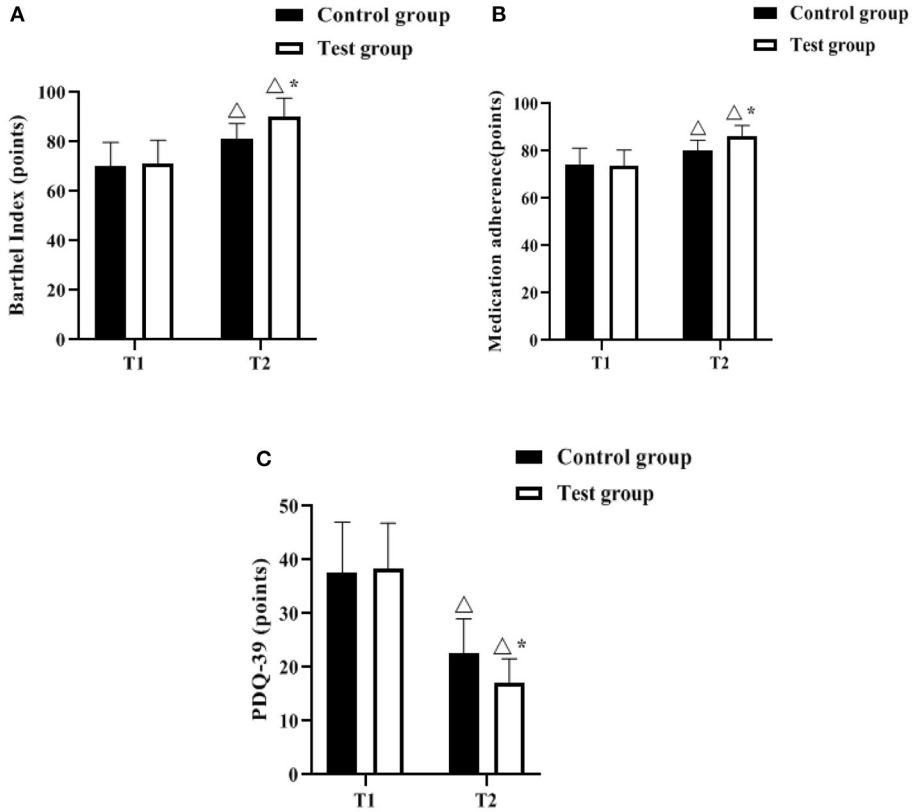

FIGURE 3 | Comparison of barthel index, medication adherence, PDQ-39 scores (n, $\bar{x} \pm$ s). **(A–C)** indicate the Barthel Index, Medication adherence and PDQ-39 scales, respectively. Icon Δ indicates the difference between T2 period and T1 period between the same groups, $P < 0.05$. Icon * indicates the difference between the two groups in T2 period, $P < 0.05$.

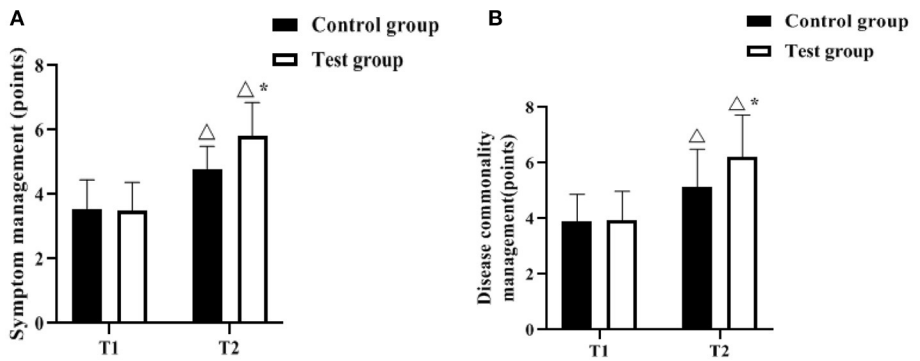

FIGURE 4 | Comparison of self-management effectiveness scores (n, $\bar{x} \pm$ s). **(A,B)** indicate the symptom management, disease commonality management scores, respectively. Icon Δ indicates the difference between T2 period and T1 period between the same groups, $P < 0.05$. Icon * indicates the difference between the two groups in T2 period, $P < 0.05$.

DISCUSSION

PD is a typical example of a functional neurosurgical disorder that is a movement disorder with genetic, age-related and environmental causes and a pathology that results from the deformation and loss of pigment-containing neurons (15, 16). It is characterized clinically by slowly progressive movement disorders (resting tremor, bradykinesia, bradykinesia and postural gait abnormalities) and, as the disease progresses, by intellectual disability in advanced stages (17). As research into the pathophysiology of PD progressed, it was discovered that PD pathology can involve the peripheral nervous system and cerebral cortex, leading to non-motor symptoms such as anxiety, depression, sleep disturbances and cognitive changes, which are

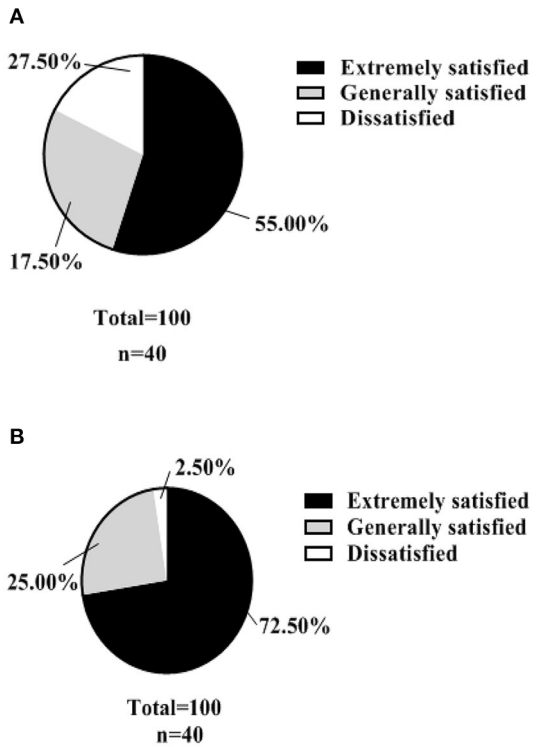

FIGURE 5 | Nursing satisfaction (*n*, %). **(A)** shows the satisfaction rate of patients in the control group with the management of their care. **(B)** shows the satisfaction rate of patients in the test group with the nursing management.

easily overlooked (18). In the early stages of PD, drug treatments such as dopamine preparations are effective in improving symptoms such as tremor and motor fluctuations, but as the disease progresses, the effectiveness of clinical interventions decreases and there are many problems such as adverse effects and drug interactions (19, 20). In addition to the prolonged duration of the disease, the patient's social and life skills are severely diminished, which not only affects the patient's quality of life, but also places a burden on the family and society, so the implementation of effective nursing interventions for patients based on clinical treatment has a positive impact on improving motor and non-motor symptoms (21).

The Triangle Chronic Disease Stratified Management Model suggests that different populations need to be identified and managed at the correct level of care for different conditions, increasing the effectiveness of management while reducing overall costs (22, 23). In this study, we envisage and attempt to develop a tiered and graded management model based on the Triagle Chronic Disease Tiered Management Model suitable for ambulatory PD patients and apply it to the management of ambulatory PD patients and the practice of tiered and graded management of ambulatory PD patients. The results of this study showed that there was a significant improvement in both motor and non-motor symptoms in both groups after 12 months of management intervention, with the test group outperforming the control group ($p < 0.05$). This suggests that Triangle's graded management significantly improved cognitive function, sleep quality and limb movement, mainly due to the fact that the test group developed a personalized exercise programme and follow-up programme based on the patients' graded condition, which helped to improve the patients' muscle and neurological functional limitations. In addition, the patient's confidence and adherence to treatment were enhanced by tailor-made care and individualized health education, which helped to improve non-motor symptoms such as cognitive function and sleep disturbance, as well as the recovery of social function (24, 25). The results also showed that Triangle stratified management significantly improved patients' activities of daily living, medication adherence, quality of life and self-management effectiveness, as evidenced by significantly higher Barthel Index, Medication adherence and Chronic Disease Self-Efficacy Scale scores in the test group than in the control group and before the intervention, and significantly lower PDQ-39 scores than in the control group and before the intervention ($P < 0.05$). Simplified personalized medication regimens, self-monitoring of symptoms, medication behavior management strategies, cognitive interventions, changes in dosing regimens, emotional management and reduced financial burdens can all contribute to improved medication adherence and self-management effectiveness in PD patients, thereby improving their quality of life and ability to perform daily activities (26, 27). In addition, the results of the nursing satisfaction survey showed that the test group was significantly more satisfied with the nursing management work than the control group, suggesting that Triangle's tiered and graded management can meet the needs of patients and their families for nursing services to a certain extent, with high acceptability, which is conducive to promoting patients' recovery.

In summary, Triangle's tiered and graded management applied to the home care of ambulatory PD patients was effective in improving their non-motor and motor symptoms, improving their ability to perform daily living activities, medication adherence and self-management effectiveness, and improving the overall survival 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 Hengyang Medical School, University of South China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YZ is the mainly responsible for the writing of the article. JH is mainly responsible for research design. XT and TW are mainly

responsible for data analysis. SC 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.

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ORIGINAL RESEARCH
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Efficacy of Laparoscopic Surgery Combined With Leuprorelin in the Treatment of Endometriosis Associated With Infertility and Analysis of Influencing Factors for Recurrence

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Objective: To explore the curative effect of laparoscopic surgery combined with leuprorelin in the treatment of endometriosis with infertility and the related factors of recurrence after treatment.

Methods: A total of 158 patients with endometriosis and infertility were selected in our hospital from January 2019 to June 2020. Patients were randomly divided into the control group and the observation group, with 79 patients in each group. Patients in the control group was treated by laparoscopy surgery combined with dydrogesterone, while those in the observation group was treated with laparoscopic surgery combined with leuprorelin. The hormone levels, recurrence rate, pregnancy rate and adverse reaction of the two groups were compared. Combined with clinical and pathological information, the related factors of postoperative recurrence were analyzed.

Results: After treatment, the levels of luteinizing hormone, follicle-stimulating hormone and estradiol in the observation group were lower than those in the control group ($P < 0.05$). The recurrence rate at 12 months after operation in the observation group was lower than that in the control group, and the pregnancy rate was higher than that in the control group ($P < 0.05$). However, there was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$). Preoperative dysmenorrhea was an independent risk factor for postoperative recurrence in patients with endometriosis, and postoperative pregnancy was a protective factor for postoperative recurrence in patients with endometriosis ($P < 0.05$).

Conclusion: Laparoscopy combined with leuprorelin in the treatment of endometriosis with infertility can improve hormone levels, increase the pregnancy rate and reduce the recurrence rate. Preoperative dysmenorrhea is an independent risk factor for postoperative recurrence, which should be quantified and included in the recurrence

risk prediction model. Postoperative pregnancy can reduce the recurrence rate after operation, and patients with fertility requirements should be encouraged to make activ preparations for postoperative pregnancy.

Keywords: endometriosis, leuprorelin, laparoscopic surgery, efficacy, recurrence

INTRODUCTION

Endometriosis is a common gynecological disease, which is characterized by the fact that active endometrial cells are planted outside the endometrium. Uterus is connected to the pelvis through fallopian tubes. During the menstrual period, menstrual reflux, abnormal secretion of gonad hormones, abnormal stimulation of inflammatory reaction, abnormal metastasis of lymphatic system, defects of immune system, etc. Will make endometrial cells grow outside endometrium and cause endometriosis (1, 2). Among them, pelvic organs and parietal peritoneum are the most commonly involved parts of ectopic endometrium. Women of childbearing age are the main patients with endometriosis, and the clinical manifestations of endometriosis are dysmenorrhea, abnormal menstruation, and sexual pain (3). When the staging standard of endometriosis reaches the stage III-IV of the revised American Fertility Society classification (r-AFS) scoring system, it will lead to infertility and greatly affect the daily life and fertility of patients (4).

At present, laparoscopic surgery is often used in clinical treatment of endometriosis. Because of its advantages such as less trauma and rapid postoperative recovery, most patients need conservative surgery to preserve their ovary. However, the fertility of patients with endometriosis who have infertility symptoms has not improved significantly. In recent years, clinical observation and related data show that laparoscopic surgery alone in the treatment of moderate to severe endometriosis patients with low actual cure rate, high recurrence rate and low success rate of postoperative pregnancy (5, 6). Therefore, some scholars suggest that laparoscopic surgery combined with drug therapy can promote the recovery of patients' fertility (7). Leuprorelin is a gonadotropin which can inhibit the function of the pituitary-gonadal system, inhibit the secretion of estrogen, regulate the level of ovarian hormone and promote pregnancy. In this study, laparoscopic surgery combined with leuprorelin was used to treat endometriosis with infertility, to explore the effect of this method on the hormone level and pregnancy rate, and to analyze the clinical records and follow-up data, so as to further explore the risk factors for postoperative recurrence, and to provide a theoretical basis for the treatment and prevention of recurrence of endometriosis with infertility.

DATA AND METHODS

General Information

A total of 158 patients with endometriosis associated with infertility were selected from January 2019 to June 2020 in our hospital and divided into the control group and the observation group using the random number method, with 79 patients in each group. Inclusion criteria: (1) Not pregnant for more than 1 year without contraception; (2) Ultrasonography showed that there was growth and infiltration outside endometrium, and repeated bleeding formed nodules and masses, which caused pain; (3) Patients who did not take hormone drugs within 6 months before the study; (4) The clinical data are complete. Exclusion criteria: (1) Cognitive dysfunction or mental illness; (2) Accompanied with dysfunction of heart, liver, kidney and other organs; (3) There are contraindications for operation; (4) There are drug contraindications; (5) Failed to meet the follow-up conditions. The control group: The age was (28.91 ± 3.06) years old, BMI was (22.19 ± 0.84) kg/m^2, and the duration of infertility was (4.13 ± 0.54) years. The observation group: The age was (29.43 ± 3.17) years old, BMI was (22.37 ± 0.92) kg/m^2 and the duration of infertility was (4.28 ± 0.62) years. There was no significant difference in general information such as age between the two groups ($P > 0.05$), indicating that they were comparable.

Research Methods

Laparoscopic Surgery

Both groups underwent routine examination after admission, and the operation time was from day 3 to day 7 after menstrual period. After general anesthesia, CO_2 pneumoperitoneum was performed. Various organs and tissues in the pelvic cavity and peritoneum were explored under the guidance of laparoscope, to master the specific location and scope of the lesions. According to the position, size and distribution of the lesions. For patients with pelvic adhesions, pelvic adhesions should be removed, and pelvic anatomy should be restored as quickly as possible. Electrocoagulation was performed in patients with obvious punctate deposits to reduce and remove ectopic focus. When clearing the ovarian cyst, the normal ovarian tissue should be kept as much as possible, and the ovary should be sutured after the operation to restore the normal morphology. During the operation, under the condition of not damaging bilateral ovaries and uterus, electrocoagulation was performed on the tiny lesions located on the surface of uterus, sacral ligament, peritoneum and pelvic wall. Then the pelvis was rinsed with normal saline, and sodium hyaluronate gel was applied to the wound surface to prevent secondary adhesion after the operation. After treatment, the patients in the two groups were followed up for 12 months.

The Control Group Was Treated With Laparoscopic Surgery Combined With Dydrogestone

On day 3 after laparoscopic surgery, 10 mg of dydrogestone (Manufacturer: Abbott Biologicals B.V, Registration CertificateNo. H20130110) was administered orally, twice a week, for a continuous period of 3 months.

Observation Group Using Laparoscopic Surgery Combined With Leuprorelin Treatment

The patient was given three subcutaneous injections of leuprorelin (Manufacturer: Ipsen Pharma Biotech, registration number H20090247) 3.75 mg on the 4th or 5th day after surgery, once every 1 menstrual cycle and for 3 months.

Observation Indicators

(1) Comparison of hormone levels between the two groups: On the 2nd and 3rd day of menstrual period before and after treatment, 4 ml of fasting venous blood were collected in the morning, and the hormone levels of luteinizing hormone, follicle stimulating hormone and estradiol were detected by ELISA after centrifugation.

(2) Comparison of the recurrence after 12 months between the two groups. Recurrence rate = number of recurrent cases/total cases ×100%.

(3) Comparison of pregnancy rates between the two groups: The number of successful pregnancies within 12 months after surgery in the two groups was counted. Successful pregnancy: On day 45 of gestation, gestational sac was found in the uterus by ultrasonography. Pregnancy rate = cases of successful pregnancy/total cases ×100%.

(4) Comparison of the incidence of adverse reactions between the two groups: The incidence of adverse reactions such as abnormal liver function, gastrointestinal reactions and irregular vaginal bleeding after treatment in the two groups was counted. Incidence of adverse reactions = cases of adverse reactions/total cases ×100%.

(5) According to the recurrence of patients after surgery, they were divided into recurrence group and non-recurrence group. The clinical medical records were collected to record the dysmenorrhea, r-AFS staging, unilateral/bilateral, maximum cyst diameter, rupture or not, and postoperative medication of the patients. Return visit was mainly conducted through telephone call and outpatient re-examination, to collect information about patients' postoperative recurrence and pregnancy. Criteria for recurrence: B-scan ultrasonography after surgery revealed new ovarian cysts, in which dense punctiform echoes with a diameter of at least 2 cm were more common, and the cysts did not disappear after several consecutive menstrual cycles, with or without elevated CA-125 and dysmenorrhea. To analyze the related factors of recurrence of endometriosis after treatment.

Statistical Methods

SPSS22.0 software was used for processing. Experimental data the measurement data such as luteinizing hormone, follicle stimulating hormone and estradiol level are expressed by mean standard deviation ($\bar{x}\pm s$), and the counting data such as recurrence rate and pregnancy rate are expressed by (%). Pairwise comparison of measurement data between groups was analyzed by t test. Data were counted by χ^2 test. Cox regression model includes variables that have influence on recurrence and clinically valuable factors by single factor analysis, and carries out multivariate analysis. The test level was $\alpha = 0.05$, and $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of Hormone Levels Between the Two Groups

There was no significant difference in hormone levels between the two groups before treatment ($P > 0.05$). After treatment, the levels of luteinizing hormone, follicle-stimulating hormone and estradiol in the two groups were significantly lower than those before treatment, and the levels in the observation group were significantly lower than those in the control group ($P < 0.05$). As shown in **Figures 1–3**.

Comparison of Recurrence After 12 Months Between the Two Groups

The recurrence rate at 12 months after operation in the observation group was lower than that in the control group ($P < 0.05$). As shown in **Figure 4**.

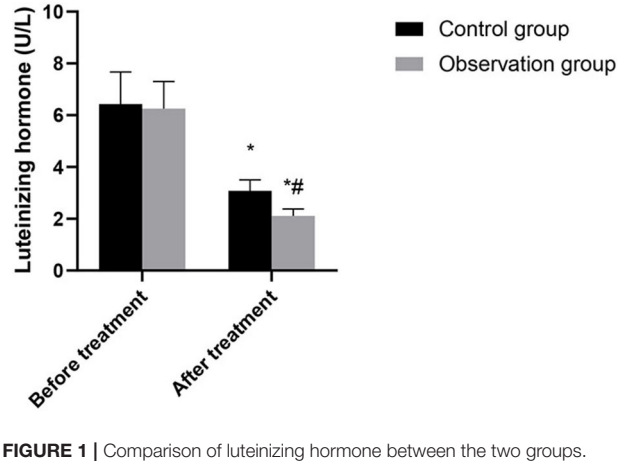

FIGURE 1 | Comparison of luteinizing hormone between the two groups. Compared with before treatment, $^{*}P < 0.05$. Compared with control group, $^{\#}P < 0.05$.

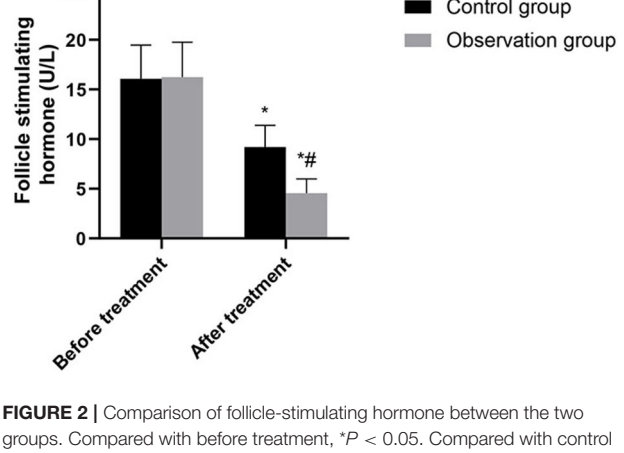

FIGURE 2 | Comparison of follicle-stimulating hormone between the two groups. Compared with before treatment, $^{*}P < 0.05$. Compared with control group, $^{\#}P < 0.05$.

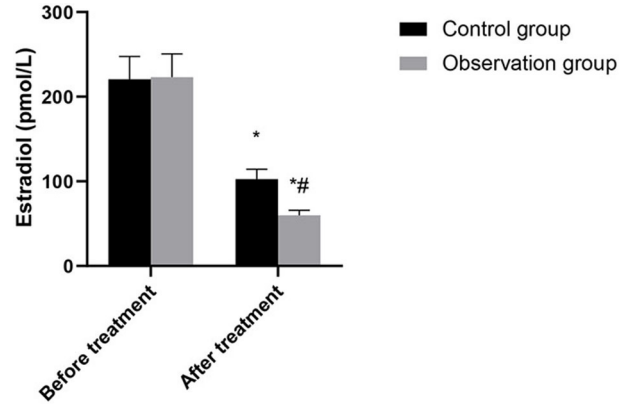

FIGURE 3 | Comparison of estradiol between the two groups. Compared with before treatment, $^{*}P < 0.05$. Compared with control group, $^{\#}P < 0.05$.

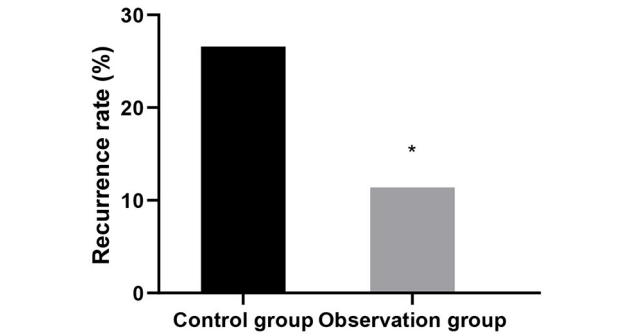

FIGURE 4 | Comparison of recurrence after 12 months between the two groups. Compared with control group,$^{*}P < 0.05$.

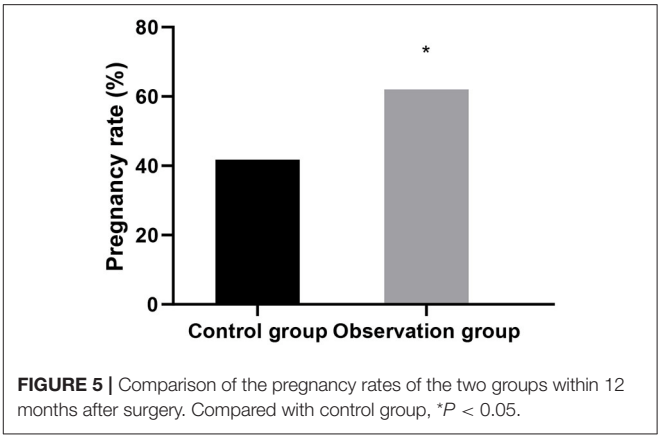

FIGURE 5 | Comparison of the pregnancy rates of the two groups within 12 months after surgery. Compared with control group, $^{*}P < 0.05$.

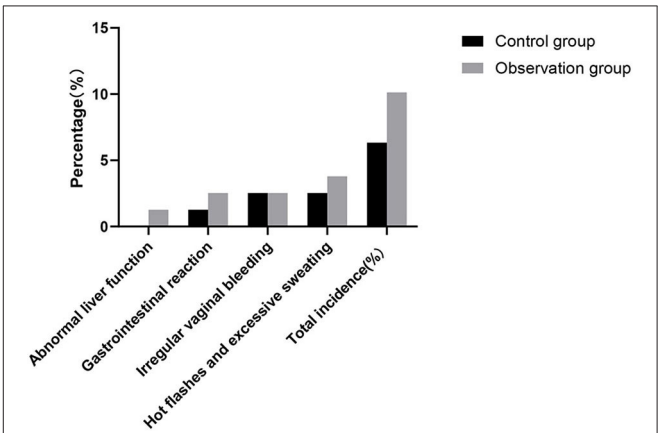

FIGURE 6 | Comparison of the incidence of adverse reactions between the two groups.

Comparison of the Pregnancy Rates of the Two Groups Within 12 Months After Surgery

The pregnancy rate in the observation group 12 months after surgery was higher than that in the control group ($P < 0.05$). See **Figure 5**.

Comparison of the Incidence of Adverse Reactions Between the Two Groups

The incidence rates of adverse reactions in the control group and the observation group were 6.33 and 10.13%, respectively. There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$). As shown in **Figure 6**.

Analysis of Single Factor Affecting Postoperative Recurrence in Patients With Endometriosis

Univariate analysis showed that preoperative dysmenorrhea, postoperative medication, and postoperative pregnancy had an impact on the postoperative recurrence of endometriosis ($P > 0.05$). As shown in **Table 1**.

Analysis of Multiple Factors Affecting Postoperative Recurrence in Patients With Endometriosis

Multivariate regression analysis showed that preoperative dysmenorrhea was an independent risk factor for postoperative recurrence in patients with endometriosis ($P < 0.05$). Postoperative pregnancy was a protective factor for postoperative recurrence in patients with endometriosis ($P < 0.05$). As shown in **Tables 2**, **3**.

DISCUSSION

Endometriosis often occurs in middle-aged women in the growing period. It does not occur before adolescence, while the ectopic focus after menopause shrinks and degrades gradually due to the decline of hormone levels. And the incidence rate is greatly reduced. Although endometriosis is a benign disease, its strong growth and metastasize ability

TABLE 1 | Univariate analysis of postoperative recurrence in patients with ems (*n*,%).

Factor	Recurrence group ($n = 30$)	Non-recurrent group ($n = 128$)	χ^2 value	*P*-value
Age (years)			2.294	0.130
≥30	17 (56.67)	53 (41.41)		
<30	13 (43.33)	75 (58.59)		
Body mass (kg/m^2)			2.557	0.110
≤24	24 (80.00)	83 (64.84)		
>24	6 (20.00)	45 (35.16)		
Preoperative dysmenorrhea			14.948	<0.001
Yes	26 (86.67)	61 (47.66)		
No	4 (13.33)	67 (52.34)		
r-AFS staging			3.738	0.053
Stage III	11 (36.67)	72 (56.25)		
Stage VI	19 (63.33)	56 (43.75)		
Cyst location			0.336	0.562
Unilateral	18 (60.00)	84 (65.62)		
Bilateral	12 (40.00)	44 (34.38)		
Maximum diameter of cyst (cm)			1.609	0.205
≤5	10 (33.33)	59 (46.09)		
>5	20 (66.67)	69 (53.91)		
Cyst rupture			0.834	0.361
Yes	2 (6.67)	4 (3.13)		
No	28 (93.33)	124 (96.88)		
Postoperative medication			5.925	0.015
Yes	9 (30.00)	70 (54.69)		
No	21 (70.00)	58 (45.31)		
Postoperative pregnancy			12.104	0.001
Yes	7 (23.33)	75 (58.59)		
No	23 (76.67)	53 (41.41)		

TABLE 2 | Assignment for multivariate logistic regression analysis.

Factors	Variables	Assignment
Preoperative dysmenorrhea	X1	No = 0, yes = 1
Postoperative medication	X2	No = 0, yes = 1
Postoperative pregnancy	X3	No = 0, yes = 1

TABLE 3 | Multi-factor analysis of postoperative recurrence in patients with endometriosis.

Variables	*B*	*S.E*	*Wals*	*P*	*OR*	95% *CI*
Preoperative dysmenorrhea	−1.284	0.427	9.042	0.015	0.277	0.120–0.639
Postoperative medication	0.841	0.537	2.453	0.241	2.319	0.809–6.642
Postoperative pregnancy	1.314	0.382	11.832	0.008	3.721	1.759–7.867

accelerates the development of the disease. Therefore, once the diagnosis is made clinically, effective treatment should be given as soon as possible, and surgical resection is the main treatment (1, 8, 9). Based on the pathogenesis of endometriosis and the treatment principle of laparoscopic surgery, we can know that laparoscopic surgery can loosen the adhered pelvic tissue, clear away the lesions, improve the pelvic environment and promote the recovery of the patient's body, but it can not effectively solve the infertility problem of patients.

In this study, dydrogesterone selected by the control group is a commonly used drug for the treatment of endometriosis. By inhibiting the activity of endometrial and ectopic focus cells, the diseased tissue gradually shrinks, but it can inhibit ovulation and endometrial development, which is not conducive to the implantation of pregnant eggs. At present, gonadotropin-releasing hormone agonists commonly used in clinic include goserelin, triptorelin and leuprorelin. It has been believed by Li et al. (10) that leuprorelin has a relatively mild effect on the ovary, and the incidence of adverse reactions is lower than that of triproline. Leuprorelin belongs to a luteinizing hormone releasing hormone derivative, can treat endometriosis by improving the pituitary function of patient, enhancing the resistance to proteolytic enzyme, reducing the response of women's ovaries, and relieve menstrual disorder caused by ovarian hormone secretion disorder. It is a relatively safe and reliable

adjuvant drug for laparoscopic surgery, which can promote the clinical treatment of endometriosis complicated with sterility (11–13).

This study showed that the levels of luteinizing hormone, follicle-stimulating hormone and estradiol in the observation group were lower than those in the control group after treatment. Accurately verified the mechanism of action of leuprorelin, that is, blocking the pituitary-gonadal axis and effectively inhibiting the release of sex hormones, so as to achieve the conditions of feedback inhibition of endometriosis (14). In addition, leuprorelin's treatment of endometriosis can effectively reduce the concentration of endogenous estrogen in patients, reduce the synthesis of protein, lead to atrophy of related tissues, inactivation of nucleic acids and uterine contraction, thus alleviating the symptoms of dysmenorrhea, obesity, infertility andso on (15). In this study, the recurrence rate and pregnancy rate after operation in the observation group were superior to those in the control group. It was confirmed that laparoscopic surgery combined with subcutaneous injection of leuprorelin could significantly improve the infertility and fertility status of patients. There was no significant difference between the two groups in the incidence of adverse reactions. The results showed that Mingliang Bingruilin was safe. After subcutaneous or intramuscular injection, leuprorelin can be hydrolyzed into four degradation products in the body, which are metabolized by the kidney. Therefore, the absorption rate of drug effect is high, and the effect on other organs and tissues of the body is weak, so drug safety is good (16).

At present, there are many versions of the mechanism of endometriosis, among which the widely accepted theory is endometrial implantation, which means that the endometrium debris dropped off during menstrual period flows backwards with the menstrual blood, enters the abdominal cavity through the fallopian tube, and is implanted on the surface of the ovary or other parts of the pelvis (17). After treatment, with the recovery of menstruation, endometrial cells in the menstrual blood may grow to form new endometriosis lesions, and ovulation may also lead to endometriosis. The problem of reducing the recurrence rate of endometriosis after operation has not yet been solved. Therefore, it is particularly important to explore the factors that affect the recurrence of endometriosis after operation, which is helpful to predicting the recurrence risk of patients, and then provide personalized treatment and long-term management for patients. This study showed that preoperative dysmenorrhea was an independent risk factor for postoperative recurrence, and postoperative pregnancy was a protective factor for postoperative recurrence. This result is the same as that reported in previous study (18). Progressive aggravation of dysmenorrhea is a common clinical symptom of endometriosis patients. Inflammatory response plays an important role in endometriosis. Interleukin-1 promotes prostaglandin synthesis leading to dysmenorrhea, while interleukin-6 accelerates the proliferation of ectopic endometrium cells leading to disease progression. Preoperative dysmenorrhea patients may have a more pelvic inflammatory environment, which will promote the emergence of new lesions and the recurrence of residual lesions after operation. As pointed out in the research by Chon et al. (19), dysmenorrhea and peeling of ovarian cyst are closely related to the recurrence rate after surgery. After 6–12 months of surgical treatment, the pelvic environment and ovarian function were improved, which is the key period of pregnancy. Therefore, for patients with endometriosis who are eager to give birth, we should encourage active pregnancy preparation after operation, which can not only effectively prevent postoperative recurrence, but also promote the patients' natural conception.

To sum up, laparoscopic surgery combined with leuprorelin in the treatment of endometriosis complicated with infertility can improve hormone levels of patients, increase pregnancy rate, and have a low recurrence rate. Preoperative dysmenorrhea is an independent risk factor for postoperative recurrence, which should be quantified and included in the recurrence risk prediction model. Postoperative pregnancy can reduce the recurrence rate after surgery, and patients with fertility requirements should be encouraged to actively prepare for pregnancy after surgery.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Zhoushan Women and Children Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LY is mainly responsible for the writing of the article and research design. YS is mainly responsible for data analysis. QF is responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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OPINION
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Application of Drug and Exercise Intervention in Postoperative Rehabilitation: A New Evaluation of Health Coordination Effect

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INTRODUCTION

Postoperative rehabilitation is an important process of physical function recovery after surgery. Surgery is an effective means to treat sport injuries, cardiovascular diseases, cancer and other physical diseases. However, some major operations are still accompanied by postoperative complications, such as pain, infection and physical dysfunction. Therefore, postoperative rehabilitation has become an important means to restore physical function and health after surgery. Rehabilitation includes a series of activities, such as pharmacology, exercise, nutrition, diet and social psychology (1). A large number of studies showed that drug and exercise intervention play an important role in postoperative rehabilitation.

Postoperative pain is a normal phenomenon after surgery, which requires drug intervention to relieve the pain. Some drugs have anti-inflammatory, analgesic and nutritional effects, such as dexamethasone, lidocaine, vitamin B12 and normal saline (2). It can relieve postoperative edema, pain and infection. There are also some analgesic drugs with few adverse reactions, such as non-steroidal anti-inflammatory drugs and opioid partial agonists, which also play an important role in relieving postoperative pain. Exercise therapy refers to rehabilitation therapy based on functional exercise. It can promote the energy metabolism of musculoskeletal, prevent joint spasm and slow down osteoporosis. At the same time, it can also improve the muscle strength and exercise endurance of the body. After operation, the patient's physical function is greatly reduced, and complications may occur. Rehabilitation is the continuation of surgery, which can restore the patient's physical function. As shown in **Figure 1**, patients receive treatment with some rehabilitation drugs. With the relief of body pain, they can do some basic physical activities.

A large number of studies have shown that drug and exercise intervention play an indispensable role in postoperative rehabilitation. In order to provide new ideas for the development of postoperative rehabilitation, this paper systematically studies the application of drug intervention, exercise intervention and their collaborative intervention in postoperative rehabilitation.

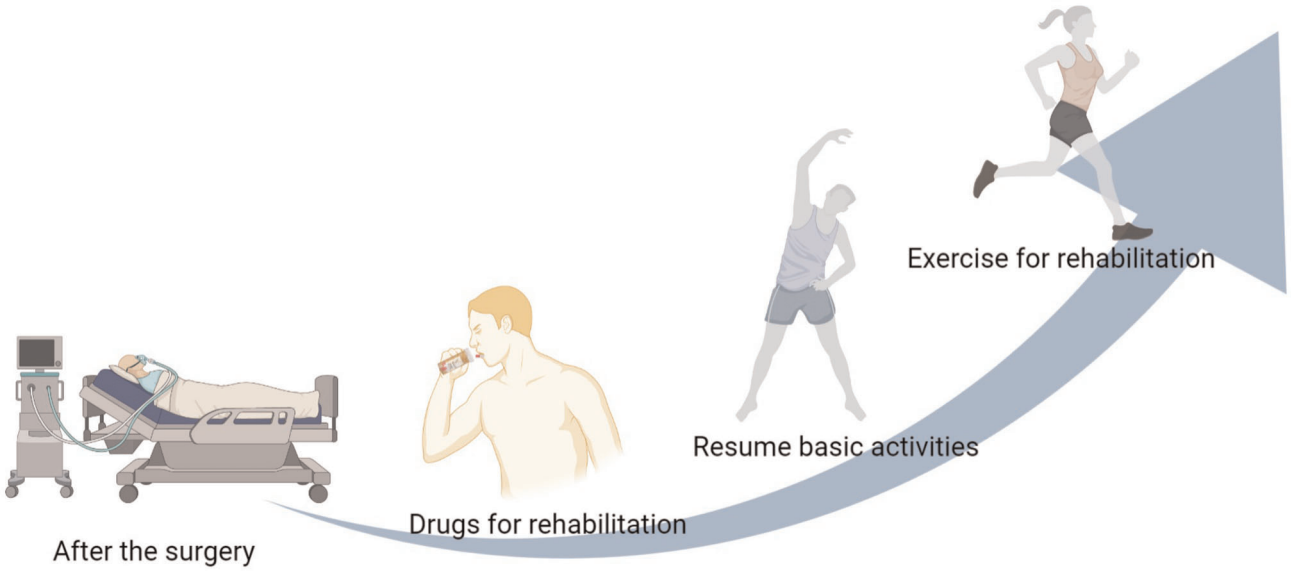

FIGURE 1 | Postoperative rehabilitation process.

POSTOPERATIVE REHABILITATION METHODS

Drug Intervention

Postoperative drug intervention is mainly used for anti-inflammation and analgesia. Traditionally, the main methods of postoperative analgesia are oral analgesia by intravenous injection of opioids and patient-controlled analgesia (PCA). Although opioid analgesics have certain effects, they usually cause side effects, for example, nausea, vomiting, itching, dizziness, insanity, bladder and intestinal dysfunction, etc (3). Some experience has been summarized in clinic for better pain management and accelerate patient rehabilitation. Some experience has been summarized in order to do a good job in pain management and accelerate the rehabilitation of patients clinically. For example, multi-mode labor analgesia is adopted, i.e., different labor analgesia techniques are combined and different analgesics with different action mechanisms are applied, so as to exert the additive or synergistic effect of analgesia.

Periarticular multimodal drug injection (PMDI), which included ropivacaine, epinephrine, and ketoprofen. It can effectively relieve postoperative pain and reduce the consumption of analgesic, and promote postoperative rehabilitation (4). Multimodal analgesia can be combined with pre-operative analgesic administration, for example, it can be composed of paracetamol, opioids and Cox-2 inhibitors. This approach is to reduce pain by preventing peripheral and central hypersensitivity reactions. Peripheral nerve block (PNB) is also used to control postoperative pain (3). Based on the fact that multiple drugs are mixed for nerve block during the operation, some researchers have proposed the method of impregnating drugs with gelatin sponge to increase the concentration of liquid around local nerve roots to treat reactive pain due to nerve root edema in the early stage after operation. Drug mixtures used include ropivacaine, dexamethasone, and vitamin B12 (2). This method also has certain limitations, such as repeated pain after surgery and drug dependence.

Drug intervention is no longer limited to one drug or method for postoperative rehabilitation. The combination of multiple drugs can improve the efficacy, but there are also certain side effects.

Exercise Intervention

Exercise has the effect of a "multi-effect drug". Moderate and regular physical activity can reduce the occurrence of cardiovascular disease. Improvements in cardiovascular health and functional capacity can accelerate postoperative recovery and reduce mortality (5). Exercise is an important complement to all surgery. The types of exercise intervention are: aerobic exercise, resistance exercise, aerobic combined resistance exercise, home exercise and multi-mode exercise.

Resistance training is one of main components of postoperative rehabilitation and musculoskeletal system injuries. Exercise interventions for early postoperative patients after lung transplantation, mainly including power cycling, walking and resistance exercise, showed significant improvements in walking distance, lower limb muscle strength and quality of life (6, 7). In a one-year randomized controlled trial, a combination of high-intensity repetitive training and endurance training (cycling) significantly improved knee joint function after degenerative meniscectomy over other exercise programs that emphasized seperate elements (8). Muscle volume and strength will decrease significantly in older patients after surgery. Although high-intensity resistance training may pose a risk for musculoskeletal injury (9), chronic resistance (CR) exercise and chronic aerobic (CA) exercise are conducive to the postoperative functional

recovery and reduction of complications in elderly patients (10). Blood flow restriction (BFR) therapy, as a postoperative exercise intervention, has attracted wide attention in recent years. BFR therapy can stimulate muscle hypertrophy with benefits for cardiovascular health and postoperative pain (11).

Scientific and reasonable exercise intervention has the characteristics of high safety. It has a certain degree of relief and stability on postoperative pain in patients. Exercise intervention has increasingly become an effective way of postoperative rehabilitation.

Collaborative Interventions

Collaborative intervention refers to postoperative rehabilitation under the joint action of drugs and exercise. The goal of postoperative rehabilitation is to restore range of motion, intensity, endurance and body function while avoiding complications. Single technologies and drugs cannot eliminate postoperative morbidity and mortality. The combination of medication and exercise therapy may have a better effect on postoperative rehabilitation.

The use of postoperative analgesic drugs was controlled in two groups of experimental patients. Patients took non-steroidal anti-inflammatory drugs twice a day for the first 7 days. For the remaining 14 days, the dose of celecoxib was reduced to 100 mg. The group that started ROM on the first postoperative day showed significantly less postoperative pain than the group that started ROM on the seventh day (12).

While drug intervention in the early postoperative period played a role in analgesia and reducing inflammation, exercise is needed in the later postoperative period to better facilitate body recovery. Exercise earlier after surgery may also relieve pain.

CONCLUSION

(1) The effects of drug intervention and exercise intervention on postoperative rehabilitation have been confirmed by a large number of studies. Postoperative patients suffer from physical pain and decreased body function, and they must rely on drugs and exercise to recover health. (2) Drugs are used for postoperative rehabilitation, with the main purposes of anti-inflammation and analgesia. A mixture of multiple drugs was often used for intraoperative nerve block to relieve postoperative pain. Exercise intervention is mainly used to restore the body function, and it is also possible to avoid complications caused by postoperative long-term lying. (3) Both of them have some limitations and side effects while promoting postoperative rehabilitation. For example, long-time postoperative administration of analgesics may result in drug dependence, and inappropriate rehabilitation exercise may hinder wound healing or even lead to secondary injury. Drug and exercise synergy may work better in postoperative rehabilitation.

DISCUSSION

Drugs and exercise play an extremely important role in postoperative rehabilitation. The form and effect of a single drug or exercise need to be improved. Synergistic intervention of drugs and exercise is more conducive to the postoperative rehabilitation of patients, but at the same time, it puts forward higher requirements for the selection of drug dosage and exercise. There are few related studies. In the future, we should pay more attention to the role of exercise in the prevention of disease, and develop personalized and targeted disease prevention exercise prescription.

AUTHOR CONTRIBUTIONS

The manuscript was written through the contributions of all authors. All authors have read and agreed to the published version of the manuscript.

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Comparative Study of Dezocine and Ketorolac Tromethamine in Patient-Controlled Intravenous Analgesia of Laparoscopic Cholecystectomy

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Purpose: This study aimed to observe the application value of dezocine and ketorolac tromethamine in patient-controlled intravenous analgesia (PCIA) of patients undergoing laparoscopic cholecystectomy (LC).

Methods: A total of 154 patients who underwent LC surgery in our hospital and received PCIA after surgery from September 2020 to September 2021 were selected, they were divided into group A ($n = 77$) and group B ($n = 77$). Group A was given dezocine and group B was given ketorolac tromethamine. The analgesia, sedation, comfort, and adverse reactions of the two groups were closely observed at 4, 8, 12, and 24 h after surgery.

Results: At 4, 8, 12, and 24 h after surgery, the visual analog scale scores in group B were lower than those in group A ($P < 0.05$). At 4, 8, 12, and 24 h after surgery, the Ramsay scores in group B were higher than those in group A ($P < 0.05$). At 4, 8, 12, and 24 h after surgery, there was no significant difference in Bruggrmann comfort scale scores between the two groups ($P > 0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$).

Conclusion: Both dezocine and ketorolac tromethamine have high clinical application value in patients who underwent LC surgery and received PCIA, with higher patient comfort and fewer adverse reactions. But compared with dezocine, ketorolac tromethamine can achieve better sedative and analgesic effects, which is worthy of clinical promotion.

Keywords: laparoscopic cholecystectomy, dezocine, ketorolac tromethamine, patient-controlled intravenous analgesia, sedation

INTRODUCTION

Laparoscopic cholecystectomy (LC) has the advantages of short surgery time, good surgical vision, less trauma, less blood loss, easy recovery, and low infection rate, among others. It has been favored and accepted by clinicians and patients and has become the routine surgery of cholecystectomy (1). However, after LC, surgical trauma and pneumoperitoneum will lead to different degrees of physiological pain and discomfort in patients after surgery. This will cause a series of strong stress reactions in the body and may lead to fear, anxiety, irritability, and other adverse emotions, as well as respiratory, circulatory, endocrine, and other dysfunction of the body. These circumstances thus increase the disease burden of patients, slow down the recovery speed after surgery, and lower the quality of life (2, 3). According to the research report, the incidence of postoperative incision pain in patients who underwent LC is as high as 79.2%, and it mainly occurs within 24 h after surgery, which is not conducive to the physical and mental health of patients (4). Therefore, the analgesia and sedation for patients after LC has become an important link for patients to get through the postoperative pain period smoothly.

Relieving postoperative pain of patients undergoing LC is one of the important tasks for clinicians. At present, patient-controlled intravenous analgesia (PCIA) after LC has been widely used in clinics. PCIA refers to when patients feel pain, they can adjust the timing and dosage of intravenous injection of painkillers according to their needs, so as to meet the patient's analgesic needs (5). This method is easy to operate, has an obvious analgesic effect, and embodies the consciousness of patients' active participation in analgesia. Moreover, the injection dose of painkillers is within the range set by doctors, and it is safe (6). PCIA can relieve patients' pain, promote early recovery of patients, and reduce economic burden and medical disputes (7).

In recent years, a variety of analgesic drugs have been continuously and widely developed in the PCIA field. Dezocine and tromethamine ketorolac are both favored for PCIA in clinics. Both of them have certain analgesic effects, but there is limited clinical research on the difference of analgesic effects between these two analgesic methods. In this study, 154 patients who underwent LC surgery and were given PCIA after surgery were selected as the research object. We investigated the analgesic and sedative effects, comfort, and safety of dezocine and tromethamine ketorolac for PCIA.

MATERIALS AND METHODS

Research Object

In this study, 154 patients who underwent LC surgery in our hospital and received PCIA after surgery from September 2020 to September 2021 were selected, they were divided into group A ($n = 77$) and group B ($n = 77$). (1) Inclusion criteria were: compliance with surgical indications; normal mental and cognitive function; and complete case data. (2) Exclusion criteria were: already received second surgery; used drugs within 24 h of surgery that could affect the efficacy of the study drug; important organ dysfunction; drug dependent and/or drug addict; with severe immune system diseases; with severe hypertension and diabetes; and allergic to research drugs.

Research Methods

Patients in both groups were not given analgesia treatment before surgery. Patients were treated with LC, and the venous channel was established. Induction of anesthesia in the patient was carried out using midazolam 1.5 mg/kg, sufentanil 0.3 μg/kg, and rocuronium 0.6 mg/kg. Then, tracheal intubation anesthesia was administered using sevoflurane, sufentanil 0.15–0.3 μg/kg, and propofol 4 with a concentration of 1–2% during surgery. In the process of using PCIA, patients and their families should be informed of the correct use of analgesic pumps, including how to make analgesic score, how to give medicine by pressing, common side effects, and so on. After surgery, the two groups were connected with the patient-controlled analgesia pump, and all patients were given sufentanil 2 μg/kg. On this basis, group A was given dezocine 0.3 mg/kg, diluted with 100 ml normal saline, and intravenously pumped. Group B was given ketorolac tromethamine 2 mg/kg, diluted with 100 ml normal saline, and intravenously pumped. The infusion rate of the two groups was 2 ml/h, the single self-controlled pressing dose was 2 ml, and the locking time was 15 min. The duration of analgesia was individualized according to the patient's needs.

Observation Index

The analgesia, sedation, comfort, and adverse reactions of the two groups were closely observed at 4, 8, 12, and 24 h after surgery, and detailed records were made. (1) Analgesia: the visual analog scale (VAS) score was used. In brief, we took a 10 cm scale ruler and asked the patient to mark a scale that can represent their pain degree on the top using a scale of 10 points, with 0 point being painless and 10 points being severe pain. VAS score was assessed by medical staff who were unaware of the patient's condition. (2) Sedation: the Ramsay score was used with the following indicators: 1 point: Sober but anxious; 2 points: Quiet cooperation; 3 points: Sleepy but awake; 4 points: Shallow sleep could wake up; 5 points: Deep sleep but slow response; and 6 points: Deep sleep, no response to call. (3) Comfort: the Bruggrmann comfort scale (BCS) was used with the following scores: 0 point: Persistent pain; 1 point: Painless when quiet, heavy pain when breathing deeply or coughing; 2 points: Painless when quiet, slightly painful when breathing deeply or coughing; 3 points: Painless breathing; 4 points: Cough or other actions are painless; and 5-6 points: Excessive sedation. (4) Adverse reactions were recorded whether there were any adverse reactions such as nausea, vomiting, dizziness, dry mouth, skin pruritus, and urinary retention within 3 days after surgery in both groups.

Statistical Methods

For statistical analysis, SPSS 22 (Armonk, NY: IBM Corp.) was used for data processing. The measurement data conforming to the normal distribution were expressed as mean ± *SD*. Paired sample *t*-test was used for intra-group comparison, while an independent-sample *t*-test was used for inter-group comparison. The counting data were expressed by %, and the χ^2 test was used for comparison. $P < 0.05$, the difference was statistically significant.

TABLE 1 | Comparison of two groups of general information.

Group	Case number	Gender		Age(years)	Intraoperative blood loss (ml)	Surgery time (min)
		Male	Female			
Group A	77	42 (54.55%)	35 (45.45%)	45.92 ± 9.36	8.73 ± 1.24	90.35 ± 6.91
Group B	77	39 (50.65%)	38 (49.35%)	46.27 ± 9.50	8.56 ± 1.19	92.11 ± 7.05
χ^2/*t value*		0.234		0.230	0.867	1.564
P value		0.628		0.818	0.386	0.119

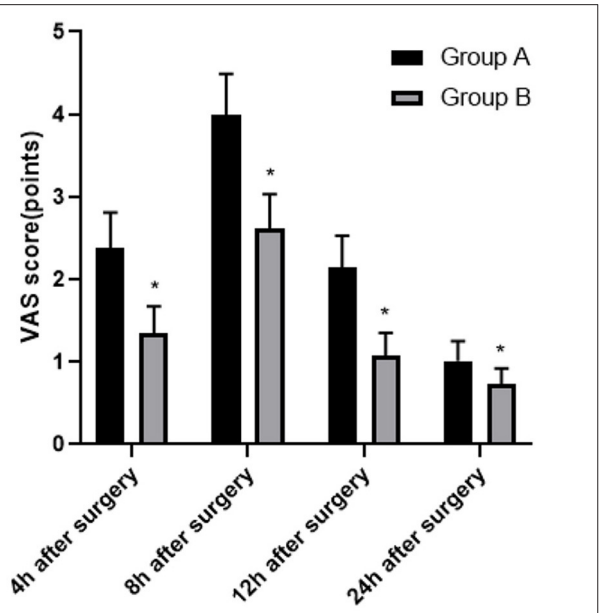

FIGURE 1 | Comparison of the analgesic situation between two groups. Compared with group A, *$P < 0.05$.

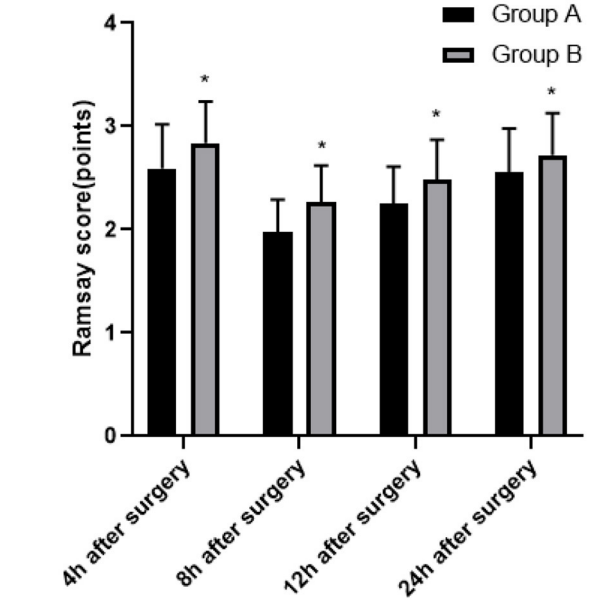

FIGURE 2 | Comparison of sedation situation between two groups. Compared with group A, *$P < 0.05$.

RESULTS

General Information

There was no significant difference in gender, age, intraoperative blood loss, and surgery time between the two groups ($P > 0.05$; **Table 1**).

Analgesic Situation

At 4, 8, 12, and 24 h after surgery, the VAS scores in group B were lower than those in group A ($P < 0.05$; **Figure 1**).

Sedation Situation

At 4, 8, 12, and 24 h after surgery, the Ramsay scores in group B were higher than those in group A ($P < 0.05$; **Figure 2**).

Comfort Situation

At 4, 8, 12, and 24 h after surgery, there was no significant difference in BCS scores between the two groups ($P > 0.05$; **Figure 3**).

Adverse Reactions

There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$; **Table 2**).

DISCUSSION

Laparoscopic cholecystectomy surgery has a significant positive effect as an effective method for the clinical treatment of cholecystitis, cholecystolithiasis, and other gallbladder diseases (8). However, due to factors such as diaphragm traction and visceral mucosa hypoxia after CO_2 pneumoperitoneum, patients after LC are prone to pain symptoms, which affects their physical and mental health and prognosis recovery (9). Postoperative pain can inhibit the patient's breathing activity, increase the patient's blood pressure, increase the oxygen consumption of myocardium, inhibit gastrointestinal peristalsis, reduce the body's resistance, and easily cause some negative emotions, thus affecting the prognosis of the disease (10, 11). Therefore, how to effectively relieve postoperative pain of patients is of great significance to the physical and mental health of patients. At

present, dezocine and ketorolac tromethamine are widely used in PCIA.

Dezocine is a potent opioid analgesic with both exciting and antagonistic effects (12). On the one hand, dezocine mainly achieves analgesic and sedative effects by exciting K receptors distributed in the brain, spinal cord, and brain stem (13). On the other hand, dezocine is also a μ-receptor antagonist, which has no typical μ-receptor dependence, so it can relax gastrointestinal smooth muscle with fewer adverse reactions (14). At the same time, dezocine can inhibit the activities of endothelin and renin in the body, reduce the release of angiotensin II and inflammatory factors, thereby reducing the excessive stress reaction of patients after LC (15). Dezocine has similar effects to morphine in onset time, action time, and intensity of action, and it is not easy to produce tolerance and can maintain the relative stability of blood volume and hemodynamics (16).

Ketorolac tromethamine is a non-steroidal anti-inflammatory drug with the best analgesic effect at present, and its analgesic effect is 7.5 times that of morphine, which is suitable for short-term treatment of acute moderate, and severe pain (17). It has strong analgesic and sedative effects in many aspects, and the specific mechanisms are as follows: ① Prostaglandin is an important mediator that causes inflammation such as redness, swelling, heat, and pain in the body. Ketorolac tromethamine can reduce the synthesis of prostaglandins by inhibiting the activity of peripheral and central cyclooxygenase, thereby reducing the degree of inflammatory reaction in tissues and relieving the stimulation of inflammatory medium to nerve endings, so as to achieve the analgesic effect (18). ② The medicine can reduce the response of pain nerves to endogenous inflammatory factors, and passivate peripheral nerves in advance to prevent peripheral nerve sensitization, thereby reducing the body's response to stressors, inhibiting sympathetic nerve excitation and thus reducing the level of stress factors, reducing the pain of patients after LC (19). ③ This medicine is not only beneficial to alleviate the wound inflammatory reaction and tissue edema caused by LC, but also affects the synthesis and activity of other nerve active substances and prevents the nerve active substances of nociceptive stimulation from being conducted to the spinal nerve (20). ④ Ketorolac tromethamine can selectively aggregate the pain site, thus increasing the drug concentration, which makes the analgesic effect stronger, the action time longer, and the sedative effect stronger (21). ⑤ Some scholars have found that ketorolac tromethamine may have an effect on the hypothalamic prostate system In addition, its analgesic effect may be related to the synthesis and participation of nitric oxide (22, 23). However, more experiments are needed to confirm this conclusion.

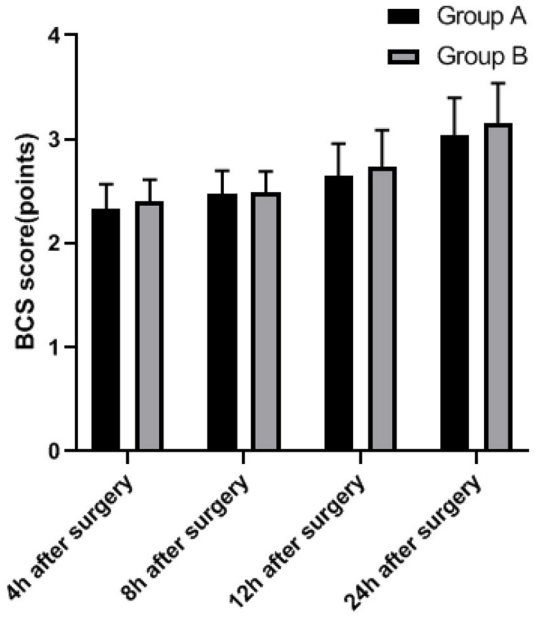

FIGURE 3 | Comparison of comfort between two groups.

The commonly used multimodal analgesia in clinical practice is sufentanil combined with dezocine. Sufentanil has a longer sedative effect time and less inhibitory effect on respiratory function. Sufentanil has strong lipophilicity and a higher rate of passing through the blood-brain barrier, thereby increasing the binding rate to plasma proteins, subsequently achieving an analgesic effect. The results showed that within 24 h after surgery, the VAS score of group B was lower, the Ramsay score of this group was higher, and there was no significant difference in BCS score and incidence of adverse reactions between group A and group B. We believe that both dezocine and ketorolac tromethamine have high clinical application value in patients who underwent LC surgery and received PCIA, with higher patient comfort and less adverse reactions. But compared with dezocine, ketorolac tromethamine can achieve better sedative and analgesic effects. At present, the common clinical adverse reactions are nausea and vomiting, and serotonin receptor blockers and glucocorticoids are the first-line drugs to deal with nausea and vomiting. If both are ineffective, droperidol can be used. In addition, other possible adverse reactions include dizziness, dry mouth, skin pruritus, and urinary retention, which

TABLE 2 | Comparison of adverse reactions between two groups.

Group	Case number	Nausea	Vomiting	Dizziness	Dry mouth	Skin pruritus	Urinary retention	Total
Group A	77	4 (5.19%)	2 (2.59%)	1 (1.30%)	1 (1.30%)	1 (1.30%)	0 (0.00%)	9 (11.69%)
Group B	77	2 (2.59%)	2 (2.59%)	1 (1.30%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	5 (6.49%)
χ^2 *value*								1.257
P value								0.262

generally do not require special treatment. It is worth mentioning that there are still some shortcomings in this study, such as the following: the scheme is a single-center study, and hence multi-center research needs to be carried out in the follow-up study. The infusion rates of both groups were 2 ml/h, and only one PCIA infusion rate was used. The PCIA infusion rate should be adjusted individually according to the needs of patients. The doses of dezocine and ketorolac tromethamine have not been classified hierarchically, and we still need to improve the research (24–26).

CONCLUSION

Both dezocine and ketorolac tromethamine have high clinical application value in patients who underwent LC surgery and received PCIA, with higher patient comfort and fewer adverse reactions. However, compared with dezocine, ketorolac tromethamine can achieve better sedative and analgesic effects, which 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 the Ethics Committee of the Second Affiliated Hospital of South China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YY is the mainly responsible for the writing of the article. SF is mainly responsible for research design. ZZ and XQ are mainly responsible for data analysis. ZC is responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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Analysis of Targeted Post-operative Nursing Outcome in 1246 Patients with Percutaneous Transhepatic Biliary Drainage

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Jaundice is a detection index in many disease conditions commonly characterized by yellowish staining of the skin and mucous membranes. This work studies the postoperative care outcome in 1,246 patients (669 males and 577 females) with obstructive jaundice who underwent percutaneous transhepatic biliary drainage (PTBD). These patients were admitted to the interventional vascular surgery department of our hospital from February 2017 to February 2022. From the results, frequent wound re-dressing and maintenance of the drainage tube had significant positive influence on wound healing and patient recovery. The data also showed strict adherence by patients to the doctor's recommendation advising them to visit the interventional specialist care clinic in time for wound dressing change and drainage tube maintenance. As a result, there was no significant difference in wound allergy, exudation, redness and loosening among patients. A cross-sectional analysis of the effect of age on recovery revealed variations in the healing pattern (wound loosening and the redness) between patients of different ages although the relationship is not very clear due to the limited sample size. Efficient drainage tube maintenance promoted recovery and prevented the occurrence of related complications such as PTBD tube blockage and biliary tract infection. The establishment of the interventional specialist care clinic used in this study additionally ensures patients' safety, and the incidence of complications have been reduced drastically. These achievements are attributable to the implementation of regular dressing change, drainage tube maintenance and health education for patients with PTBD tube. These practices have also improved on the level of specialty in nursing practice, increased the professional value of nurses and better recognition by the society.

Keywords: obstructive jaundice, Percutaneous transhepatic biliary drainage (PTBD), interventional specialist care clinic, data analysis, postoperative targeted nursing

INTRODUCTION

The occurrence of jaundice usually diagnosed by the yellowing of skin and mucous membrane serves as a marker in many diseases with its symptoms, treatment and prognosis varying accordingly (1–4). The Statistical Package for the Social Sciences (SPSS) software has been widely applied in the analysis of jaundice related data (5), whereas pathological analysis is

gradually used more frequently in jaundice works (6–8). Data analysis can be used to establish the relationship between some neonatal diseases and the rate of jaundice diagnosis (9–11). Gallbladder carcinoma (GBC) patients presenting with jaundice can benefit from resection (12–14). Another data-based research has analyzed mathematical models relevant in predicting the survival rates of patients with biliary atresia (15–17). Similarly, retrospective analysis of patients suffering from autoimmune pancreatitis (18, 19) and acute onset autoimmune hepatitis (20) has uncovered interesting conclusions about the clinical diagnosis of jaundice. These studies have contributed remarkably to the diagnosis and treatment of patients with jaundice-related symptoms and are also beneficial in motivating researchers to carry out retrospective statistical analysis preferably of large-scale data collected over a longtime span. Our review of the existing studies conducted on jaundice and its related pathologies reveal the need to conduct more research focused on analyzing the type and quality of clinical (nursing) care offered to patients with jaundice and how they influence recovery and patients' safety.

Obstructive jaundice is a clinical disease often caused by malignant tumors (1). It is treatable by percutaneous transhepatic biliary drainage (PTBD); a procedure involving percutaneous insertion of a special puncture needle into the intrahepatic bile duct under the guidance of X-ray or B-ultrasound, followed by catheterization and drainage to relieve the symptoms of obstruction (21, 22). Rapidly visualization of the intrahepatic and extrahepatic bile duct is guided by the injection of contrast agents. PTBD can reduce serum bilirubin in patients with malignant obstructive jaundice (MOJ), which aids to restore the patients' liver and kidney functions and improves on quality of life. PTBD also increases survival time during which different treatment options can be explored. For patients with benign obstructive jaundice, PTBD can benefit the rapid relief of symptoms of jaundice and infection, and provide access for subsequent treatment.This method was first proposed by Remolar in 1956 and has been widely employed in clinical practice ever since (23). Along with biliary stent implantation, PTBD can effectively alleviate obstructive jaundice. It has been extensively used as the preferred measure for clinical treatment of obstructive jaundice due to advantages such as ease of operation, higher success rate and relatively few postoperative complications (24, 25).

Many patients require long-term PTBD tube after surgery Therefore, standardized PTBD drainage tube care is pertinent to reduce related complications, ensure efficacy of the interventional surgery and improve patient's quality of life (26, 27). On the basis of providing continuous care, our hospital opened the first interventional specialist care clinic in China in February, 2017.Where we perform targeted nursing techniques and implement measures such as regular wound dressing change, replacement of catheter fixation devices, maintenance of drainage tubes, and specialized health education for patients after PTBD surgery. Our team also published the work titled "Expert consensus on drainage tube nursing of percutaneous transhepatic biliary drainage" (28).

The present study analyzes the effect of postoperative specialized outpatient nursing care on 1,246 patients (669 males and 577 females) treated with PTBD. The one-way analysis of variance (ANOVA) was used to study the impact of gender on wound loosening, wound health, redness, exudation, and allergy. Also, Chi-square test (cross-analysis) was used to analyze the relationship between age and treatment outcomes. Finally, Poisson regression analysis was used to investigate the significance of dressing change and drainage tube maintenance to superior wound healing. The results obtained from this study will enrich the research status of obstructive jaundice, emphasize on the importance of quality patient centered clinical care and supplement studies aimed at data analysis of conditions related to postoperative PTBD tube care in patients with obstructive jaundice.

OBJECTIVE AND METHODS

General Description

A total of 1,246 patients (669 males and 577 females) with obstructive jaundice were selected as the research subjects. These patients were admitted to the interventional vascular surgery department of our hospital from February, 2017 to February, 2022.

Inclusion and Exclusion Criteria

Inclusion criteria:

(1) Age: 20–83 years old;
(2) Conscious; can communicate and agreed with the data collection

Exclusion criteria:

(1) Unconscious; can't communicate effectively
(2) For various reasons, the patients are unable go to the intervention specialist nursing department for drainage tube care
(3) Abnormal cardiopulmonary function; patient's condition is not stable

Treatment

All the patients were treated successfully with PTBD in our hospital and advised to visit the interventional specialist care clinic after discharge where we performed puncture wound dressing change and drainage tube maintenance. The standardized procedure included patient evaluation, drainage tube rinse, replacement of drainage device and dressing change (including replacement of catheter fixation device), handling of special cases (emergencies), medical evaluation, specialized health education and other targeted approaches. Overall, the possibility was reduced for unscheduled emergency hospitalization due to various reasons like infection of the puncture wound, biliary tract infection, accidental tube blockage and extubation caused by loosening of a catheter fixing device. Also, patients experienced less discomfort due to effective pain management and medical expenses were reduced, benefiting the sustenance of national medical resources.

Observation Indicators

The relationship between wound healing and patient factors including gender, age and general conditions (including Stooling and urination, jaundice, fatigue and abdominal pain) was analyzed. Also, the effects of the regular interventions (dressing change and drainage tube maintenance) on the wound and drainage conditions were evaluated in outpatients with PTBD surgery.

Time Observation

The recorded data included the clinical symptoms of patients after surgery and the recovery time.

Statistical Analysis

Statistical analysis was performed on all experimental data using SPSS 23.0 software. Run-length analysis, ANOVA, chi-square test, correlation analysis, and Poisson regression analysis were used.

TABLE 1 | Gender and discharge diagnosis analysis.

Subject	Name	Gender		Amount to
		Woman	Man	
Discharge diagnosis	Malignant obstructive jaundice	557	614	1,171
	Obstructive jaundice	7	0	7
	Hepatolith	0	8	8
	Hepatapostema	0	30	30
	Hilar cholangiocarcinoma	5	3	8
	Liver metastasis of intestinal cancer	0	3	3
	Malignant tumor of pancreas ampulla	2	0	2
	Cholangiocarcinoma	1	3	4
	Gall stone	1	6	7
	Biliary obstruction	0	2	2
	Carcinoma of head of pancreas, malignant obstructive jaundice	3	0	3
Amount to		577	669	1,246

TABLE 2 | Age statistic analysis.

Name	Sample size	Statistical value z	p
Age	1,246	−1.384	0.166

TABLE 3 | Gender and wound analysis.

	Gender (mean ± standard deviation)		F	p
	woman ($n = 576$)	man ($n = 670$)		
wound loosening	1.95 ± 0.41	1.92 ± 0.42	0.572	0.450
recovered wound	10.57 ± 3.71	10.70 ± 3.54	0.195	0.659
wound redness	2.87 ± 1.43	3.17 ± 1.66	2.813	0.095
wound exudation	8.51 ± 4.06	9.02 ± 3.72	1.192	0.276
wound allergy	1.87 ± 0.41	1.93 ± 0.25	0.523	0.472

TABLE 4 | Analysis of variance between gender and general situation.

	Gender (mean ± SD)		F	p
	woman ($n = 576$)	man ($n = 670$)		
Stooling and urination	9.74 ± 2.24	9.70 ± 2.30	0.069	0.792
Jaundice	1.85 ± 0.35	1.91 ± 0.29	3.036	0.082
Fatigue	1.85 ± 0.36	1.92 ± 0.28	2.429	0.121
Abdominalgia	2.06 ± 0.67	2.15 ± 0.59	0.463	0.498

TABLE 5 | Age and wound Chi-square test statistics process values.

Item	name	value
Age * wound loose	Pearson Chi-square	105.930 ($p = 0.000$**)
	Continuously correct Yates chi-square	105.930 ($p = 0.000$**)
	Fisher chi-square	-
	$E \geq 5$	69 (54.76%)
	$1 \leq E < 5$	40 (31.75%)
	$E < 1$	17 (13.49%)
	Cnt	126
	N	1,231
	Df value of degree of freedom	62
Age * redness of wound	Pearson chi-square	87.095 ($p = 0.020$*)
	Continuously correct Yates chi-square	87.095 ($p = 0.020$*)
	Fisher chi-square	-
	$E \geq 5$	61 (48.41%)
	$1 \leq E < 5$	45 (35.71%)
	$E < 1$	20 (15.87%)
	Cnt	126
	n	1,201
	Df value of degree of freedom	62
Age * wound exudation	Pearson chi-square	64.641 ($p = 0.385$)
	Continuously correct Yates chi-square	64.641 ($p = 0.385$)
	Fisher chi-square	-
	$E \geq 5$	55 (43.65%)
	$1 \leq E < 5$	48 (38.10%)
	$E < 1$	23 (18.25%)
	Cnt	126
	n	1,198
	Df value of degree of freedom	62
Age * wound allergy	Pearson chi-square	53.801 ($p = 0.761$)
	Continuously correct Yates chi-square	53.801 ($p = 0.761$)
	Fisher chi-square	-
	$E \geq 5$	45 (35.71%)
	$1 \leq E < 5$	38 (30.16%)
	$E < 1$	43 (34.13%)
	Cnt	126
	n	1,234
	Df value of degree of freedom	62

*$p < 0.05$; **$p < 0.01$.

RESULTS AND DISCUSSION

Data screening: Originally, 1,297 patients were screened from the original data, where 1,246 patients were deemed valid with information suitable for analysis. **Table 1** shows the Gender and discharge diagnosis analysis. The invalid data including patients absent from the hospital after online registration, or had missing information like age and gender were deleted. In total, 1,246 patients (577 females and 669 males) were studied in this work.

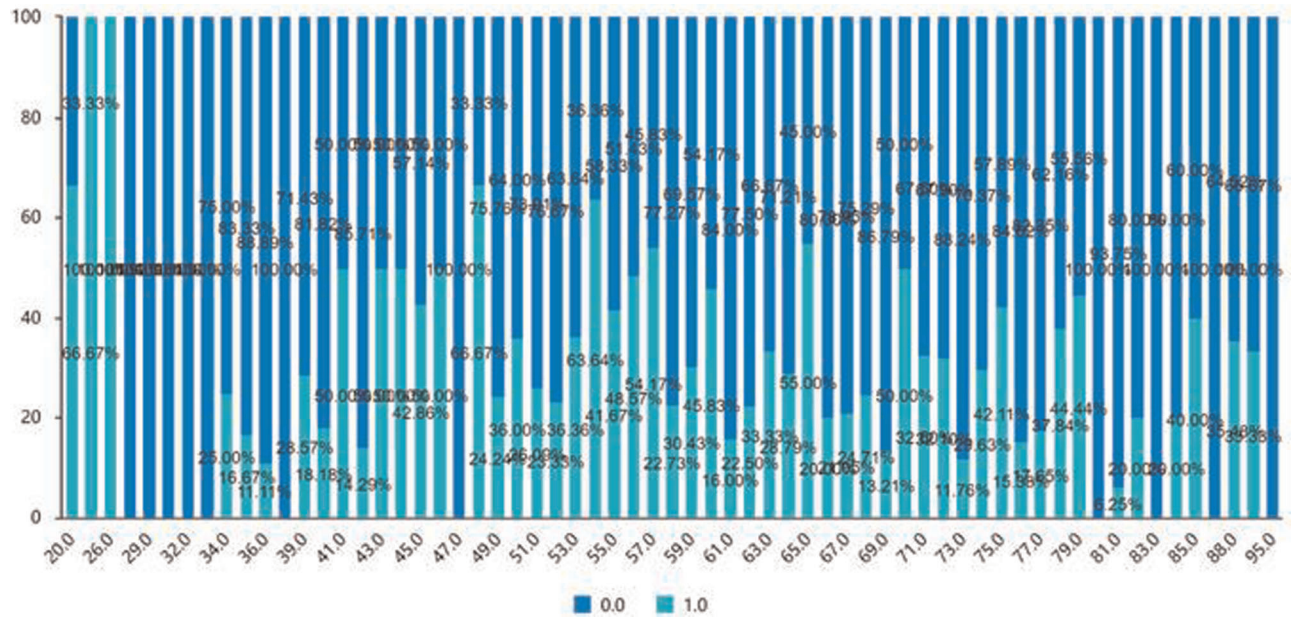

FIGURE 1 | Cross-sectional view of age and wound loosening (0 = none, 1 = yes).

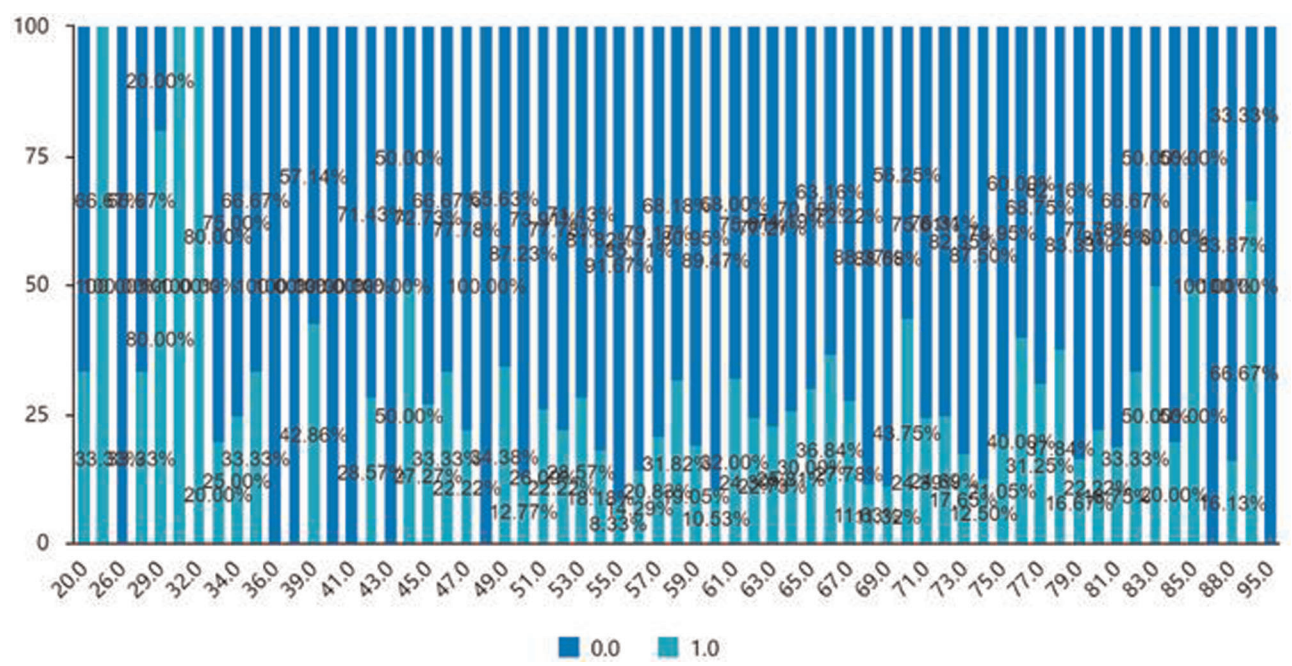

FIGURE 2 | Cross-sectional view of age and redness of the wound (0 = none, 1 = yes).

As shown in **Table 2**, the run-length test was used to analyze whether the ages of the patients used in the study followed a randomly distributed data sequence. The resulting p value ($p > 0.05$) confirms the original assumption that the data were subject to random distribution and true.

As shown in **Table 3**, one-way ANOVA was used to study the effect of gender on the differences observed in wound loosening, recovered wound, wound redness, wound exudation and wound allergy among patients. The analysis reveals that the patient's gender had no significant effect ($p > 0.05$) on the assessed parameters, suggesting that the healthy appearance and healing of the PTBD puncture site is not gender specific.

The one-way ANOVA (**Table 4**) was used to study the possible gender differences between observed stooling and urination, jaundice, fatigue and abdominal pain. Similar to the result obtained for the effect of gender on wound conditions, there was no significant differences in the appearance of these symptoms among both sexes ($p > 0.05$), meaning that there was consistency in the diagnosis of stooling and urination, jaundice, asthenia and abdominal pain.

The chi-square test (cross-analysis, **Table 5**) was used to study the differences in wound loosening, wound redness, wound exudation, and wound allergy among ages of patients. The analysis shows no significant age dependent differences between wound exudation and wound allergy ($p > 0.05$). Conversely, wound loosening and redness were significantly influenced by age ($p < 0.05$). As shown in **Figures 1** and **2** (the cross-sectional view of age and patients' conditions), age affects the wound loosening and the redness of the wound, although the relationship is not very clear due to the limited sample size.

Correlation analysis (**Table 6**) was used to study the relationship between age and general conditions including defecation, jaundice, fatigue, and abdominal pain. The Pearson correlation coefficient was used to indicate the strength of the correlation. The analysis showed no relationship between age and the symptoms ($p > 0.05$).

As shown in **Table 7**, correlation analysis was used to study the relationship between the time interval between two hospital visits and respective wound conditions (wound allergy, exudation, redness, loosening, recovered wound). Pearson correlation coefficient was used to indicate the strength of the correlation. The findings denote a lack of correlation between the time interval between two hospital visits and the wound parameters ($p > 0.05$). This result confirms the relevance of strict compliance. and timely visits to the intervention specialist care clinic for wound re-dressing and drainage tube maintenance.

As shown in **Table 8**, Poisson regression analysis was performed to ascertain the impact of the treatments (dressing change and drainage tube maintenance) on wound healing. The Poisson regression models were obtained as $\log(u) = 2.067 + 0.122$ and $\log(u) = 2.067 + 0.001$ for dressing change and drainage tube maintenance respectively, where u represents the expected mean.

Dressing change had a significant positive impact on wound healing as it showed significant statistics ($z = 9.936$, $p < 0.01$). It has an odds ratio (OR) value of 1.129, implying a 1.129-fold increase in wound healing with a unit increase in wound re-dressing.

Similarly, good drainage tube maintenance supported wound healing ($z = 2.839$, $p = 0.005 < 0.01$). An OR value of 1.001 indicates a 1.001-fold increase in wound healing following a unit increment in proper drainage tube maintenance.

Therefore, it is logical to recommend adequate dressing change and drainage tube maintenance to achieve wound healing and quicker patient's recovery.

Lastly, Pearson analysis was used to study the correlation between drainage tube maintenance and normal drainage condition as well as slag entrainment during drainage (**Table 9**). Pearson correlation coefficient was used as a measure of the strength of the correlation.

TABLE 6 | Pearson correlation analysis between age and general situation.

		Urine and stool	jaundice	fatigue	abdominalgia
Age	correlation coefficient	0.060	0.000	0.000	0.007
	p value	0.050	1.000	1.000	0.941

*$p < 0.05$; **$p < 0.01$.

TABLE 7 | Pearson correlation-detailed format.

		Wound allergy	Wound exudation	The wound was red	The wound is loose	The wound is good
Interval between two visits	correlation coefficient	−0.021	−0.032	−0.020	0.013	0
	p value	0.451	0.256	0.472	0.638	0.993

*$p < 0.05$; **$p < 0.01$.

TABLE 8 | Summary of Poisson regression analysis results ($n = 659$).

item	coefficient of regression	Standard error	*z value*	*p* value	OR value	OR value 95% CI
Dressing change	0.122	0.012	9.936	$p < 0.01$	1.129	1.103~1.157
Drainage tube maintenance	0.001	0.000	2.839	0.005	1.001	1.000~1.001
intercept	2.067	0.037	56.496	$p < 0.01$	7.900	7.354~8.488

Dependent variable: recovered wound.
Independent variables: dressing change and drainage tube maintenance.
McFadden R formula: 0.023.

TABLE 9 | Pearson correlation-detailed format.

Treatment Opinion: Dressing change		Treatment Opinion: pipe maintenance
Normal drainage	correlation coefficient	0.089**
P value	*P* value	0.006
Drainage slag	correlation coefficient	−0.109*
P value	*P* value	0.040

*$p < 0.05$; **$p < 0.01$.

A significant correlation between drainage tube maintenance and normal drainage condition ($p = 0.006$) informs us that ensuring correct maintenance of the PTBD tube is necessary for complication-free biliary drainage.

CONCLUSION

This work analyzed data obtained from 1,246 patients (669 males and 577 females) with obstructive jaundice who underwent PTBD surgery and subsequent follow up at the interventional specialist care clinic of our hospital from February 2017 to February 2022.

The results show:

(1) Dressing change and drainage tube maintenance both had significant positive influence on wound recovery.
(2) Timely (on-schedule) visits to the interventional specialist care clinic for wound dressing change and drainage tube maintenance encouraged desirable wound healing pattern and indifference in observed wound allergy, exudation, redness and loosening among patients.
(3) As discovered in the cross-sectional view of gender and age versus patients' conditions, gender was found to have no influence on any of the wound properties while age to a significant extent controlled wound loosening and redness. Nevertheless, this effect of age on wound healing remains unclear (due to the limited sample size in our study) signifying the need for further studies to unravel the underlying mechanism(s).
(4) Finally, appropriate drainage tube maintenance was imperative to guarantee normal biliary drainage, thus avoiding related complications such as PTBD tube blockage and biliary tract infection.

We can therefore conclude that the institutionalization of the interventional specialist care clinic and the incorporation of targeted post-operative nursing care (regular dressing change, good drainage tube maintenance and health education of patients after PTBD surgery) has contributed enormously to ensuring patients' recovery and safety, rightfully so because the incidences of complications have been remarkably minimized. The quality of overall nursing care has also improved and attracted well-deserved appreciation by the society.

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 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. The written informed consent includes The Handbook of Health Education and Nursing for Interventional Therapy of Biliary Tract, and the records of operation, wound dressing change and catheter maintenance.

AUTHOR CONTRIBUTIONS

XY contributed to conception and design of the study, and wrote the first draft of the manuscript. YQ, WM, HX, JL and BX contributed to manuscript revision, read, and project management. ZL contribute to the data collection and analysis. All authors contributed to the article and approved the submitted version.

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Impact of Medical Community Model on Intravenous Alteplase Door-to-Needle Times and Prognosis of Patients With Acute Ischemic Stroke

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Objective: In this study, we retrospectively analyzed 795 AIS patients who received intravenous alteplase for thrombolytic therapy in one third-class hospital or three second-class hospitals in Dongyang City and sought to evaluate the effects of the medical community model on intravenous alteplase door-to-needle time (DNT) and prognosis of patients with acute ischemic stroke.

Methods: According to whether the medical community model is established or not, 303 AIS patients (204 cases from the third-class hospital and 99 cases from three second-class hospitals) were assigned to control group unavailable to the medical community model and 492 AIS patients (297 cases from the third-class hospital, and 195 cases from three second-class hospitals) into observational group available to the medical community model.

Results: A higher thrombolysis rate, a shorter DNT, more patients with DNT $\leq$ 60 min and DNT $\leq$ 45 min, a shorter ONT, lower National Institutes of Health Stroke Scale (NIHSS) scores at 24 h, 7 d, 14 d, and modified Rankin scale (mRS) scores at 3 months after thrombolytic therapy, a shorter length of hospital stay, and less hospitalization expense were found in the observational group than the control group. Subgroup analysis based on different-class hospitals revealed that the medical community model could reduce the DNT and ONT to increase the thrombolysis rate of AIS patients, especially in low-class hospitals. After the establishment of the medical community model, the AIS patients whether from the third-class hospital or three second-class hospitals exhibited lower NIHSS scores at 24 h, 7 d, 14 d after thrombolytic therapy ($p < 0.05$). After a 90-day follow-up for mRS scores, a significant difference was only noted in the mRS scores of AIS patients from the third-class hospital after establishing the medical community model ($p < 0.05$). It was also found that the medical community model led to reduced length of hospital stay and hospitalization expenses for AIS patients, especially for the second-class hospitals.

Conclusion: The data suggest that the medical community model could significantly reduce intravenous alteplase DNT and improve the prognosis of patients with AIS.

Keywords: medical community model, acute ischemic stroke, tissue-type plasminogen activator, intravenous alteplase, door-to-needle time

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INTRODUCTION

Stroke is a leading cause of death worldwide and a huge risk factor for disability. As reported in 2004, 15 million people suffered from stroke annually, including 5 million deaths and another 5 million permanent physical disabilities (1). Despite strengthened prevention and better control of risk factors such as smoking and blood pressure control. From 1990 to 2016, the overall incidence rate of stroke decreased, but more than 13 million people were newly diagnosed with stroke every year (2). The incidence of stroke increases with age and people aged 65 and over are at higher risk of stroke. In general, younger age groups under 50 cause a greater burden of stroke, especially in low and middle-income countries (3). Stroke is classified into five subtypes including ischemic stroke, hemorrhagic stroke, subarachnoid hemorrhage, cerebral venous thrombosis, and spinal cord stroke. Ischemic stroke is caused by a blockage of blood vessels that reduces the blood supply to a certain area of the brain (4).

Ischemic stroke is the most common subtype of stroke worldwide (5). The occurrence of ischemic stroke is associated with unalterable factors such as age, gender, and ethnicity, and accumulating risk factors such as unhealthy diet, alcohol consumption, smoking, hypertension, and physical inactivity increase stroke incidence (6). The intervention of intravenous thrombolysis (IVT) with tissue-type plasminogen activator (tPA) has been well established in patients with acute ischemic stroke (AIS). Intravenous alteplase as a recombinant tissue plasminogen activator (rtPA) is commonly used in the treatment of AIS (7, 8). The earlier IVT treatment stroke patients get, the greater the possibility of a good prognosis. Door-to-needle time (DNT) refers to the time from arrival at the hospital emergency room to the beginning of IVT. It is used to evaluate the quality of AIS care (9) and prognosis (10). Therefore, reducing the median DNT is the basic goal in the treatment of AIS patients. Hospital factors such as delayed diagnosis and the inability to determine eligibility are the leading reasons for extended DNT (11, 12).

Reduction in time for intravenous thrombolysis treatment increases the possibility of good results. Actually, previous studies have indicated that the establishment of new models, such as the Royal Melbourne Hospital thrombolysis model (13) and the Helsinki stroke thrombolysis model (12) for stroke patients might address hospital factors affecting increased DNT. In China, the majority of AIS patients had their first visits to second-class hospitals or community hospitals. Lack of experienced neurologists, equipment, and technologies due to hospital-level variation limited the rapid delivery of thrombolytic therapy rapidly to AIS patients after hospital admission, which may increase the risk of neurological deficits and poor prognosis (14). Accordingly, a new therapy model, known as the medical community model, has been developed to avoid considerably varied hospital-level outcomes for AIS patients in China. This study attempted to analyze the effect of the medical community model on DNT and the prognosis of AIS patients.

METHODS

Study Participants

At the end of December 2018, the medical community model covering one third-class hospital (Dongyang People's Hospital Affiliated to Wenzhou Medical University) or three second-class hospitals in Dongyang City of Zhejiang Province (China) has been established and implemented. There were 4,287 AIS patients who were admitted into either one third-class hospital (n = 2,552) or three second-class hospitals (n = 1,735) in Dongyang City between January 2017 and December 2018, and all of them were unavailable to the medical community model. There were 5,306 AIS patients who were admitted into either one third-class hospital (n =2,961) or three second-class hospitals (n =2,345) in Dongyang City between January 2019 and December 2020, and all of them were available to the medical community model. All in all, from January 2017 to December 2020, a total of 795 AIS patients had received intravenous alteplase for thrombolytic therapy in one third-class hospital (Dongyang People's Hospital Affiliated to Wenzhou Medical University) or three second-class hospitals in Dongyang City. According to whether the medical community model is established or not during patient admission, 303 AIS patients admitted the hospital between January 2017 and December 2018 were assigned into a control group; 492 AIS patients admitted to the hospital between January 2019 and December 2020 were assigned into an observational group. There were 204 cases from the third-class hospital and 99 cases from three second-class hospitals among 303 AIS patients unavailable to the medical community model and there were 297 cases from the third-class hospital and 195 cases from three second-class hospitals among 492 AIS patients available to the medical community model. The diagnosis of AIS was made according to the guidelines for diagnosis and treatment of AIS initiated by the Chinese Stroke Association (CSA) (15). AIS patients undergoing thrombolytic therapy eligible for recruitment must (1) be aged 18 years or older; (2) have the admission be the first for stroke during the study period; (3) be treated with intravenous rt-PA within 4.5 h of symptom onset; and (4) have a documented DNT. AIS patients undergoing thrombolytic therapy were excluded if they (1) experienced severe head trauma within the previous 3 months; (2) received arterial puncture at a noncompressible site within the previous 7 days; (3) had previous or current intracranial hemorrhage, such as cerebral parenchymal hemorrhage, intraventricular hemorrhage, subarachnoid hemorrhage, subdural/epidural hematoma; (4) had elevated blood pressure (systolic blood pressure $\geq$ 180 mmHg or diastolic blood pressure $\geq$ 100 mmHg); (5) had active bleeding or platelet counts $<100 \times 10^9$/L; (6) underwent oral anticoagulants therapy, with INR $>$ 1.7 or PT $>$ 15 s; (7) were diagnosed with intracranial tumor or massive intracranial aneurysm; (8) underwent intracranial or intraspinal surgery within the previous 3 months; (9) underwent low-molecular weight heparin therapy within the previous 24 h; (10) had oral administration of thrombin inhibitor or factor Xa inhibitor within 48 h; (11) had a level of blood glucose <2.8 mmol/L or 22.22 mmol/L; (12) showed CT or MRI signs of $>$ 1/3 middle

cerebral artery infarctions; (13) were treated with a concomitant therapy with intra-arterial reperfusion techniques; or (14) were transferred to another acute care hospital, left against medical advice, or without a documented site of discharge disposition.

Before the Establishment of the Medical Community Model

Those who received intravenous alteplase for thrombolytic therapy in either one third-class hospital or three second-class hospitals in Dongyang City between January 2017 and December 2018 when the medical community model was absent were classified into the control group. At that time, AIS patients experienced a series of prehospital first aid processes before receiving thrombolytic therapy and some of them failed to receive rapid delivery of thrombolytic therapy resulting from the first visit to the hospital lack of thrombolytic therapy leading to delay in hospitalization.

After the Establishment of the Medical Community Model

Those who received intravenous alteplase for thrombolytic therapy in either one third-class hospital or three second-class hospitals in Dongyang City between January 2019 and December 2020 when the medical community model has been in service were classified into the observational group. The medical community model requires (1) an expert team with 10 neurologists including; (2) regular group learning knowledge about the guidelines for diagnosis and treatment of AIS initiated by the CSA and relevant scales used to evaluate AIS, training operation procedures for thrombolytic therapy, and communication for consensus on plan for thrombolytic therapy among team members; (3) optimization of thrombolytic therapy process, including modular training protocols for neurologists of medical community model, regular assignment of chief physicians to low-class hospitals belonging to medical community model for outpatient service and guidance, and designation of associate chief physicians and specialists into low-class hospitals belonging to medical community model as director or important members; (4) monthly regular training delivered by specialists of the medical community model, focusing on AIS, intravenous thrombolysis, rapid transfer, risk factors influencing DNT, how to reduce DNT and increase thrombolysis rate; and (5) constant optimization of thrombolytic therapy process under the medical community model, including rapidly handling 120 emergency phones, availability of neurologists for patients with suspected stroke within 15 min after arrival, availability of results of routine blood tests, blood biochemistry, coagulation analysis, and ECG examination within 45 min after arrival, CT examinations for initial diagnosis concurrent with patient data collection from family members within 25 min after arrival, initiation of intravenous thrombolysis in the absence of intracranial hemorrhage once the informed consent was obtained, and a series of examinations including National Institutes of Health Stroke Scale (NIHSS) scores, blood pressure, heart rate, and blood glucose.

Protocols for Intravenous Alteplase

All patients fulfilled indicators for IV-tPA administration (16) and were treated with intravenous alteplase (0.9 mg/kg body weight, maximum 90 mg) (Boehringer Ingelheim GmbH), with 10% of the dose given as a bolus followed by a 60-min infusion.

Data Collection

Demographic and clinical characteristics of AIS patients including gender, age, NIHSS scores on admission, smoking status, hypertension, diabetes mellitus, previous atrial fibrillation, hyperlipidemia, coronary heart disease, previous stroke (not within the previous 3 months), family history of cardiovascular diseases, hyperhomocysteinemia, systolic pressure, and diastolic pressure, thrombolysis rate, DNT, the proportion of patients with DNT $\leq$ 60 min and DNT $\leq$ 45 min, onset-to-needle time (ONT), National Institutes of Health Stroke Scale (NIHSS) scores 24 h, 7 days and 14 days after thrombolytic therapy with the purpose to evaluate the severity of neurological deficits, death or discharge, modified Rankin scale (mRS) scores at 3 months after thrombolytic therapy to evaluate the functional outcomes, length of hospital stay, and hospitalization expense were recorded.

The NIHSS contains 15 items of measures to evaluate the impact of AIS on different areas referring to the level of consciousness, neglect, motor strength, facial palsy, ataxia, dysarthria, and sensory loss, with scores ranging from 0 [no deficit] to 45 [most severe]. The mRS is a clinician-reported, 6-level outcome measure of global disability or dependence in the daily activities of stroke patients or other causes of neurological disability. The mRS scores range from 0 to 6, indicating a lack of symptoms to death. The mRs scores $\leq$ 2 at 90-day follow-up reflect good functional outcomes.

Statistical Analysis

Data analysis was performed using SPSS 20.0 software (IBM, USA). The normal distribution of measurement data was examined by the Shapiro Wilk test. If the data fail to be normally distributed, they are expressed as median (interquartile, range) and analyzed by the Mann-Whitney *U* test otherwise the data were expressed as mean $\pm$ standard deviation and analyzed by *t*-test. The enumeration data were presented as percentages and compared using the chi-square test. If the possibility (p) of difference were <0.05, the difference was considered statistically significant.

RESULTS

The Medical Community Model Increased the Thrombolysis Rate of AIS Patients

Among 4,287 AIS patients unavailable to the medical community model, there were 303 AIS patients who received intravenous alteplase for thrombolytic therapy in either one third-class hospital or three second-class hospitals, with the thrombolysis rate of 7.07%. Among 5,306 AIS patients available to the medical community model, there were 492 AIS patients who received intravenous alteplase for thrombolytic therapy in either one third-class hospital or three second-class hospitals, with the thrombolysis rate of 9.27%. A higher thrombolysis rate was found

TABLE 1 | Demographic and clinical characteristics of AIS patients receiving intravenous alteplase before and after medical community model.

Characteristic	Before ($n = 303$)	After ($n = 492$)	p
Gender (male/%)	169 (55.78%)	303 (61.59%)	0.105
Age (year)	69.71 ± 12.77	69.90 ± 12.90	0.840
NIHSS scores on admission	5 (3, 11)	4 (2, 9)	<0.001
Smoking status (yes/%)	53 (17.49%)	76 (15.45%)	0.448
Hypertension (yes/%)	208 (68.65%)	355 (72.15%)	0.291
Diabetes mellitus (yes/%)	54 (17.82%)	83 (16.87%)	0.730
Previous atrial fibrillation (yes/%)	50 (16.50%)	70 (14.23%)	0.384
Hyperlipidemia (yes/%)	19 (6.27%)	33 (6.71%)	0.809
Coronary heart disease (yes/%)	48 (15.84%)	70 (14.23%)	0.534
Previous stroke (yes/%)	35 (11.55%)	69 (14.02%)	0.315
Hyperhomocysteinemia (yes/%)	23 (7.59%)	23 (4.67%)	0.087
Systolic pressure (mmHg)	151.38 ± 19.75	153.86 ± 19.59	0.084
Diastolic pressure (mmHg)	84.75 ± 13.60	85.58 ± 12.92	0.389

TABLE 2 | The DNT and ONT of AIS patients receiving intravenous alteplase before and after medical community model.

Item	Before ($n = 303$)	After ($n = 492$)	t/χ^2	p
DNT (min)	58.16 ± 23.40	44.00 ± 18.82	9.374	<0.001
DNT ≤ 60 min (n/%)	187 (61.72%)	426 (86.59%)	8.106	<0.001
DNT ≤ 45 min (n/%)	77 (25.41%)	319 (64.84%)	10.800	<0.001
ONT (min)	145.50 ± 70.44	125.25 ± 58.12	2.089	<0.001

in the observational group than in the control group ($p < 0.001$). The control group consisted of 204 cases from the third-class hospital and 99 cases from three second-class hospitals and the observational group contained 297 cases from the third-class hospital and 195 cases from three second-class hospitals. As shown in **Table 1**, there was no significant difference with regard to gender, age, smoking status, hypertension, diabetes mellitus, previous atrial fibrillation, hyperlipidemia, coronary heart disease, previous stroke (not within the previous 3 months), hyperhomocysteinemia, systolic pressure, and diastolic pressure between the observational group and the control group ($p > 0.05$). Only the NIHSS scores on admission exhibited significant differences between the observational group and the control group ($p < 0.001$), showing that AIS patients had a reduced risk of neurological deficits after establishing the medical community model.

The Medical Community Model Reduced the DNT of AIS Patients Receiving Intravenous Alteplase

We next compared the DNT, the proportion of patients with DNT ≤ 60 min and DNT ≤ 45 min, and ONT of AIS patients between the observational group and the control group. It was found that the observational group exhibited shorter DNT and ONT, higher proportions of patients with DNT ≤ 60 min and DNT ≤ 45 min than the control group ($p < 0.001$, **Table 2**).

The Medical Community Model Improved the Prognosis of AIS Patients Receiving Intravenous Alteplase

To investigate the effects of medical community model establishment on the prognosis of patients with AIS, we compared the NIHSS scores 24 h, 7 days, and 14 days after thrombolytic therapy, death or discharge, mRS scores at 3 months after thrombolytic therapy, length of hospital stay, and hospitalization expense of AIS patients between the observational group and the control group. As listed in **Table 3**, AIS patients in the observational group showed lower NIHSS scores at 24 h, 7 d, 14 d, and mRS scores at 3 months after thrombolytic therapy, a shorter length of hospital stay, and less hospitalization expense than those in the control group ($p < 0.01$). These data revealed that the establishment of a medical community model could lead to a favorable prognosis for AIS patients receiving intravenous alteplase and reduce their economic burden.

The Medical Community Model Increased the Thrombolysis Rate of AIS Patients Whether in Third-Class or Second-Class Hospitals

Before the establishment of the medical community model, the thrombolysis rate of the third-class hospital was 8.00% (204/2,552), which was higher than that of three second-class hospitals 5.71% (99/1,735) ($p = 0.004$). Afore the establishment of the medical community model, the thrombolysis rate of the third-class hospital was 10.03% (297/2,961), which was higher than that of three second-class hospitals 8.32% (195/2,345) ($p = 0.036$). It was also noted that the establishment of the medical community model could increase the thrombolysis rate of the third-class hospital and the second-class hospital, respectively (8.00% vs. 10.03%, $p = 0.010$; 5.71% vs. 8.32%, $p = 0.001$). No significant difference was noted concerning gender, age, smoking status, hypertension, diabetes mellitus, previous atrial fibrillation, hyperlipidemia, coronary heart disease, previous stroke (not within the previous 3 months), hyperhomocysteinemia, systolic pressure, and diastolic pressure between AIS patients from the third-class hospital and three second-class hospitals before and after the establishment of medical community model (**Table 4**, $p > 0.05$).

The Medical Community Model Reduced the DNT of AIS Patients Receiving Intravenous Alteplase in Third-Class or Second-Class Hospitals

We next performed a subgroup analysis to investigate the effects of the medical community model establishment on the DNT and prognosis of AIS patients receiving intravenous alteplase from the third-class hospital and three second-class hospitals (**Table 5**). Whether before or after the establishment of the medical community model, the three second-class hospitals

TABLE 3 | The effects of medical community model establishment on the prognosis of AIS patients receiving intravenous alteplase.

Item	Before ($n = 303$)	After ($n = 492$)	*Z/t*	*p*
NIHSS scores at 24 h	4 (2, 8)	2 (1, 5)	−3.931	<0.001
NIHSS scores at 7 d	2 (0, 6)	1 (0, 4)	−3.204	0.001
NIHSS scores at 14 d	2 (0, 5)	1 (0, 4)	−2.651	0.008
mRS scores at 3 months	1 (1, 3)	1 (0, 3)	−2.592	0.010
Length of hospital stay (d)	12.43 ± 8.17	10.33 ± 5.31	4.392	<0.001
Hospitalization expense (yuan)	23,419.92 ± 20,130.52	18,532.58 ± 16,089.44	3.773	<0.001

TABLE 4 | Demographic and clinical characteristics of AIS patients receiving intravenous alteplase from the third-class hospital and three second-class hospitals before and after medical community model.

Characteristic	Before (n = 303)		After (n = 492)	
	Third-class ($n = 204$)	Two-class ($n = 99$)	Third-class ($n = 297$)	Two-class ($n = 195$)
Gender (male/%)	116 (56.86%)	54 (53.54%)	189 (63.64%)	114 (58.46%)
Age (year)	69.10 ± 13.05	70.97 ± 12.15	69.06 ± 13.59	71.18 ± 11.70
NIHSS scores on admission	5 (3, 10)	7 (3, 12)	4 (2, 9)	4 (2, 9)
Smoking status (yes/%)	38 (18.63%)	15 (15.15%)	48 (16.16%)	28 (14.36%)
Hypertension (yes/%)	140 (68.63%)	68 (68.69%)	207 (69.70%)	148 (75.90%)
Diabetes mellitus (yes/%)	35 (17.16%)	19 (19.19%)	44 (14.81%)	39 (20.00%)
Previous atrial fibrillation (yes/%)	39 (19.12%)	11 (11.11%)	43 (14.48%)	27 (13.85%)
Hyperlipidemia (yes/%)	9 (4.41%)	10 (10.10%)	21 (7.07%)	12 (6.15%)
Coronary heart disease (yes/%)	32 (15.69%)	16 (16.16%)	36 (12.12%)	34 (17.44%)
Previous stroke (yes/%)	23 (11.27%)	12 (12.12%)	36 (12.12%)	33 (16.92%)
Hyperhomocysteinemia (yes/%)	19 (9.31%)	4 (4.04%)	11 (3.70%)	12 (6.15%)
Systolic pressure (mmHg)	150.21 ± 19.06	153.80 ± 21.00	152.81 ± 18.91	155.46 ± 20.53
Diastolic pressure (mmHg)	83.97 ± 13.50	86.36 ± 13.73	84.99 ± 13.16	86.49 ± 12.53

TABLE 5 | The effects of medical community model establishment on the DNT and prognosis of AIS patients receiving intravenous alteplase from the third-class hospital and three second-class hospitals.

Item	Before ($n = 303$)		*p*	After ($n = 492$)		*p*
	Third-class ($n = 204$)	Two-class ($n = 99$)		Third-class ($n = 297$)	Two-class ($n = 195$)	
DNT (min)	61.93 ± 19.40	50.37 ± 28.60	<0.001	46.21 ± 16.35*	40.73 ± 21.63*	0.002
DNT ≤ 60 min (*n*/%)	119 (58.33%)	68 (68.69%)	0.101	261 (87.88%)*	165 (84.62%)*	0.344
DNT ≤ 45 min (*n*/%)	29 (14.22%)	48 (48.48%)	<0.001	177 (59.60%)*	142 (72.82%)*	0.003
ONT (min)	154.75 ± 76.42	126.42 ± 51.46	< 0.001	138.90 ± 68.75*	112.68 ± 43.42*	<0.001
NIHSS scores at 24 h	4 (1, 8)	4 (2, 6)	0.824	3 (1, 6)*	2 (1, 4.5)*	0.022
NIHSS scores at 7 d	2 (0, 6)	2 (0, 4)	0.253	1 (0, 4)*	1 (0, 3)*	0.059
NIHSS scores at 14 d	2 (0, 6)	2 (0, 4)	0.113	1 (0, 4)*	1 (0, 3)*	0.059
mRS scores at 3 months	1 (1, 3)	1 (0, 3)	0.307	1 (0, 3)*	1 (0, 3)	0.410
Length of hospital stay (d)	11.31 ± 7.40	14.75 ± 9.17	< 0.001	9.89 ± 5.40*	11.00 ± 5.11*	0.023
Hospitalization expense (yuan)	24,883.84 ± 23,241.18	20,403.36 ± 10,782.09	0.069	20,629.52 ± 19,614.99	15,254.49 ± 7,113.62*	<0.001

**Indicates the presence of a significant difference ($p < 0.05$) when before vs. after.*

showed shorter DNT and ONT, with a higher proportion of AIS patients with DNT ≤ 45 min than the third-class hospital ($p < 0.01$). These data might be explained by the phenomenon that some AIS patients regarded the third-class hospital as the first choice for admission instead of the second-class hospital, closer to their homes, leading to longer DNT and ONT in the

third-class hospital than that in three second-class hospitals. After the establishment of the medical community model, the AIS patients whether from the third-class hospital or three second-class hospitals exhibited shorter DNT and ONT, with higher proportions of DNT $\leq$ 45 min and 60 min ($p < 0.01$), suggesting that the medical community model could reduce the DNT and ONT to increase the thrombolysis rate of AIS patients, especially for low-class hospitals.

The Medical Community Model Improved the Prognosis of AIS Patients Receiving Intravenous Alteplase in Third-Class or Second-Class Hospitals

With regard to the effects of medical community model establishment on the prognosis of AIS patients receiving intravenous alteplase from the third-class hospital and three second-class hospitals, we found that only the NIHSS scores at 24 h after thrombolytic therapy exhibited a significant difference between the third-class hospital and three second-class hospital and the patients from three second-class hospitals had lower NIHSS scores at 24 h after thrombolytic therapy than those from the third-class hospital after the establishment of the medical community model ($p = 0.022$). These data might be explained by more critically ill patients with higher NIHSS scores at baseline transferred into the third-class hospital by establishing the medical community model. However, it was revealed that, after the establishment of the medical community model, the AIS patients whether from the third-class hospital or three second-class hospitals exhibited lower NIHSS scores at 24 h, 7 d, 14 d after thrombolytic therapy ($p < 0.05$), implying that the medical community model could significantly improve the prognosis of AIS patients receiving intravenous alteplase for both third- and second-class hospitals. After 90-day follow-up for mRS scores, a significant difference was only noted in the mRS scores of AIS patients from the third-class hospital after establishing the medical community model ($p < 0.05$), which may be also caused by mild-disease AIS patients arranged into the second-class hospital. Whether the medical community model was established or not, the AIS patients from the third-class hospital displayed a shorter length of hospital stay than those from three second-class hospitals, which may result from the fact that some patients from the third-class hospital would be transferred to the second-class hospitals upon disease stabilization. It was also found that the medical community model led to reduced length of hospital stay and hospitalization expenses of the AIS patients, especially for the second-class hospitals. The detailed data are listed in **Table 5**.

DISCUSSION

The treatment of AIS includes a multidisciplinary approach, which urgently needs the participation of intensive care experts. In early clinical trials, cerebral hemorrhage complications are easy to occur in thrombolytic therapy of AIS (17, 18). The first breakthrough innovation that significantly changed acute stroke care was the approval of intravenous tissue plasminogen activator (IV-tPA) by the Federal Drug Administration (FDA) in 1995 (19). IV-tPA has been the main treatment for stroke for about 25 years. For some patients with AIS, IV-tPA has proved to be an effective treatment as long as 4.5 h after onset (20). In recent years, increasing evidence indicated that every minute delay in IV-tPA is associated with worse clinical outcomes (20, 21). In this study, we focused on investigating the role of hospital factors affecting delays in IV-tPA treatment for AIS patients.

Actually, better outcomes have been achieved in some studies due to changes in medical intervention for stroke patients. Towfighi et al. (22) pointed out that intervention of team-based community health workers and advanced practice clinicians improves risk factors by controlling blood pressure after stroke, and this model was superior to usual care. A study by Sanossian et al. (23) revealed emergency medical services giving priority to sending patients with acute stroke to approved stroke centers is associated with good outcomes. It has been proven that the use of IV-tPA significantly increased (from 3.8 to 10.1%) and DNT decreased remarkably after patients with suspected stroke were sent directly to a stroke center (24). This present study implemented the usual care model (the patients received intravenous treatment in third-class or second-class hospitals in Dongyang city) and the medical community model for AIS patients in IV-tPA treatment and found that the thrombolysis rate was 7.07 and 9.27%, respectively. DNT is the main standard to evaluate thrombolytic quality of ASI. Our study discovered the patients in the medical community model showed shorter DNT and ONT than those treated with the usual care model, and there are more patients with DNT $\leq$ 60 min and DNT $\leq$ 45 min. These findings were similar to another research by Tran et al. (25), which demonstrated IVT rate of AIS patients with and without stroke team intervention was 20 and 14.4%, and the median DNT in stroke team intervention decreased 23 min. In addition, the proportion of patients with DNT $\leq$ 60 min and DNT $\leq$ 45 min was higher in stroke team intervention than that in non-intervention. Ajmi et al. (26) also manifested the median DNT decreased significantly from 27 min to 13 min after the implementation of team intervention. Although the correlation between DNT and the prognosis of ASI patients has been well-established in enormous studies, the factors related to the prognosis are different. Darehed et al. revealed each minute delay in DNT caused a series of problems including reduced survival, increased rate of cerebral hemorrhage and mobility, and worse activities of daily living (27). Since the conversion of the ischemic penumbra to irreversible infarction is time-dependent, the efficacy of IV-tPA treatment for AIS patients mainly depends on time. Early administration of IV-tPA increases the chance of saving brain injury and improves clinical outcomes (28, 29). In this study, the NIHSS scores at 24 h, 7 d, 14 d and mRS scores at 3 months after administration were lower in the AIS patients using the medical community model than those treated with the usual care model. Furthermore, the medical community model decreased length of hospital stay and hospitalization expense. Another research indicated the AIS patients receiving IV-tPA within 60 min of stroke symptom onset

have a higher complete recanalization rate, showed improvement in the nervous system, and obtained better mRS scores and lower mortality at 90-day follow-up compared to the patients receiving administration after 60 min of onset (21). Tsivgoulis et al. (30) found that administration of IV-tPA within "golden hour" (60 min of symptom onset) achieved favorable functional outcome (mRS $\leq$ 1 at 3 months) and better clinical recovery at 2 and 24 h (reduction in NIHSS score by $\geq$10 points or an absolute NIHSS score of $\leq$ 3 at 2 and 24 h, respectively). All these findings above suggested early IV-tPA treatment and reduction in DNT were beneficial to good clinical outcomes. The subgroup analysis in the present study showed that the medical community model reduces DNT, increased the thrombolysis rate, and improves the prognosis of the AIS patients whether from the third-class hospital or three second-class hospitals.

In summary, the medical community model was helpful to the early treatment of AIS patients, which might provide the chance to reduce time in DNT and increase the thrombolysis rate, and improve clinical outcomes. However, cross-sectional multicenter studies with more than 1-year or 3-year long-term follow-up analysis should be performed to strengthen the reliability of our results. Additionally, the case data were collected from the third-class or second-class hospitals in Dongyang city and the applicability in other hospitals needs to be discussed due to hospital-level variations in medical equipment and experiences of medical 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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Dongyang People's Hospital, Wenzhou Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HFL contributed significantly to the initiation and design of the study, manuscript drafting, and manuscript editing. DJX made efforts to conception, design of the study, and manuscript revision. YYX and LYW carried out clinical data collection, data analysis, and table making. All authors approved the manuscript.

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Clinical Study on Treatment of Acute Lower Extremity Arterial Embolism With Straub Thrombus Removal System

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Background: Acute lower extremity arterial embolism (ALEAE) is a common and frequently occurring disease in clinics. Although thrombectomy with arteriotomy has been widely used and developed in clinics, there is a high probability of embolic recurrence after operation. The present study investigated the clinical efficacy of the Straub Rotarex system in the treatment of ALEAE, as it could remove exfoliative substances in acute and chronic cavities and expose diseased vessels.

Materials and Methods: We accessed our institutional database and retrospectively screened all patients with ALEAEs who received surgical treatment between April 2018 and April 2021. To observe the clinical efficacy, surgical indicators, incidence of postoperative complications, and recurrence rate of treatment with Straub Rotarex system and arteriotomy thrombectomy and analyze the risk factors for recurrence of embolism after treatment with Straub Rotarex system by multivariate Logistic regression model.

Results: Finally, 64 patients were included as the research object. The total effective rates of the observation group and the control group after operation were 100 and 93.75% respectively, and there was no significant difference between the two groups ($P > 0.05$). The intraoperative blood loss, postoperative off-bed time and hospital stay time in the observation group were significantly lower than those in the control group, and the operation time and hospitalization expenses were significantly higher than those in the control group ($P < 0.05$). The incidence of postoperative complications in the observation group was 3.13%, which was significantly lower than 18.76% of that in the control group ($P < 0.05$). The recurrence rates of the observation group and the control group were 15.63 and 18.76%, respectively. There was no significant difference in the recurrence rate between the two groups ($P > 0.05$). Atrial fibrillation was an independent risk factor for recurrence after the Straub thrombus removal system ($P < 0.05$).

Conclusion: Straub thrombus removal system is an effective method for the treatment of ALEAE. Although it prolongs the operation time and increases the operation cost as compared with thrombectomy, it effectively improves the operation safety, postoperative life quality, and postoperative recovery, thus, worthy of clinical promotion. Atrial fibrillation

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is an independent risk factor for recurrent embolism after the Straub thrombus removal system. Paying attention to the clinical diagnosis and treatment of patients with atrial fibrillation is of great significance for patients to choose a reasonable treatment, prevent a recurrence, and improve the prognosis.

Keywords: acute lower extremity arterial embolism, straub thrombus removal system, minimally invasive interventions, influencing factor, curative effect

INTRODUCTION

Acute lower extremity arterial embolism (ALEAE) is a vascular surgical emergency caused by thrombus, atherosclerotic plaque, and other emboli falling off the heart or artery wall flowing with the blood and forming embolism at the artery of the lower extremity (1). There are many causes for the formation of AE, most of which are caused by slow blood flow and changes in blood viscosity of such patients, based on vascular stenosis caused by atherosclerotic plaques. Arteriotomy and thrombectomy is a common method for the treatment of ALEAE, which can effectively reduce the disability rate and mortality rate of patients with ALEAE. However, it also has the disadvantages of large trauma of thrombectomy and large postoperative reperfusion reaction (2). The Straub Rotarex system is suitable for the treatment of acute and chronic arterial thrombosis, and the system can be used for quickly removing intra-arterial thrombosis of the lower limbs, so that a good long-term patency rate is obtained after arterial surgery of the lower limbs. Due to its safe, reliable, and efficient clinical advantages, the Straub Rotarex system has been widely used abroad. However, there are few reports on it in China (3, 4). In this study, the therapeutic effects of the Straub thrombectomy system on ALEAE were investigated by comparison with thrombectomy through arteriotomy. Also, the related factors affecting the recurrence of Straub thrombectomy were analyzed, in order to provide a reference for the treatment selection and prognosis of patients with ALEAE.

INFORMATION AND METHODS

Research Object

This study was approved by our Ethics Committee and all patients were informed and agreed upon. All the data have been confirmed.

We visited our institutional database to retrospectively screen patients with ALEAE, who were treated in our hospital between April 2018 and April 2021.

Inclusion Criteria

All the patients met the AE diagnostic criteria (5) in Guidelines for Diagnosis and Treatment of Lower Limb Arteriosclerosis Obliterans issued by the Chinese Medical Association, including the sudden onset of pain, paresis, paresis, pulseless and pale symptoms in the affected limb of the patient, and the presence of emboli in the affected limb detected by computed tomography (CTA), as well as the existence of organic heart disease, atherosclerosis or a history of arterial embolism. 2) Informed of the study and signed an informed consent form.

Exclusion Criteria

Patients with combined distal arterial occlusion; 2) Patients with extensive gangrene of limbs due to excessive embolism time; 3) Those who had a taboo on the thrombolytic drugs used in this study; 4) Patients with moderate to severe anemia; 5) Patients who could not tolerate the surgical protocol selected in this; 6) Patients who cannot be treated with surgery.

Methods

The patients in observation group were treated with Straub Rotarex system. Preoperative evaluation results of CTA or doppler ultrasound examination of lower limbs were used to select an appropriate surgical approach. During the operation, standard angiography was performed using a sheath tube under DSA. After measuring the diameter of the target lesion vessel, a Rotarex catheter with an appropriate diameter was selected. During the operation, a 4F vertebral arterial catheter was used together with the guidewire of 0.035 inch and 0.018 inch through the occlusion segment, and the GW-0.018 inch guidewire was exchanged, followed by guidewire insertion into a Rotarex catheter and proximal to the occlusion segment. Heparin saline was injected into the catheter lumen before catheter sheath and vascular insertion. Heparin saline was infused into the catheter through the opening in the front of the catheter head. A sterile plastic syringe of appropriate size and without a needle was used to aspirate heparin saline and fill the entire catheter lumen. The catheter tip was moistened with heparin saline to ensure smooth passage through the catheter sheath. Under DSA fluoroscopy, a small forward or backward movement was performed at a speed of 5 mm/s through the occlusive segment and exceeded the occlusive segment by 1 cm. The angiographic evaluation was performed after the whole process was completed. If the residual stenosis is $> 30\%$ or there is no straight flow, PTA is feasible or stenting is performed if necessary, and at least one outflow tract of the inferior genicular artery is ensured.

Control group was treated with arterial resection and thrombectomy. Dissection of the distal artery at the site of the embolism was performed, and blocking forceps were used to control blood flow and prevent the thrombus from moving to other sites. The proximal artery was dissected and dissociated, and flow control continued with the forceps. A longitudinal incision was made at the embolization segment. Then, proximal blocking forceps were opened. The embolus was removed with Fogarty catheter and blocked again after the blood flow was cleared. Open the distal blocking forceps. If there is no blood

gusher, the distal embolus remains. Suture the vascular wall after unobstructed blood flow at both ends.

Both groups were treated with anti-infection and vasodilation as well as long-term anti-platelet and anticoagulation therapy.

Observation Index

The curative effects, operation indexes, postoperative complications, and recurrence of patients in the two groups were observed. The criterion for recurrence was the presence of thrombus in the lower extremities on CTA examination.

The efficacy, surgical indicators, postoperative complications, and recurrence of the two groups were observed. Efficacy was evaluated according to Cooley criteria (6). Cure: after treatment, the distal artery pulsation of the affected limb returned to normal, the symptoms of limb ischemia disappeared. Good: after treatment, the pulse of the distal limb was recovered, but weaker than that of the healthy side, and the symptoms of limb ischemia were improved. Poor: after treatment, the distal blood flow of the affected limb did not recover, the limb was compensated by collateral circulation, and there was ischemia Total effective rate= (cured cases + good cases)/total cases × 100%.

Statistical Methods

The SPSS22.0 software was used for processing. The continuous variable data of experimental data were expressed as mean standard deviation (± s) and adopted *t* test. The classified variable data and descriptive analysis were expressed as (%) and adopted χ^2 test. Multivariate Logistic regression model was used to analyze the significant factors in single-factor analysis. The test level was $\alpha = 0.05$, and $P < 0.05$ was considered statistically significant.

RESULTS

Finally, according to the inclusion and exclusion criteria, 64 patients were finally included as the research object. There was no significant difference in general information between the two groups ($P < 0.05$), as shown in **Table 1**.

As shown in **Table 2**, the total effective rate (100%) of the observation group was not significantly different from that of the control group (93.75%) ($P > 0.05$).

As shown in **Table 3**, the intraoperative blood loss, postoperative off-bed time, and hospital stay time in the observation group were lower than those in the control group, and the operation time and hospitalization expenses were higher than those in the control group. The differences were statistically significant ($P < 0.05$).

In the observation group, 1 (3.13%) case of reperfusion syndrome occurred after the operation. In the control group, there were 1 (3.13%) case of wound infection, 1 (3.13%) case of hematoma formation, 2 (6.25%) cases of reperfusion syndrome and 2 (6.25%) cases of post-embolization syndrome after operation. The incidence of postoperative complications in the observation group (3.13%) was lower than that in the control group (18.76%) ($P < 0.05$). There were 5 cases (15.63%) of postoperative recurrence in the observation group and 6 cases

TABLE 1 | Comparison of general data of patients between the two groups.

Group	*n*	Gender (*n*)		Age (years old)	Average course of disease (h)	Smoking history (*n*)		Basic diseases (*n*)				
		Male	Female			Yes	No	Hypertension	Diabetes	Hyperlipidemia	Coronary heart disease	Atrial fibrillation
Control group	32	19	13	66.78 ± 8.94	13.07 ± 3.67	15	17	12	14	9	11	8
Observation group	32	18	14	67.25 ± 8.46	13.25 ± 3.87	13	19	14	15	9	9	7
χ^2/t	-	0.064	0.216	0.191	0.254	0.455						
P	-	0.800	0.830	0.849	0.614	0.978						

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

Group	*n*	Cure	Good	Poor	Total response rate
Control group	32	18 (56.25%)	12 (37.50%)	2 (6.25%)	30 (93.75%)
Observation group	32	21 (65.62%)	11 (34.38%)	0 (0.00%)	32 (100.00%)
χ^2					1.953
P					0.162

TABLE 3 | Comparison of surgical indexes between the two groups (*n*, ± s).

Group	*n*	intraoperative blood loss (mL)	operative time (min)	postoperative off-bed time (d)	hospital stay time (d)	hospitalization expenses (million Yuan)
Control group	32	67.73 ± 17.23	95.83 ± 19.45	4.23 ± 1.26	7.19 ± 2.07	5.78 ± 1.07
Observation group	32	56.41 ± 10.14	108.17 ± 22.47	1.54 ± 0.47	3.37 ± 1.03	8.63 ± 1.21
t		3.203	2.349	11.315	9.163	9.981
P		0.002	0.022	0.000	0.000	0.000

(18.76%) of postoperative recurrence in the control group, and the difference was not statistically significant ($P > 0.05$).

As shown in **Table 4**, univariate analysis showed that patients with recurrent or non-recurrent embolism had statistically significant differences in hypertension, diabetes, hyperlipidemia, coronary heart disease, and atrial fibrillation ($P < 0.05$).

The recurrence of embolism was taken as a dependent variable, and the factors with significant differences in **Table 4** were taken as independent variables to be included in the Logistic regression model. The assignments of the dependent variable and independent variable are shown in **Table 5**.

As shown in **Table 6**, atrial fibrillation was an independent risk factor for recurrence after treatment with the Straub Rotarex system ($P < 0.05$).

DISCUSSION

The ALEAE is a thrombotic disease caused by cardiac thrombosis, proximal arterial thrombosis and medical implants that fall off and embolize popliteal, femoral, and other lower limb arteries along with blood flow, seriously affecting the lower limb function and quality of life of patients (7, 8). Once embolization is formed, the distal limbs at the embolization site will suffer severe pain due to acute ischemia, which can lead to limb necrosis and gangrene in a short period of time, and even amputation and death and other serious consequences (9, 10). Therefore, timely intervention for patients with ALEAE is the key to improve the prognosis of patients.

The Straub Rotarex System Is an Effective Treatment for ALEAE After Systemic Therapy

Arteriotomy and thrombectomy are the main methods for clinical treatment of AE, which can effectively improve the ischemic symptoms of patients with AE. However, this method has some practical defects, such as large trauma of thrombectomy, inability to timely intervene in potential artery stenosis, and large reperfusion reaction (11). The Straub Rotarex system is a highly efficient mechanical thrombectomy device consisting of a rotary catheter package, power parts, and control handles. In addition, conventional Seldinger technique puncture and intubation can be used during surgery, with less trauma. Also, due to the guidance of guidewires during the operation, the rotary-cut catheter is easy to reach the position, and it is not easy to damage the blood vessel with the protection of the guide wires. In addition, the catheter and the power component can be separated automatically when the resistance is too high through electromagnetic linkage. If the fibrous tissue is stuck to the catheter head, it can be relieved by reverse rotation, and no lubricant or cooling equipment is required, so the Straub Rotarex system thrombosis cutter is easy to operate and safe to use (12).

In this study, the Straub Rotarex system was compared with thrombectomy in terms of surgical efficacy, surgical indicators, postoperative complications, and embolic recurrence, to explore its clinical application value. The results showed that the therapeutic effect of Straub Rotarex system reached 100%, and the recurrence rate of postoperative embolism was not significantly different from that of open thrombectomy. Also, compared with the thrombectomy and thrombectomy, the operation intraoperative blood loss with the Straub Rotarex system was significantly reduced, the patient's getting out of bed and hospital stay-time were shortened, and the incidence of postoperative complications was reduced. The reason is that the catheter head is shorter, and the knife head does not directly contact the vascular wall, which reduces the stimulation and injury to the vascular wall (13). At the same time, the Straub Rotarex system removes thrombus from the iliac, superficial femoris, popliteal and deep femoris, anterior and posterior tibial arteries, and the beginning of the peroneal artery. The emboli are, then, smashed and transported externally with a built-in blade, effectively preventing distal embolism. Also, the time

TABLE 4 | Univariate analysis of embolic relapse after treatment with the straub rotarex system (*n*, %).

Clinical pathological features		Recur ($n = 5$)	No recur ($n = 27$)	χ^2	*P*
Ggender	Male	4 (80.00%)	15 (55.56%)	1.045	0.307
	Female	1 (20.00%)	12 (44.44%)		
Age (year)	≤65	2 (40.00%)	17 (62.96%)	0.922	0.337
	>65	3 (60.00%)	10 (37.04%)		
Smoking history	Yes	4 (80.00%)	11 (40.74%)	2.611	0.106
	No	1 (20.00%)	16 (59.26%)		
Hypertension	Yes	4 (80.00%)	8 (29.63%)	4.567	0.033
	No	1 (20.00%)	19 (70.37%)		
Diabetes	Yes	5 (100.00%)	9 (33.33%)	7.619	0.006
	No	0 (0.00%)	18 (66.67%)		
Hyperlipidemia	Yes	4 (80.00%)	5 (18.52%)	7.889	0.005
	No	1 (20.00%)	22 (81.48%)		
Coronary heart disease	Yes	4 (80.00%)	7 (25.93%)	5.468	0.019
	No	1 (20.00%)	20 (74.07%)		
Atrial fibrillation	Yes	5 (100.00%)	3 (11.11%)	4.678	0.031
	No	0 (0.00%)	24 (88.89%)		
Types of postoperative antiplatelet drugs	Aspirin	2 (40%)	14 (51.85%)	0.237	0.626
	Clopidogrel	3 (60%)	13 (48.15%)		
Types of anticoagulants after operation	warfarin	4 (80.00%)	12 (44.44%)	2.133	0.144
	rivaroxaban	1 (20.00%)	15 (55.56%)		

of intracavitary operation is short, which reduces the risk of intraoperative bleeding (14, 15).

Atrial Fibrillation Is an Independent Risk Factor for Recurrent Embolic Events After Straub Thrombus Removal System

Patients with ALEAE are at high risk for re-embolization after surgery. In this study, 10 relevant factors including combination of basic diseases, cardiovascular diseases, and drug use were included as variables in the multivariate logistic regression model to analyze the influencing factors of relapse in patients with ALEAE after the Straub Rotarex system treatment, in order to provide a reference for the selection of treatment plan for patients after operation and improvement of patient prognosis. Univariate analysis showed significant differences in hypertension, diabetes, hyperlipidemia, coronary heart disease, and atrial fibrillation between relapsed and non-relapsed patients ($P < 0.05$). Hypertension, diabetes, and hyperlipidemia can all induce the formation of cardiovascular plaques and increase the risk of thrombosis. Coronary heart disease is an incomplete and complete cardiovascular occlusion due to the formation of plaques in the coronary artery. If the plaques are ruptured, thrombus may be formed (16). Atrial fibrillation can lead to blood deposition in the atrium, thus, increasing the risk of thrombosis (17). Cardiac thrombosis is the main embolus source of ALEAE, and rheumatic heart disease and atrial fibrillation are the most common cardiovascular diseases. A cardiac thrombus

TABLE 5 | Variable assignment table of the risk factors for recurrence of embolism after treatment with the straub rotarex system.

Variable	The assignment
Dependent variable	
Recurrent embolism	No = 0, Yes = 1
Independent variables	
Hypertension	No = 0, Yes = 1
Diabetes	No = 0, Yes = 1
Hyperlipidemia	No = 0, Yes = 1
Coronary heart disease	No = 0, Yes = 1
Atrial fibrillation	No = 0, Yes = 1

TABLE 6 | Multifactor analysis of embolic recurrence after treatment with the straub rotarex system.

Factors	B	SE	Walds	df	Sig.	EXP (B)
Hypertension	0.451	0.922	0.531	1	0.077	1.570
Diabetes	0.823	1.291	0.494	1	0.089	2.277
Hyperlipidemia	0.547	1.035	0.511	1	0.084	1.728
Coronary heart disease	0.239	0.482	1.029	1	0.053	1.270
Atrial fibrillation	0.472	0.583	1.388	1	0.025	1.603

that falls off and flows with blood in the blood vessels and forms embolism at the arteries of lower limbs will cause the occurrence or recurrence of ALEAE (18). Multivariate analysis showed that atrial fibrillation was an independent risk factor for embolic recurrence after treatment with the Straub Rotarex system. Combined with previous studies, the reason is that atrial fibrillation, as a persistent arrhythmia, can cause irregular heart beating and atrial enlargement, resulting in blood stasis in the atrial and easily forming mural thrombi. Such blood clots are easy to fall off and lead to the recurrence of ALEAE. In addition, patients with atrial fibrillation often present with excessive heart rate, which is likely to lead to the occurrence of unstable heart thrombosis and thus the recurrence of embolism (19, 20).

CONCLUSION

In summary, Straub Thrombus removal system is an effective method for the treatment of ALEAE. Although it prolongs the operation time and increases the operation cost as compared with thrombectomy, it effectively improves the operation safety, postoperative life quality, and postoperative recovery, thus, worthy of clinical promotion. Atrial fibrillation is an independent risk factor for recurrent embolism after the Straub Thrombus removal system. Paying attention to the clinical diagnosis and treatment of patients with atrial fibrillation is of great significance for patients to choose a reasonable treatment, prevent recurrence, and improve the prognosis. In addition, the inadequacy of this study is affected by the small sample size, and the feasibility of the results of this study can be further verified by enlarging the sample size 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 our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LZ and QS are the mainly responsible for the writing of the article. HC is mainly responsible for research design. All authors contributed to the article and approved the submitted version.

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Analysis of the Therapeutic Effect and Prognostic Factors of 126 Patients With Hypertensive Cerebral Hemorrhage Treated by Soft-Channel Minimally Invasive Puncture and Drainage

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Background: Surgery is the main method for the clinical treatment of hypertensive cerebral hemorrhage. Traditional craniotomy faces the disadvantages of the long operation time, easy to cause secondary injury to patients during the operation, and prone to infection after the operation, which is not conducive to the rehabilitation of patients. At present, it is urgent to find a surgical scheme, which can clear hematoma in time, protect brain tissue, and effectively reduce surgical trauma in the clinic.

Materials and Methods: The case database of our hospital was consulted, and the clinical data of patients with hypertensive intracerebral hemorrhage (HICH) treated with soft channel minimally invasive puncture and drainage from February 2018 to October 2021 were retrospectively analyzed. Patients were evaluated for efficacy, and the changes in serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), homocysteine (Hcy), endothelin (ET), and vasopressin (AVP) levels before surgery, 3 days after surgery, and 7 days after surgery were analyzed. Clinical data were collected and Logistic regression was used to analyze the prognostic factors.

Results: Finally, according to the inclusion and exclusion criteria, 126 patients were selected as the research object. Among them, there were 24 cases (19.05%) of recovery, 47 cases (37.30%) of markedly effective, 34 cases (26.98%) of effective, 11 cases (8.73%) of ineffective, and 10 cases (7.94%) of death. The total effective rate was 83.33%. The hematoma was basically removed in 116 cases (92.06%). The average evacuation time of hematoma was (7.82 ± 1.63) days. Post-operative intracranial infection occurred in 2 cases (1.59%) and post-operative rebleeding occurred in 5 cases (3.97%). The average hospital stay was (34.16 ± 16.59) days. Serum CRP, TNF-α, IL-6, Hcy, ET, and AVP levels of all patients on the third and seventh days after surgery were lower than those before surgery, and those on the seventh day after surgery were lower than those on the third day after surgery ($p < 0.05$). The differences in pre-operative

Glasgow Coma Scale (GCS) score, bleeding volume, ventricular rupture, complicated cerebral hernia, and attack time to surgery between the good prognosis group and the bad prognosis group were statistically significant ($p < 0.05$). Pre-operative GCS score, bleeding volume, ventricular rupture, complicated cerebral hernia, and onset time to surgery were all independent factors that affect the prognosis of patients ($p < 0.05$).

Conclusion: Soft-channel minimally invasive puncture and drainage treatment of HICH has a significant effect, which is conducive to the complete removal of hematoma, reducing hospitalization time, while adjusting the balance and stability of various cytokines, and improving patient prognosis. Pre-operative GCS score, bleeding volume, rupture into the ventricle, complicated cerebral hernia, and time from onset to operation are all independent factors that affect the prognosis of patients.

Keywords: hypertensive cerebral hemorrhage, soft-channel minimally invasive puncture and drainage, efficacy, vasoactive factor, prognosis

INTRODUCTION

Hypertensive intracerebral hemorrhage (HICH) is a common acute lesion of cerebral vessels. It is a space-occupying lesion, which is caused by rupture, and hemorrhage of the cerebral artery is caused by long-term high blood pressure in patients, which then compresses the surrounding brain tissue, with a high mortality rate (1). In the past, craniotomy was usually performed to remove the intracerebral hematoma in patients. However, craniotomy takes a long time, which easily causes secondary injury to patients and post-operative infection, which is not conducive to patients' recovery. In addition to effectively reduce the surgical trauma of patients, promptly removing the hematoma and protecting the brain tissue are of great significance for improving the efficacy of HICH and the prognosis of patients (2). Soft-channel minimally invasive puncture and drainage has the advantages of no need for general anesthesia, small wound, and shortened operation time. It can not only effectively reduce intracranial pressure but also avoid damage to brain tissue by positioning the intracranial hematoma through CT and guiding the minimally invasive puncture and drainage, so the prognosis of most patients is good (3). Studies have found that in the progression of HICH, the activation of inflammatory factors and the destruction of the balance of vasoactive factors in patients have an impact on hemodynamics and vascular permeability *in vivo* and will further aggravate the progression of intracranial hematoma and brain tissue damage. Therefore, monitoring the dynamic changes of inflammatory factors and vasoactive factors is conducive to judging the progression and prognosis of patients with HICH (4). At present, there are no innovative findings about the value of soft-channel minimally invasive puncture and drainage in the treatment of HICH, and there are also few reports on the risk factors that affect the efficacy of this treatment. In this study, the clinical data of patients with HICH who were treated with soft-channel minimally invasive puncture and drainage were retrospectively analyzed, the efficacy of this surgical scheme for HICH was explored, and the factors affecting the prognosis of HICH patients were analyzed.

MATERIALS AND METHODS

This study was approved by our Ethics Committee and all patients were informed and agreed. All the data have been confirmed.

The case database of our hospital was consulted, and the clinical data of patients with HICH who were treated with soft-channel minimally invasive puncture and drainage from February 2018 to October 2021 were retrospectively analyzed. Inclusion criteria were as follows: all the patients met the relevant diagnostic criteria for HICH in the Guidelines for Diagnosis and Treatment of Intracerebral Hemorrhage in China (5) and were not complicated with other types of cerebral hemorrhage confirmed by cranial CT; all patients were treated within 24 h of onset. There was no prior history of stroke and no complications of circulatory and respiratory diseases. All follow-up data were complete and true.

All patients received soft-channel minimally invasive puncture drainage. A 64-row spiral HEAD CT was used to stereotaxically locate the midpoint of the largest layer of intracerebral hematoma as the puncture site, and the puncture was performed at the temporal part to avoid the main middle meningeal artery. After local anesthesia, an incision of 0.6–0.8 cm was made on the scalp at the puncture site. A hole was made in the skull, and the dura was electrocoagulation under direct vision, followed by a postcruciform incision of the dura, and cerebral cortical vessels were avoided. A core 12F silica gel drainage tube was used to puncture the hematoma cavity. When old blood was educed, the drainage tube was implanted with 1.0 cm toward the hematoma, and a small amount of normal saline was slowly injected for washing. After the drainage tube was placed, the scalp was sutured for fixation, and the three-way tube and the special external drainage device were connected for drainage. During the

operation, the drainage tube should pass through the center of the hematoma once as possible to avoid arbitrary adjustment of puncture direction. The strength should be controlled during aspiration, and fresh hemorrhage caused by violent aspiration of the hematoma under large negative pressure should not be allowed. After surgery, hematoma drainage was monitored dynamically under cranial CT, and urokinase was administered to dissolve the clot if necessary. After 3–5 days of catheter placement, the drainage tube was removed according to the drainage situation.

Patients were assessed according to the National Institute of Health Stroke Scale (NIHSS) score for efficacy that includes cured (no disability, 91–100% reduction in NIHSS score), markedly effective (achieving Grade 1–3 disability, 46–90% reduction in NIHSS score), effective (10–45% reduction in NIHSS score), and ineffective (<10% reduction or increase in NIHSS score). The total effective rate is the sum of recovery rate, apparent efficiency, and response rate. The death of patients in the two groups was recorded.

The clinical data that include the average evacuation time of hematoma, the incidence of post-operative intracranial infection, the incidence of post-operative rebleeding, and the average hospital stay were analyzed.

Serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), homocysteine (Hcy), endothelin (ET), and vasopressin (AVP) levels before surgery, 3 days after surgery, and 7 days after surgery in all patients were analyzed. CRP, IL-6, and TNF-α levels were detected by chemiluminescence enzyme analysis. The instrument adopts IMMULITE automatic chemiluminescence instrument produced by Siemens, and the detection reagent is provided by Siemens. The operation is carried out in accordance with the instrument regulations and reagent instructions. The levels of Hcy, ET, and AVP were determined by immunoturbidimetry.

All patients were followed up for 3 months. Patients with cured and effective clinical efficacy were divided into a good prognosis group, and patients with dead and ineffective were divided into a poor prognosis group. The basic conditions of all patients were recorded in detail, such as name, gender, age, admission, onset time, and follow-up for prognosis analysis.

SPSS22.0 software was used for processing. The continuous variable data of experimental data were expressed as mean standard deviation (SD) ($\bar{x} \pm s$) and adopted the t test. The classified variable data and descriptive analysis were expressed as (%) and adopted the χ^2 test. Logistic regression was used to analyze the related factors that affect the prognosis of patients with HICH. The test level was $\alpha = 0.05$, and $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

Finally, according to the inclusion and exclusion criteria, 126 patients were selected as the research object. There were 77 men and 49 women, with an average age of 56.38 ± 9.84 years old and an average bleeding volume of 45.82 ± 6.51 ml. There were 88 cases of basal ganglia hemorrhage, 19 cases of lobar hemorrhage, 13 cases of thalamic hemorrhage, 6 cases of cerebellar hemorrhage, and 21 cases of cerebral hemorrhage breaking into the ventricle.

As shown in **Table 1**, there were 24 cases (19.05%) of recovery, 47 cases (37.30%) of markedly effective, 34 cases (26.98%) of effective, 11 cases (8.73%) of ineffective, and 10 cases (7.94%) of death. The total effective rate is 83.33%.

As shown in **Table 2**, the hematoma was basically removed in 116 cases (92.06%). The average evacuation time of hematoma was 7.82 ± 1.63 days. Post-operative intracranial infection was occurred in 2 cases (1.59%) and post-operative rebleeding was occurred in 5 cases (3.97%). The average hospital stay was 34.16 ± 16.59 days.

As shown in **Table 3**, the serum levels of CRP, TNF-α, IL-6, Hcy, ET, and AVP of all patients on the 3 and 7 days after surgery were lower than those before surgery, and those on post-operative 7 days were lower than those on post-operative 3 days, the differences were statistically significant ($p < 0.05$).

As shown in **Table 4**, the differences in pre-operative GCS score, bleeding volume, ventricular rupture, complicated cerebral hernia, and attack time to surgery between the good prognosis group and the bad prognosis group were statistically significant ($p < 0.05$).

The prognosis of patients was taken as a dependent variable, and the factors with significant differences in **Table 4** are taken as independent variables to be included in the Logistic regression model. The assignments of the dependent variable and independent variable are shown in **Table 5**.

As shown in **Table 6**, pre-operative GCS score, bleeding volume, ventricular rupture, complicated cerebral hernia, and

TABLE 1 | Analysis of post-operative efficacy in all patients with hypertensive intracerebral hemorrhage (HICH) (*n*, %).

Cured	Markedly effective	Effective	Ineffective	Die	Total effective rate
24 (19.05%)	47 (37.30%)	34 (26.98%)	11 (8.73%)	10 (7.94%)	105 (83.33%)

TABLE 2 | Improvement of post-operative clinical symptoms in all patients with hypertensive intracerebral hemorrhage (HICH) (%, $\bar{x} \pm s$).

Evacuation of hematoma (cases)	Evacuation time of hematoma (days)	Post-operative intracranial infection (cases)	Post-operative rebleeding (cases)	Average hospitalization time (days)
116 (92.06%)	7.82 ± 1.63	2 (1.59%)	5 (3.97%)	34.16 ± 16.59

TABLE 3 | Changes in serum inflammatory factors and vasoactive factors in all patients before and after treatment (n, $\bar{x} \pm s$).

Time	CRP (mg/ml)	TNF-α (ng/ml)	IL-6 (pg/ml)	Hcy (μmol/L)	ET (ng/L)	AVP (ng/L)
Pre-operative	30.58 ± 4.92	3.85 ± 0.68	264.18 ± 32.08	25.62 ± 3.74	94.16 ± 10.83	19.84 ± 8.73
3 days after operation	24.09 ± 4.35*	2.59 ± 0.41*	174.51 ± 22.46*	19.65 ± 2.95*	82.56 ± 9.84*	15.49 ± 6.18*
7 days after operation	14.92 ± 3.86*#	1.74 ± 0.34*#	108.63 ± 17.54*#	13.58 ± 2.44*#	74.16 ± 8.37*#	10.95 ± 3.27*#
F	4.865	3.259	5.016	3.568	4.152	4.328
P	0.008	0.025	0.006	0.021	0.015	0.012

*Compared with that before surgery, *$p < 0.05$. Compared with the situation 3 days after surgery, #$p < 0.05$.*

TABLE 4 | Single-factor analysis of influencing prognosis of patients with hypertensive intracerebral hemorrhage (HICH) (n, %).

	Good prognosis group ($n = 105$)	Bad prognosis group ($n = 21$)	χ^2	P
Gender				
Male	64 (60.95%)	13 (61.90%)	0.167	0.934
Female	41 (39.05%)	8 (38.10%)		
Age				
≥50 years old	68 (64.76%)	10 (47.62%)	2.181	0.139
<50 years old	37 (35.24%)	11 (52.38%)		
Dyslipidemia				
Yes	83 (79.05%)	17 (80.95%)	0.201	0.653
No	22 (20.95%)	4 (19.05%)		
GCS score of pre-operative				
≥8 points	85 (80.95%)	8 (38.10%)	5.824	0.007
<8 points	20 (19.05%)	13 (61.90%)		
Amount of bleeding				
≥50 ml	64 (60.95%)	18 (85.71%)	5.235	0.010
<50 ml	41 (39.05%)	3 (14.29%)		
Bleeding site				
Basal ganglia hemorrhage	76 (72.38%)	12 (57.14%)	2.241	0.524
Lobar hemorrhage	14 (13.34%)	5 (23.81%)		
Thalamic hemorrhage	10 (9.52%)	3 (14.29%)		
Cerebellar hemorrhage	5 (4.76%)	1 (4.76%)		
Rupture into ventricle				
Yes	7 (6.67%)	14 (66.67%)	5.983	0.006
No	98 (93.33%)	7 (33.33%)		
Complicated with cerebral hernia				
Yes	16 (32.65%)	9 (55.38%)	4.937	0.015
No	89 (67.35%)	11 (44.62%)		
Time of operation				
≥12 h	51 (48.57%)	8 (38.10%)	4.336	0.019
<12 h	54 (51.43%)	13 (61.90%)		

onset time to surgery were all independent factors that affect the prognosis of patients ($p < 0.05$).

DISCUSSION

Hypertensive intracerebral hemorrhage is a serious non-invasive cerebral hemorrhage disease (6). In patients with HICH, the intracranial artery rupture and hemorrhage and hematoma will solidify and accumulate to compress brain tissue, thereby resulting in intracranial hypertension and structural damage of brain tissue. Moreover, in severe cases, it will lead to cerebral hernia and neurological dysfunction (7). In the past, the treatment for patients with HICH was mainly evacuation of hematoma through craniotomy. Although the hematoma could be completely removed under the visual state, the craniotomy operation was complex and tedious, the operation took a long time, which was likely to cause re-injury to the patient's brain

TABLE 5 | Assignment of independent risk factors affecting the prognosis of patients with hypertensive intracerebral hemorrhage (HICH).

Variable	The assignment
Dependent variable	
Prognosis	Good prognosis = 0, Bad prognosis = 1
Independent variables	
GCS score of pre-operative	<8 points = 0, ≥8points = 1
Amount of bleeding	<50 ml = 0, ≥50 ml = 1
Rupture into ventricle	No = 0, Yes = 1
Complicated with cerebral hernia	No = 0, Yes = 1
Time of operation	<12 h = 0 ,≥12 h = 1

TABLE 6 | Multivariate analysis of prognosis of patients.

Factor	*B*	*SE*	*Walds*	Sig.	Exp(B)
GCS score of pre-operative	−2.438	0.286	4.695	0.021	2.152
Amount of bleeding	2.058	0.493	4.583	0.023	2.067
Rupture into ventricle	2.354	0.254	6.547	0.008	1.853
Complicated with cerebral hernia	2.743	0.395	5.413	0.011	1.587
Time of operation	2.038	0.216	3.159	0.037	1.957

tissue and complicated infection after surgery, and the patients tolerated it. Therefore, it has become an important purpose to remove the hematoma and protect brain tissue in time, and at the same time, to reduce the surgical trauma of patients, so as to improve the surgical effect and the prognosis of patients (8, 9).

Soft-channel minimally invasive puncture and drainage, as a surgical approach with small trauma and low damage to patients, has been gradually applied to the clinical treatment of HICH in recent years (10). In this study, first of all, we used imaging methods, such as cranial CT, to locate the bleeding site, and at the same time, under the supervision of CT, drilled the skull and placed a special drainage tube to accurately puncture the hematoma, and slowly aspirated to remove the hematoma. Finally, urokinase is added to dissolve the massive hematoma and completely remove the residual hematoma (11). The results showed that the total effective rate and hematoma removal rate of 126 patients were 83.33 and 92.06%, respectively. The evacuation time and hospitalization time of hematoma were both relatively low. Only seven patients experienced post-operative intracranial infection and post-operative rebleeding. The reason was that when patients with HICH underwent soft-channel minimally invasive puncture drainage, the front end of the drainage tube was made of a material with good flexibility, so that secondary damage to brain tissue was not easy to occur during the intubation process. In addition, a closed drainage system was used during the operation, in which the drainage speed was manually controlled according to the changes in intracranial pressure, to prevent the occurrence of excessive drainage. While the occurrence of excessive drainage is prevented, the stimulation of the drainage hose on brain tissues is reduced, the removal efficiency of hematoma is ensured, and the operation time is shortened. Thereby being beneficial to improving the curative effect and improving the prognosis of patients (12).

Inflammation also plays a role in the progression of HICH. Studies have found that the activation of inflammatory factors in patients can affect hemodynamics, increase the permeability of the blood-brain barrier, and further aggravate the progression of intracranial hematoma (13). Serum CRP, TNF-α, and IL-6 are all sensitive inflammatory factors in the body. After the occurrence of HICH, they are affected by a severe immune response, and each index is secreted in a large amount in the body (14, 15). Hcy is related to the occurrence and development of cerebral hemorrhage. A high level of Hcy can damage vascular endothelium by promoting oxidative stress reaction in the body and destroying the balance of the coagulation system in the body, thus aggravating the symptoms of cerebral hemorrhage (16). ET and AVP both play important roles in regulating cardiovascular function and maintaining basic vascular tone function. When cerebral hemorrhage occurs, the balance of vasoactive factors, such as ET and AVP, is broken, and it is difficult to maintain the normal function of the blood vessels (17, 18). In this study, the examination time of inflammatory factors and vasoactive factors was 3 days and 7 days after surgery. After post-operative treatment, the abnormal inflammatory factors and vasoactive factors caused by surgical stress reactions have been improved. The results of this study showed that the levels of inflammatory factors and vasoactive factors were significantly reduced 3 and 7 days after surgery when compared with those before surgery. These results indicated that soft-channel minimally invasive puncture and drainage could effectively reduce intracranial pressure, regulate the balance and stability of various cytokines, improve the clinical symptoms patients with of HICH, and reduce brain tissue damage, which was of great significance for the prognosis of patients (19).

In this study, the clinical data of HICH patients with good prognosis and poor prognosis were analyzed and compared. The two groups had significant differences in pre-operative GCS score, bleeding volume, rupture into the ventricle, complicated with a cerebral hernia, and time from onset to operation ($p < 0.05$). Moreover, multivariate analysis showed that pre-operative GCS score, bleeding volume, rupture into the ventricle, complicated with a cerebral hernia, and onset time to surgery were all independent factors affecting the prognosis of patients ($p < 0.05$). Many studies have proved that the GCS score of patients with cerebrovascular diseases before surgery has a significant correlation with the prognosis. The higher the GCS score indicates that the lower the degree of brain damage is, the better the post-operative prognosis will be. It is a protective factor for patients with cerebral hemorrhage (20, 21). The larger the amount of cerebral hemorrhage, the more likely it is to form a huge and irregular hematoma, which will develop into a cerebral hernia in a short period of time, seriously affecting the circulation of cerebrospinal fluid, and compressing and damaging the brain tissue in different parts, thus leading to a poor prognosis. At the same time, the range of HICH breaking into the cerebral ventricle and whether to visit the doctor in time are also closely related to the prognosis (22). Therefore, pre-operative attention to the clinical intervention of patients with risk factors is of great

value for improving the surgical efficacy and clinical prognosis of patients.

CONCLUSION

Soft-channel minimally invasive puncture and drainage treatment of HICH has a significant effect, which is conducive to the complete removal of hematoma, reducing hospitalization time, while adjusting the balance and stability of various cytokines, and improving patient prognosis. Pre-operative GCS score, bleeding volume, rupture into the ventricle, complicated cerebral hernia, and time from onset to operation are all independent factors that affect the prognosis 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

This study was approved by the Ethics Committee of our hospital (2018003). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW and SZ are mainly responsible for the writing of the article and guidance of the entire research. JW is mainly responsible for research design and data analysis. Both authors contributed to the article and approved the submitted version.

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OPINION
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Opinion: Auxiliary Role of Medical Imaging Technology in Clinical Surgery

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Keywords: medical imaging, surgery, clinical, image guided surgery (IGS), tecnology

INTRODUCTION

Medical imaging, as a biological imaging discipline, is very effective in the current clinical surgery. This digital technology using imaging can provide doctors with accurate imaging data to help them judge patients, diseases in the entire surgery process. In recent years, through the continuous research and practice of researchers, the role and importance of medical imaging technology in clinical surgery has been improved year by year. At present, the application of digital imaging means in clinical medicine has produced many kinds of derivative technologies, such as CT, MRI, color ultrasound, DSA and other new equipment or technological innovations in the 21st century as shown in **Table 1**, which have been widely used in standardized medical institutions all over the world, and have achieved satisfactory results in the diagnosis of clinical diseases, making it an indispensable means in clinical medical diagnosis and treatment. The application of medical imaging technology in clinic can not only make doctors have more efficient and accurate diagnosis in clinic, but also provide more reliable diagnosis and treatment schemes for patients and improve the success rate of final surgery.

Nowadays, doctors can keep a real-time understanding of the patient's affected areas at all times during the operation. And medical imaging equipment can perform modeling, feed back real-time images, AR analysis of various patient parts and other functions to assist doctors in the operation. This can not only reduce the surgical accidents caused by doctors' inexperience in traditional surgery, but also help doctors to find the difficult-to-find pathological parts that they didn't notice before or during the operation in time, and help doctors to better avoid nerve tissue and other non-diseased tissues through real-time medical imaging equipment during the operation, thus greatly reducing the failure rate of the operation (1). The development of medical imaging in clinical surgery also greatly reduces the burden, pressure and duration of surgery borne by doctors and patients during surgery. With the development of digitalization, networking and intelligence of modern medical imaging technology, medical imaging technology is constantly practiced and run-in on the basis of complex medical information visualization. Through computerization and virtual reality, surgery is becoming a new compound technology field to make up for the shortcomings of traditional surgery.

APPLICATION OF MEDICAL IMAGING IN SURGERY

Preparatory Work Before and After Surgery

The application of modern medical imaging can provide doctors and patients with a large number of imaging materials before and after surgery, which can help doctors to fully grasp the patients' condition. For example, the computerized X-ray photography used in preoperative and post-perative

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TABLE 1 | Application of medical imaging in surgery.

Before surgery		In surgery	
Technology	**Function**	**Technology**	**Function**
Computed radiography (CR)	It can be used for general X-ray examination in radiology department, and it can make plain X-ray examination digital.	Needle guide and Image guided surgery	1. Collect medical image data of patients in real time. 2. Quickly process and analyze data. 3. Three-dimensional visualization technology can reconstruct the lesion in real time and display the structural features around the surgical field. 4. AR real-time display of surgical path. 5. Show the possible tissue structures on the surgical path. 6. Showing important tissue structures that should be avoided, such as blood vessels, nerves and bones, can show the scope of the lesion that needs treatment. 7. Show the range of patients needing treatment. 8. The position and posture of the surgical instruments can be accurately calculated and displayed in real time. 9. Display the spatial relationship between surgical instruments and tumors, and indicate and adjust the direction of surgical instruments.
Computed tomography (CT)	It can visually display the size and adjacent relationship of the lesion on the picture, and accurately judge the volume, length, distance and angle, etc.		
Digital subtraction angiography (DSA)	Applied to whole-body cardiovascular imaging.		
Magnetic resonance imaging (MRI)	It can directly make cross-sectional, sagittal, coronal and various oblique plane tomography images.		
Ultrasound-Guided (USG)	It can be used for imaging diagnosis of thoracic cavity, heart, abdominal parenchymal organs, pelvic organs, fetus, blood vessels of limbs, small organs and superficial tumors.		

examination is one of the main auxiliary imaging methods for clinical diagnosis before and after surgery. In clinical use, according to the difference of the density and thickness of different patients' bodies, the degree of X-ray absorption is different, which makes the lesions in patients' bodies form different black and white images on X-ray films. However, with the appearance of CR and DR, the radiation dose is greatly reduced, which can better protect patients, reduce the adverse effects caused by radiation, and make the image clearer, helping doctors to confirm the location of the lesion faster. In before and after of the surgery, the clinical application of multi-slice spiral CT shows that it plays an important role in the differentiation of malignant tumors, and it can help doctors to accurately collect the volume, size, length and other data of the lesion site, which is convenient for later surgery and rehabilitation examination. In preoperative tumor diagnosis and postoperative examination, not only CT can help doctors to make a correct judgment on the patient's condition, but digital subtraction angiography (DSA) can also accurately diagnose the lesion. Similarly, in clinic, DSA is applied to the vascular imaging of various systems of the whole body, such as bronchial angiography, renal artery DSA, hepatic artery DSA, splenic artery DSA, lower limb DSA, etc., which is helpful to the imaging diagnosis of arteriosclerosis, venous thrombosis, varicose veins and other diseases. However, for complex areas in patients' bodies, such as heart and pelvic cavity, USG can efficiently perform imaging examination on chest cavity, heart, abdominal parenchymal organs, pelvic organs, fetus, blood vessels of limbs, small organs and superficial tumors. In particular, USG has real-time three-dimensional imaging technology, which can be used in prenatal diagnosis of pregnant women and before operation of patients with heart diseases (2). In clinic, it can accurately judge congenital malformations such as limb ischemia, cleft lip and spina bifida, as well as heart valvular diseases, intracardiac tumors and thrombi of patients with heart diseases. Through medical imaging researchers' research on X-ray-based imaging medicine in quantum physics, the development of magnetic resonance imaging(MRI) provides a safer and more reliable guarantee for patients' preoperative examination and regular check-up after operation without radiation, non-invasion, intubation and contrast agent injection. Moreover, doctors can collect MRI images of patients' diseased parts by using MR urography, MR pancreaticobiliary duct imaging, MR spinal cord imaging, MR inner ear water imaging, MR fallopian tube imaging and other technologies, and perform three-dimensional imaging on the cross section of patients' bodies in all directions, so as to better locate the diseased parts. According to the development of these pre-operative and postoperative imaging technologies, technology is constantly developing and innovating, such as pre-operation and postoperative medical image simulation, medical image surgery success rate measurement and so on. Patients and doctors can get more efficient and low-pressure digital information before and after the operation, which is more conducive to promoting the modernization of medical level and maximizing the interests of patients (3).

Role in Surgery

The development of modern digital medical treatment provides accurate image data for the preparation of surgery, but in most cases, doctors often need to travel back and forth between departments and image processing stations, which leads to the inability to grasp the diseased parts of patients in real time in emergency situations. Therefore, in the continuous experiments of researchers and a few clinical practices at present, medical imaging technology can analyze the patient's lesion location and other data in the body for the surgeon through real-time data transmission or accurate positioning of images during the operation. For example, holographic augmented reality navigation, which is still in the experimental and clinical pilot stage at present, realizes holographic augmented reality navigation in liver puncture surgery by means of human-

computer interface design and equipment, and doctors can analyze the location of liver lesions of patients by wearing equipment (4). This medical imaging technology can greatly help doctors to observe most parts that cannot be observed with naked eyes. Different from other rigid body operations such as orthopedics, flexible body operations such as liver require more data, resulting in lower fault tolerance rate and higher risk. Thus, in this kind of surgery, the average accuracy of liver phantom puncture guided by augmented reality is 3.23 mm, which greatly improves the surgical accuracy and the success rate of patients. In some cases, with the development of holographic technology, the compatibility of informatization can be seen (5). The multi-level interactive visualization system of medical images for surgical navigation can not only rely on large medical equipment, but also be compatible with ios and other platforms. In the process of surgery, doctors can use AR equipment carried by the cutting edge of surgical instruments to measure the distance of tumor and other pathological tissues, monitor and calculate the deviation value of surgical path in real time, and calculate the minimum dangerous distance from surrounding tissues and give real-time warning. Not only the data transmitted by the tip of the instrument, but also the coordinates and markers acquired by the tip in the AR equipment worn by doctors. And the visualization module of surgical navigation, doctors can clearly understand the actual scene in the patient's body, and can observe the layered display effect brought by holographic images on the medical display (6). AR will demarcate and display different areas in the patient's body, and render and calibrate the designated special areas through the doctor's preset interest areas, and dynamically track them in real time. And the device can be used to review the patient's original tumor part to understand the recovery after the surgery. However, at present, according to the actual use effect brought by the optimization of visualization equipment and programs, a small amount of auxiliary information may be missing in the operation process, such as the wearing problem of AR glasses or the rendering speed, so many researches and designs are still in the experimental stage (7). It is believed that in the future, the intraoperative medical imaging technology can combine the AR-assisted surgical navigation module with the three-dimensional model constructed by CT, MRI and other medical data to better obtain the pose information. And three-dimensional registration is carried out, so that doctors can see the superposition effect of the virtual model and the surgical path with real patients in real time during the operation, and help them to make more intuitive judgments and perform the operation accurately (8).

DISCUSSION

With the help of modern medical imaging, doctors can get a lot of data about patients' condition before and after the surgery through CT, MRI, DSA, USG and other imaging technologies. The data accuracy rate of medical imaging is increasing. According to the research and development of medical imaging technology, such as AR equipment and IGS medical instruments, intelligent imaging surgery auxiliary equipment can not only enable doctors to complete surgery and obtain auxiliary information more efficiently and quickly, but also promote the standardized development of clinical surgery today, greatly avoid surgical accidents caused by doctors' lack of experience or information, and can help doctors better understand the recovery status of patients after surgery and provide information support for patients' recovery after surgery. Now, the preoperative and postoperative medical imaging diagnostic equipment has been gradually improved and a complete diagnosis and treatment mechanism has been established, while the intraoperative imaging equipment is still in the development and experimental stage. However, the development prospect of medical imaging is full of opportunities (9). Advanced medical imaging diagnosis and treatment equipment is expected to solve the technical difference and the difference of operation success rate between large hospitals and small health institutions in the future, and it will also practice higher research value and more direct diagnosis and treatment effect for patients in medical imaging surgery research. In the future, medical imaging technology will continuously integrate the data cores of various disciplines, and it is also expected to rapidly move from laboratory to clinic, contributing to the development of modern medicine.

AUTHOR CONTRIBUTIONS

ZZ (First Author): Conceptualization, Methodology, Software, Investigation, Formal Analysis, Writing - Original Draft; LS: Data Curation, Writing - Original Draft; Software, Validation, ZS: Visualization, Investigation; Writing - Review & Editing ZZ: Resources, Supervision; Formal Analysis, LY (Corresponding Author): Conceptualization, Funding Acquisition, Resources, Supervision, Writing - Review & Editing. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Analysis of the Rehabilitation Efficacy and Nutritional Status of Patients After Endoscopic Radical Thyroidectomy by Fast Track Surgery Based on Nutritional Support

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Objective: To investigate and analyze the effect of fast track surgery (FTS) based on nutritional support on the improvement of rehabilitation efficacy and nutritional status of patients after radical lumpectomy for thyroid cancer.

Methods: Eighty-six patients admitted to our hospital for radical lumpectomy for thyroid cancer between April 2018 and April 2021 were selected, of which 40 patients admitted between April 2018 and April 2019 were included in the control group with conventional perioperative care. Forty-six patients admitted between May 2019 and April 2021 were included in the trial group with FTS care based on nutritional support. The two groups of patients were compared in terms of postoperative feeding time, length of stay, time out of bed, VAS scores, albumin (ALB), total protein (TP) and prealbumin (PA) levels, negative emotions [Mental Health Test Questionnaire (DCL-90)], quality of life [General Quality of Life Inventory (GQOLI-74)] and complication rates.

Results: The patients in the trial group had shorter feeding time, hospitalization time and time out of bed than the control group ($P < 0.05$). After the intervention, ALB, TP and PA levels were higher in the trial group than in the control group vs. preoperatively ($P < 0.05$); VAS scores in the trial group were lower than VAS scores in the control group during the same period ($P < 0.05$). The postoperative DCL-90 scores of the trial group were lower than those of the control group ($P < 0.05$); the GQOLI-74 scores and total scores of the trial group were higher than those of the control group at the 3-month postoperative follow-up ($P < 0.05$). The overall incidence of complications such as hoarseness, choking on water, hand and foot numbness, wound infection, and hypocalemia was lower in the trial group than in the control group ($P < 0.05$).

Conclusion: The implementation of FTS care based on nutritional support for patients after endoscopic radical thyroidectomyr can effectively improve the postoperative recovery and reduce their pain level, as well as help improve their nutritional status, negative emotions and improve their quality of life, which is worth promoting.

Keywords: lumpectomy, radical thyroidectomy, nutritional support, fast track surgery, rehabilitation outcome, nutritional status

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RESEARCH BACKGROUND

Thyroid cancer (TC) is a malignant tumor occurring in the thyroid area, with a low incidence rate, but due to its special location, the disease is more serious after its onset. TC is a common malignant tumor in endocrine, and surveys show that the incidence of TC in our population is increasing year by year, and it is mostly seen in young and middle-aged women (1, 2). Currently, the most effective way to treat thyroid cancer is surgical treatment, but conventional thyroid surgery leaves a long surgical incision scar on the neck, which affects the aesthetics and causes great psychological stress to patients (3). With the development of modern society, people have higher and higher requirements for aesthetic results after surgery. After lumpectomy thyroid surgery has been gradually carried out in China, it is popular among patients, especially female patients, for its unique cosmetic and minimally invasive effects. Although endoscopic radical thyroidectomy is a minimally invasive surgery with little damage to the patient's organism, postoperative patients are often complicated by anemia, diabetes mellitus, hypertension, coagulation dysfunction and electrolyte disorders due to the physiological tissue characteristics of cancer, which seriously affect the nutritional status and prognosis of patients (4, 5). Most patients have a slow recovery after surgery due to pain and complications, and some patients have low understanding of their disease and treatment, so they have greater doubts about the safety of treatment and postoperative life, which leads to a certain degree of negative emotions (6, 7). In this regard, the clinical should strengthen the effectiveness of perioperative nutritional support and nursing interventions.

Fast track surgery (FTS) refers to an innovative concept that perfectly combines the diagnosis and treatment plans with the latest research evidence during the perioperative period to promote the early recovery of organ function after surgery, including the latest minimally invasive techniques, anesthesia, postoperative analgesia, early postoperative enteral nutrition, early bed mobility, active rehabilitation exercises and psychological care (8, 9). Gradually applied in the perioperative period of thyroid cancer and has achieved results in relieving patient anxiety and pain, reducing postoperative complications, decreasing stress reactions, earlier postoperative bedtime, shortening hospital stay, improving quality of life, and improving quality of care and satisfaction (10, 11). We selected patients treated with radical lumpectomy for thyroid cancer and applied NRS 2002 for nutritional risk screening and daring to investigate the effect of the FTS model based on nutritional support on the recovery outcome and nutritional status of patients treated with radical lumpectomy for thyroid cancer.

OBJECT AND METHODS

Study Subjects

Eighty-six patients admitted to our hospital who underwent lumpectomy for radical thyroid cancer between April 2018 and December 2020 were selected and their clinical data were collected.

Inclusion Criteria

I. Diagnosis of thyroid cancer confirmed by puncture biopsy; II. Those who met the indications for radical thyroid cancer surgery and agreed to take surgical treatment; III. No distant metastasis on preoperative imaging, no combination of other malignant tumors, and no contraindication to relevant surgery; patients with cosmetic intention and no history of neck surgery or radiotherapy; post-hospital nutrition risk screening tool (NRS) 2002 score $\geq$ 3 points.

Exclusion Criteria

I. Those with speech impairment and impaired consciousness, unable to communicate basically; II. Combined with other thyroid diseases; III. Contraindications related to surgery and anesthesia; IV. Comorbid with other tumors.

Among them, 40 patients admitted from April 2018 to April 2019 with conventional perioperative care were included in the control group. Fort-six patients admitted between May 2019 and April 2021 with rapid rehabilitation surgical care based on nutritional support were included in the experimental group.

Data Collection

Basic data such as gender, age, tumor diameter, lesion site, body weight, preoperative albumin, total protein and prealbumin levels, nutritional score, operative time were collected and compared between the two groups, and the analysis showed that the differences were not significant and the bases were comparable ($P > 0.05$) (**Table 1**).

INTERVENTION METHODS

Control Group

Patients were perfected with preoperative routine examination and completed preoperative preparation. Combined anesthesia was used, a catheter was left in place before surgery, and patients' vital signs were closely monitored intraoperatively. Postoperatively, they gradually received rehabilitation training, and analgesic drugs were given when pain occurred during exercise. Patients in the control group ordered the regular package from the hospital nutrition cafeteria and were not given standard nutritional support treatment, while the rest were given routine perioperative care.

Trial Group

FTS care based on nutritional support was used, and nutritional support was individualized according to the patient's physical condition.

Preoperative Support

Application of parenteral nutrition support or enteral nutrition for more than 5 days was considered to be the use of nutritional support, nutritional support regimen for oral nutrition preparations and tube feeding, parenteral nutrition support regimen includes intravenous infusion of amino acids, glucose and fat emulsion. Patients without gastrointestinal motility disorders were fasted from solid diet 6 h before surgery, fasted from clear liquid 2 h before surgery, and given sugar water for energy supplement 2 h before surgery. Actively educate

TABLE 1 | Comparison of the base of 2 groups (Mean, SD; %).

Information		Control group ($n = 40$)	Trail group ($n = 46$)	t or χ^2 value	P-value
Gender	Male	10 (25.00)	11 (23.91)	0.014	0.907
	Female	30 (76.00)	35 (76.09)		
Age (years)		42.57 ± 4.51	42.26 ± 4.65	0.313	0.755
Tumor diameter (cm)		1.50 ± 0.40	1.40 ± 0.50	1.01	0.314
Body weight (kg)		56.13 ± 7.20	56.50 ± 6.89	0.243	0.808
Lesion site	Left side	18 (45.00)	20 (43.48)	0.020	0.887
	Right side	22 (55.00)	26 (56.52)		
Albumin (g/L)		37.24 ± 3.21	38.16 ± 3.37	1.291	0.200
Total protein (g/L)		67.22 ± 11.17	68.45 ± 12.10	0.487	0.627
Prealbumin (mg/L)		250.50 ± 30.89	252.37 ± 33.14	0.269	0.788
NRS 2002 score (points)		4.10 ± 0.50	4.06 ± 0.45	0.390	0.697
Operating time (min)		85.64 ± 10.56	83.18 ± 11.25	1.040	0.301

patients about the rapid recovery program to obtain better cooperation from patients. Before the operation, we perfected the routine examination and entered the operating room after completing the preoperative preparation.

Intraoperative Support

After the patient entered the room, we explained the surgical instruments and instructed the patient to cooperate well to ensure the smooth operation. Intraoperatively, a cardiac monitor was connected and all vital signs were closely monitored for 15 min/time. Control the intraoperative infusion volume <1,000 ml, and control the infusion temperature at about 36°C. The non-operative site was kept warm to prevent hypothermia and extremely wasted patients were given intraoperative warming blankets to maintain 37°C. Postoperative ECG was monitored continuously for 12 h, and pulse, blood pressure, temperature and respiratory changes were monitored.

Postoperative Support

Placed oxygen devices, suction devices and tracheotomy kits at the bedside, and reported to the physician as soon as the patient developed symptoms such as vocal cord paralysis, laryngeal edema, respiratory distress and asphyxia, and prepared for tracheotomy. Adequate postoperative pain relief can be achieved by providing patients with early intermittent neck ice, systematic pain education and, if necessary, non-steroidal analgesics, depending on the circumstances. After the patient was awake from anesthesia and the vital signs were stable, a small amount of water could be given, leg flexion and extension and turning activities could be performed in bed, and vocal exercises could be performed. Twelve hours after surgery, patients could eat semi-liquid diet and do some exercises around the bed; 24 h after surgery, they could gradually transition to general diet and walk in the corridor and rest area. On the first postoperative day, the patients were instructed to carry out functional neck exercises in a gradual manner, and the standard was that the patients did not show any discomfort symptoms, and at the same time, psychological guidance was provided to avoid patients being afraid to carry out exercises because they were worried about wound pain.

Observation Indicators

The postoperative feeding time, hospitalization time and the first postoperative bed activity time and the 24 h postoperative pain level were compared between the two groups. The pain level was assessed by visual analog scoring (VAS), which was divided as 0–10, and the higher the score, the more severe the pain symptoms.

Nutritional Status

Before the intervention and on the second postoperative day of the patient, serum albumin (ALB), prealbumin (PA) and total protein (TP) levels were measured in the morning fasting venous blood of two groups of patients using a fully automated biochemical analyzer (Hitachi, Japan).

Negative Emotion

Before the intervention and on the second postoperative day, the patient's negative emotion was evaluated using the mental health test questionnaire (DCL-90), which includes 9 dimensions such as somatization, obsessive-compulsive symptoms, interpersonal relationship, sensitivity, depression, hostility, terror, paranoia, and psychoticism, with each dimension scored from 1 to 5.

Quality of Life

Patients were followed up at 3 months after discharge and their quality of life was evaluated using the General Quality of Life Inventory (GQOLI-74), which consists of four dimensions: physical, social, psychological and role, with a score of 100 out of 100.

Complications

The occurrence of postoperative complications, including hypocalcemia, choking on water, wound infection, numbness of hands and feet, and hoarseness, was recorded in both

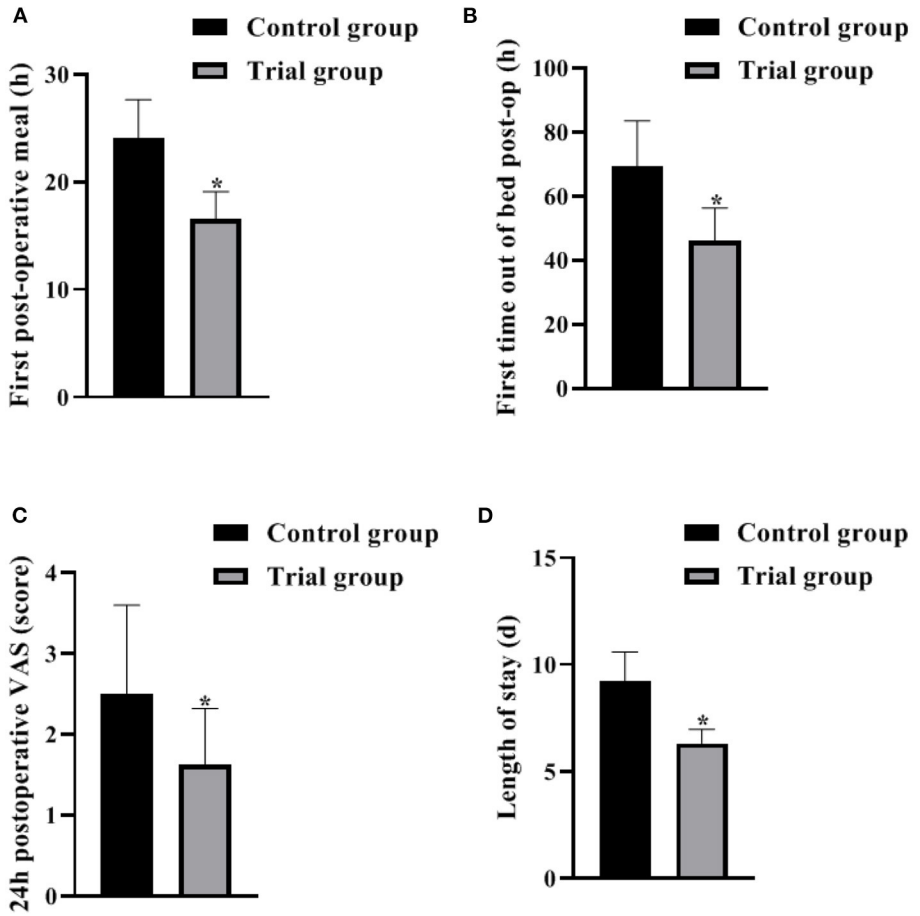

FIGURE 1 | Comparison of perioperative indicators between the 2 groups (Mean, SD). The contents in **(A–D)** are the first postoperative meal, the first postoperative bed release, and the 24 h postoperative VAS score with the length of stay, respectively. The difference between the two groups *$P < 0.05$.

groups. Among them, serum calcium <8.7 mg·dL^{-1} was defined as hypocalcemia.

Statistical Analysis

All data in this study were statistically analyzed using SPSS 20.0, and Prism 8.0 software was used to produce statistical graphs. The measures in the data were expressed as mean ± standard deviation (Mean,SD), and *t*-tests were performed between groups. The statistical data were expressed as rate (%), and the χ^2 test was performed between groups. $p < 0.05$ was considered as a statistically significant difference.

RESULTS

Comparison of the Base of 2 Groups

The results of the analysis showed that there were no significant differences between the control group and the experimental group in the general conditions of gender, age, tumor diameter, lesion site, body weight, preoperative albumin, total protein and prealbumin levels, NRS 2002 score, and operation time, and the base was comparable ($P > 0.05$) (**Table 1**).

Comparison of Perioperative Indicators Between the 2 Groups

The results of the analysis showed that the first postoperative meal, the first postoperative bed release and the hospital stay in the trail group were significantly shorter than those in the control group ($P < 0.05$), suggesting that the FTS model based on nutritional support can promote the postoperative recovery of patients and shorten the hospital stay. In addition, the VAS score of the experimental group was lower than that of the control group at 24 h after surgery ($P < 0.05$), suggesting that the FTS model based on nutritional support can effectively prevent the occurrence of postoperative pain and reduce the degree of pain in patient (**Figure 1**).

Nutritional Status of the 2 Groups

The results of the analysis showed that the preoperative ALB, TP and PA levels of the 2 groups did not differ significantly ($P > 0.05$). After the intervention, the levels of ALB, TP and PA in the control group were lower than those in the preoperative and concurrent experimental groups ($P < 0.05$), and the differences between the levels of ALB, TP and PA in the experimental group

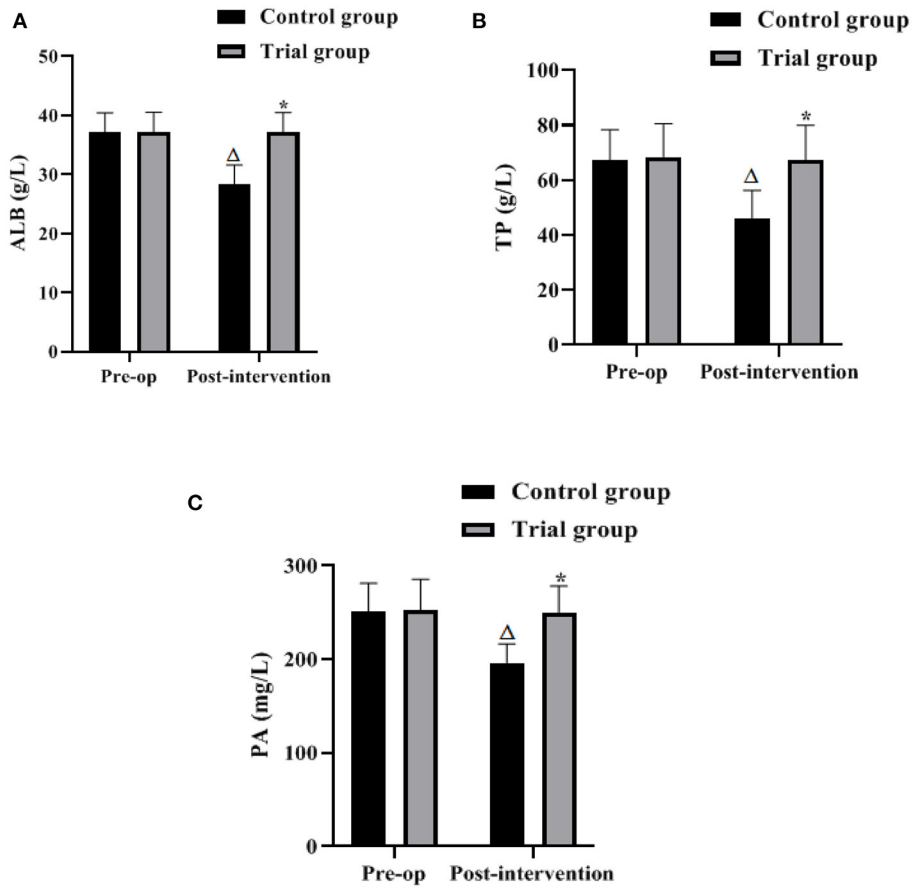

FIGURE 2 | Nutritional status of the 2 groups (Mean, SD). The contents in **(A–C)** are ALB, TP, and PA levels, respectively. Difference from the same group preoperatively $\Delta P < 0.05$; difference between the two groups $^*P < 0.05$.

and the preoperative group were not significant ($P > 0.05$). It is suggested that the FTS model based on nutritional support can effectively reduce the occurrence of nutritional risks caused by various reasons in the perioperative period and improve the clinical outcomes of patients (**Figure 2**).

Comparison of Negative Emotions Between the 2 Groups

The results of the analysis showed that the differences in the scores of somatization, obsessive-compulsive symptoms, interpersonal relationship, sensitivity, depression, hostility, terror, paranoia, and psychoticism between the two groups before surgery were not significant ($P > 0.05$). After the intervention, the DCL-90 scores in both groups decreased significantly compared with the preoperative scores, and the scores of somatization, obsessive-compulsive symptoms, interpersonal relationship, sensitivity, depression, hostility, terror, paranoia, and psychoticism in the experimental group were lower than those in the control group ($P < 0.05$). It is suggested that the FTS model based on nutritional support can improve patients' negative emotions and is conducive to improving patients' treatment adherence (**Figure 3**).

Comparison of the Quality of Life of the 2 Groups After 3 Months

The analysis showed that the GQOLI-74 scores of health status, physical function, social function, and mental health as well as the total GQOLI-74 scores were higher in the experimental group than in the control group 3 months after surgery ($P < 0.05$). It is suggested that the FTS model based on nutritional support has a better effect on the improvement of patients' quality of life (**Figure 4**).

Comparison of Complications Between the 2 Groups

In the control group, the incidence of hoarseness, choking on water, numbness of hands and feet, wound infection, hypocalcemia, and overall incidence were 5.00%, 7.50%, 10.00%, 5.00%, 2.50%, and 30.00%, respectively. In the trail group, the incidence of hoarseness, choking cough, numbness of hands and feet, traumatic infection, hypocalcemia, and overall incidence were 0.00%, 2.17%, 2.17%, 2.17%, 0.00%, and 6.52%, respectively. The analysis showed that the overall complication rate in the experimental group was lower than that in the control group ($P < 0.05$). It is suggested that the FTS model based on nutritional

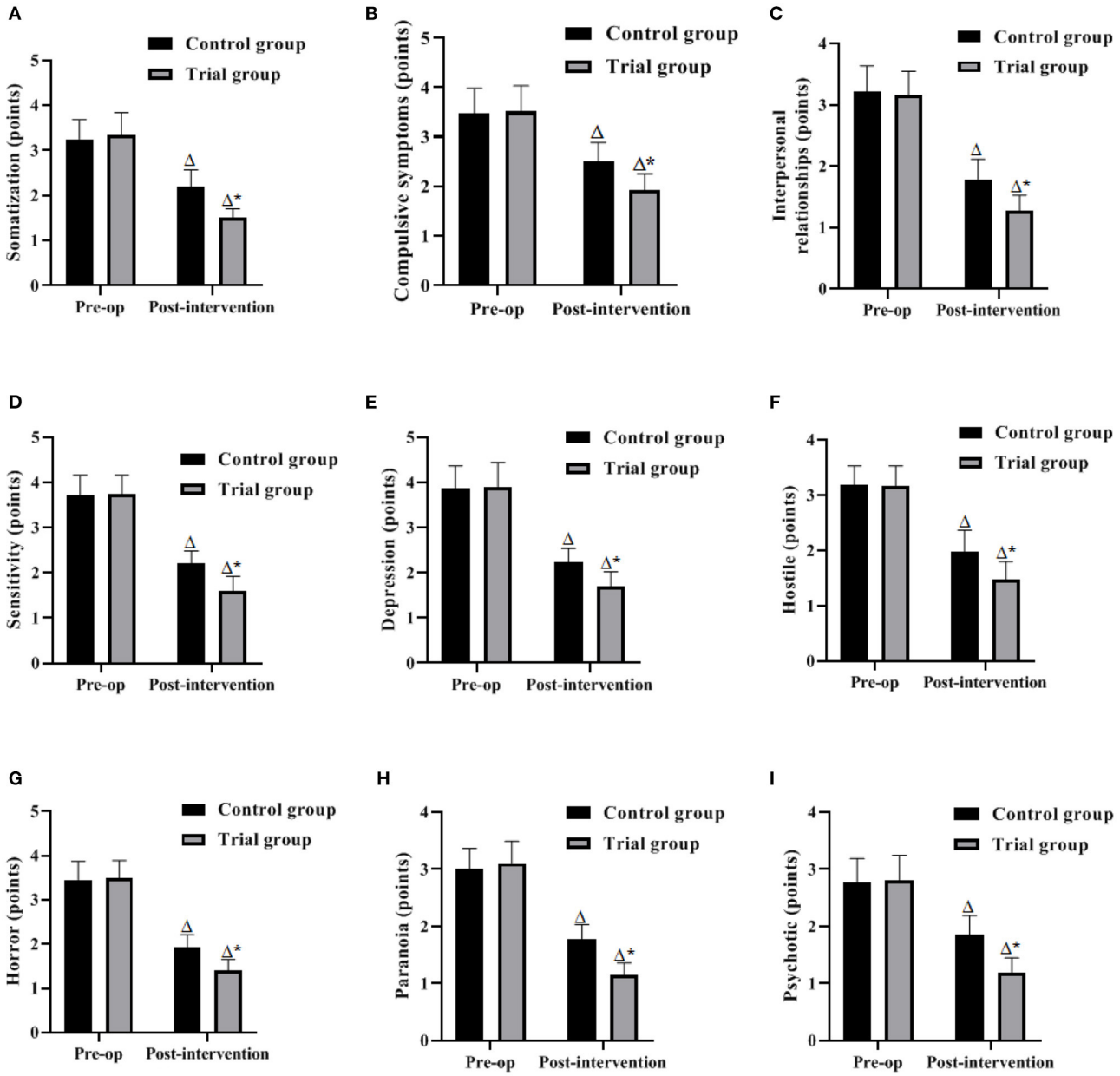

FIGURE 3 | Comparison of negative emotions between the 2 groups (Mean, SD). The contents in **(A–I)** are somatization, obsessive-compulsive symptoms, interpersonal, sensitivity, depression, hostility, phobia, paranoia, and psychoticism, respectively. Difference from the same group preoperatively $\Delta P < 0.05$; difference between the two groups $^{*}P < 0.05$.

support can reduce the incidence of perioperative complications (**Table 2**).

DISCUSSION

Thyroid cancer is a malignant tumor originating from thyroid follicular epithelial cells. It mainly presents as painless neck nodules or masses, it is more common in young adults, and the incidence in women is about 2–4 times that of men. Currently, the disease is mainly treated by surgery, radionuclide therapy and endocrine therapy (12, 13). In recent years, with the continuous development and improvement of minimally invasive techniques, lumpectomy also plays an important role in the treatment of thyroid cancer, with the advantages of less trauma, less bleeding, faster recovery and better aesthetics (14). However, radical thyroidectomy is difficult and prone to many postoperative complications. In addition, due to the pathological consumption of thyroid cancer, dysphagia symptoms, surgery and inflammation, a large amount of proteins and fats are consumed in the body, and patients may suffer

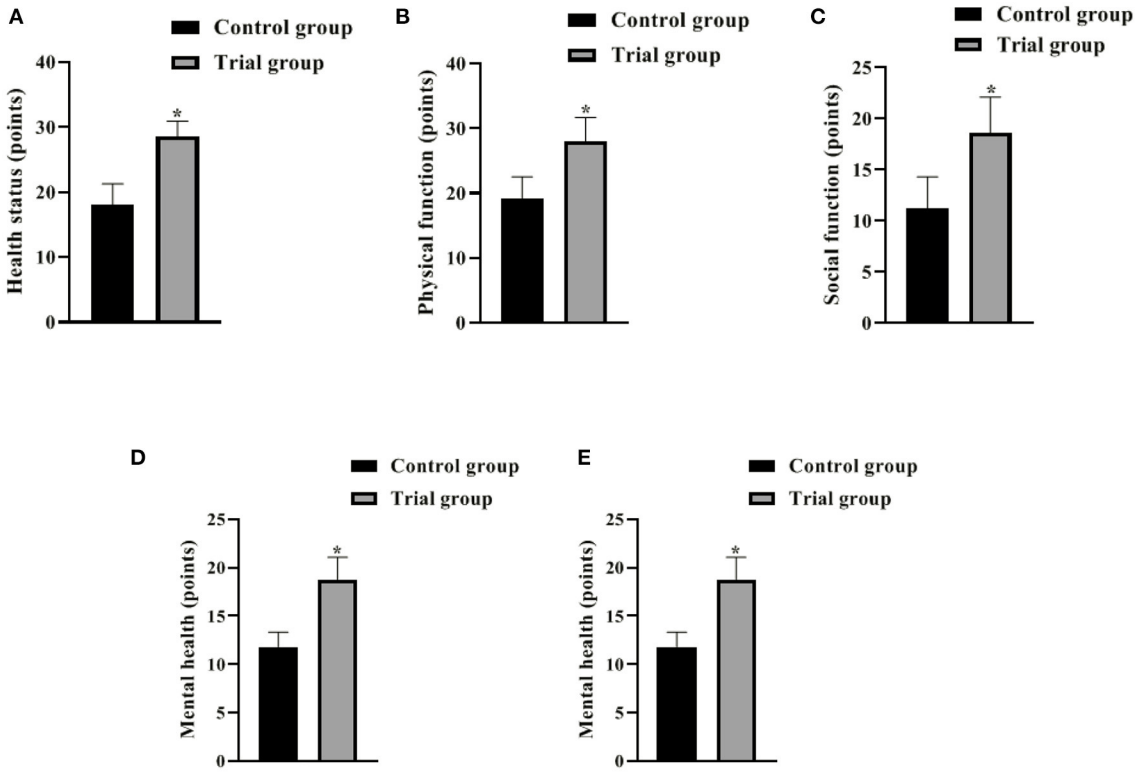

FIGURE 4 | Comparison of the quality of life of the 2 groups after 3 months (Mean, SD). The contents in **(A–E)** are health status, physical function, social function, mental health and GQOLI-74 total score, respectively. The difference between the two groups $^*P < 0.05$.

TABLE 2 | Comparison of complications between the 2 groups.

Group	Hoarseness	Choking and coughing	Numbness of hands and feet	Wound infection	Hypocalcemia	Total
Control group ($n = 40$)	2 (5.00)	3 (7.50)	4 (10.00)	2 (5.00)	1 (2.50)	12 (30.00)
Trail group ($n = 46$)	0 (0.00)	1 (2.17)	1 (2.17)	1 (2.17)	0 (0.00)	3 (6.52)
χ^2 value	-	-	-	-	-	8.190
P-value	-	-	-	-	-	0.004

from malnutrition status (15, 16). One study (17) showed that patients with nutritional risk have a significantly higher incidence of postoperative infectious complications and a significantly longer hospital stay, so clinical workers need to pay attention to nutritional screening of surgical patients and the prognostic impact of nutritional risk on surgery. The results showed that the postoperative albumin, total protein, prealbumin levels, GQOLI-74 scores and total scores of the test group were higher than those of the control group; the first postoperative meal, first time out of bed and hospital stay were shorter than those of the control group; the postoperative 24 h VAS score, postoperative DCL-90 scores and total postoperative complication rate were lower than those of the control group. The present results confirm that a FTS model based on nutritional support significantly improves the clinical outcomes of patients undergoing endoscopic radical thyroidectomy, promotes patient recovery, and contributes to the improvement of patients' postoperative quality of life.

FTS refers to the application of various methods that have been proven effective by evidence-based medicine before, during, and after surgery to reduce surgical stress and complications and accelerate postoperative recovery (18, 19). FTS as a new treatment concept has achieved great success in the fields of general surgery, gynecology, and urology, and in recent years, FTS has gradually been widely used in the clinical treatment of thyroid cancer, resulting in faster postoperative recovery and significantly shorter hospitalization. The length of hospitalization has been significantly shortened (20, 21). In this study, a rapid perioperative rehabilitation model suitable for lumpectomy for radical thyroid cancer was developed to address the special characteristics of thyroid cancer, which mainly includes active and effective health education, dietary management and postural

training before surgery, intraoperative hypothermia prevention, restrictive fluid rehydration and placement of surgical positions, and comprehensive perioperative management measures such as multimodal analgesia, early feeding, early activity and early functional exercise after surgery. The above measures obviously reduced the interference with normal body functions, and the intestinal functions of thyroid cancer patients were not significantly affected. Based on the fact that enteral nutritional support is more physiological than parenteral nutritional support and more beneficial to maintain the structural and functional integrity of intestinal mucosal cells, enteral nutritional support should be preferred (22, 23). Studies (24, 25) have shown that high protein intake increases intestinal absorption of calcium, stimulates insulin-like growth factor secretion, increases BMI, enhances muscle strength, and reduces the incidence of complications. Reasonable and standardized perioperative nutritional support can promote protein synthesis and tissue healing, improve surgical tolerance, reduce the damage caused by stress, inhibit the reduction of the body's immune function, control the inflammatory response, and promote patient recovery (26).

Improved nutrition may lead to earlier time to floor in patients undergoing radical lumpectomy for thyroid cancer, while early activity may promote gastrointestinal motility as well as reduce the incidence of perioperative complications. This study confirms that the FTS model based on nutritional support can effectively reduce the incidence of postoperative complications, shorten the number of hospital days, and promote postoperative recovery in patients undergoing lumpectomy for radical thyroid cancer, thereby improving clinical 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

This study was approved through the Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FQ and CX are the mainly responsible for the writing of the article. HB is mainly responsible for research design. FQ is mainly responsible for data analysis. LY and HL are responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Expression of miR-4739 in Gastric cancer and its Relationship with Clinical Pathological Features of Patients

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Objective: To investigate the expression level of miR-4739 in gastric cancer (GC), analyze its diagnostic value in GC and the relationship with clinical pathological characteristics, and analyze its impact on the prognosis of patients.

Methods: A total of 96 patients with GC who underwent radical gastrectomy in our hospital from March 2017 to June 2021 were selected. GC tissues from all patients were collected, and normal tissues adjacent to cancer were collected as controls. The expression level of miR-4739 in tissues was detected, the relationship between miR-4739 and different pathological features was analyzed, and the diagnostic value of miR-4739 in GC was analyzed. All patients were followed up after the operation, and the survival time of the patients was set as from the day of the first operation to 1 d when the patients died or the follow-up ended.

Results: The relative expression level of miR-4739 in the GC tissue was (0.39 ± 0.06), lower than that in the paracancerous tissue (1.18 ± 0.19) ($P < 0.05$). The AUC of miR-4739 in the diagnosis of GC was 0.705. When the Youden index was 0.320 and the optimal cutoff value was 0.37, the sensitivity was 95.30% and the specificity was 36.70%. The expression level of miR-4739 in our patient was related to the differentiation degree, lymph node metastasis, tumor diameter, and TNM stage ($P < 0.05$). During the follow-up period, 26 of 96 patients died, and the survival rate was 72.92% (26/96). The median survival time was 29 months in the miR-4739 LE group, which was shorter than 39 months in the miR-4739 HE group ($P < 0.05$). Univariate analysis showed that age, degree of differentiation, lymph node metastasis, tumor diameter, TNM staging, and miR-4739 expression were all related to the prognosis of the patient ($P < 0.05$). Multivariate analysis showed that differentiation degree, lymph node metastasis, tumor diameter, TNM staging, and miR-4739 expression were all independent factors affecting the prognosis of the patients ($P < 0.05$).

Conclusion: The expression of miR-4739 in GC tissue was down-regulated, and its level was related to the degree of differentiation, lymph node metastasis, tumor diameter, and

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TNM stage. The expression level of miR-4739 has certain diagnostic value for patients with GC, and the prognosis of patients in LE group was worse than that in HE group.

Keywords: gastric cancer, miR-4739, diagnostic value, clinical features, prognosis, influencing factors

INTRODUCTION

Gastric cancer (GC) is a common gastrointestinal malignant tumor in clinic. In China, the incidence rate of GC in gastrointestinal malignant tumors ranks first, which seriously threatens the life quality of patients (1, 2). For the past few years, with the development of medical technology, the treatment of GC has made some progress, but the overall therapeutic effect and prognosis of patients with GC are still poor (3, 4). The occurrence of GC may be related to factors such as geographical, environmental, living habits, helicobacter pylori infection, precancerous lesions, heredity and genes, etc. Patients usually have no specific clinical manifestation at the initial stage of onset. Some patients have such symptoms as nausea and vomiting, and the diagnosis of early GC is difficult (5, 6). Up to now, the specific pathogenesis of GC is still unclear. At present, among patients diagnosed with GC in hospitals, about 90% of patients with advanced GC accompanied by different degrees of lymph node metastasis. The study showed that the early stage of GC treatment had a great influence on the therapeutic effect. The inpatients with GC had a late stage of disease, and the 5-year survival rate after radical gastrectomy in large general hospitals was about 35%. Among them, the average 5-year survival rate of patients with early GC is more than 90%, while the average 5-year survival rate of patients with advanced GC is poor, even less than 10% (2, 7). Therefore, in order to improve the prognosis of patients, clinical efforts have been made to find markers for early GC. Micro ribonucleic acid (miRNA) is an endogenous non-coding small RNA, which has been found to be extensively involved in the proliferation and migration of tumor cells (8, 9). The preliminary studies on miRNA mainly focus on the target genes and expression profiles of miRNA in different tissues and different tumor tissues. GC is usually characterized by abnormal expression of multiple mirnas, so it is of great significance to find specific mirnas for the diagnosis and treatment of GC (10, 11). Abnormal expression of miRNA is related to the occurrence of many tumors, and the maladjustment of miRNA will not only affect the function of intercellular regulatory factors, but also affect tumor growth and invasion (12, 13). Wang (14) showed that miR-4739 is related to tumor progression and plays an inhibitory role in prostate cancer, and down-regulation of its expression can promote the proliferation and migration of prostate cancer cells. Studies on GC have shown that when the malignancy of tumor cells decreases, the expression level of miR-4739 is up-regulated (15). The purpose of this study was to investigate the expression level of miR-4739 in GC, analyze its diagnostic value for GC and the relationship with clinical and pathological characteristics, and analyze its impact on the prognosis of patients.

MATERIALS AND METHODS

Patients

A total of 96 patients with GC who underwent radical gastrectomy in our hospital from March 2017 to June 2021 were selected. There were 54 males and 42 females, aged from 32 to 78 years, with an average age of (61.34 ± 8.52) years. Tumor node metastasis (TNM) stages included stage I ($n = 36$), stage II ($n = 30$), stage III ($n = 26$) and stage IV ($n = 14$). Differentiation degree: 58 cases with low differentiation, 22 cases with medium differentiation and 16 cases with high differentiation. Inclusion criteria: All met the diagnostic criteria of GC (16); All patients underwent radical gastrectomy. No radiotherapy or chemotherapy was given before admission; Patients with clear clinical stages and pathologic differentiation. Exclusion criteria: patients with immune system diseases; Patients with malignant tumors in other parts; Long-term use of hormones or non-steroidal anti-inflammatory drugs; Patients with liver and kidney dysfunction, endocrine diseases and blood system diseases; Patients with incomplete clinical data or lost follow-up process. GC tissues of all patients were collected, and normal adjacent tissues (more than 5 cm away from the tumor boundary and confirmed by pathology to have no infiltration of carcinomatous tissues) were collected as controls. All tissue samples were excised, rinsed with PBS, placed in liquid nitrogen for temporary storage, and quickly transferred to −80°C for storage after quick-freezing overnight.

Expression of miR-4739 Detected by Real-Time Quantitative PCR (qRT-PCR)

The total RNA in GC tissues and adjacent tissues was extracted by Trizol method. Detect that molecular weight of the RNA by adopting gel electrophoresis; RNA concentration was detected by spectrophotometer. The RT reaction was performed using ONE STEP PrimeScript cDNA Synthesis Kit (Bao Biological Engineering Dalian Co., LTD) with DNA as the template. The 20 μL PCR reaction system was prepared in an ice bath. The primers were designed according to the data obtained from NCBI database. The primer sequences were as follows: upstream primer of miR-4739: 5′-GCTGGGACATTGAAA GTCTCA-3′; Downstream primer: 5′-GATTTCCCATCGGCG TC-3′. Upstream primer internal reference U6, 5′-CTCGC TTCGGCAGCCACA-3, and downstream primer, 5′-AAGCTT CACGAATTTGCGT-3′. The baseline was adjusted according to the instructions, the threshold was set in the linear part of the log plot of fluorescence values, and the Ct values of the miR-4739 band and the internal reference U6 band were read from the software. Δct = mean sample ct−mean internal reference ct, $\Delta\Delta ct = \Delta ct$- (mean random negative control sample Ct−mean internal reference Ct), and $2^{-\Delta\Delta Ct}$ was used to represent the relative expression level of miR-4739.

Follow-Up

Patients were followed-up by outpatient or telephone every 3 months after operation. The deadline of follow-up was December 2021. The survival time of the patient was set as 1 d from the date of the first operation to the date of her death or the end of her follow-up. According to the survival state of the patients, they were divided into the survival group and the death group.

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 ($\bar{x} \pm s$). Multivariate analysis adopts multiple Logistic regression model. The ROC curve was used to analyze the diagnostic value of miR-4739 in GC patients. Kaplan-meier survival curve was used to analyze the relationship between Mir-4739 and prognosis of gastric cancer patients, and log-rank test was used for comparison. The difference is statistically significant when $P < 0.05$.

RESULTS

Expression of miR-4739 in GC Tissue and Paracancerous Tissue

The relative expression level of miR-4739 in the GC tissue was (0.39 ± 0.06), lower than that in the paracancerous tissue (1.18 ± 0.19) ($P < 0.05$). As shown in **Figure 1**.

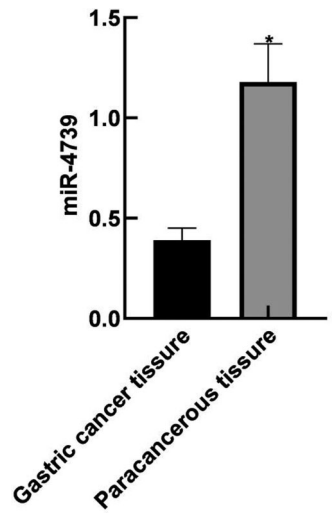

FIGURE 1 | Expression of miR-4739 in GC tissue and paracancerous tissue. Note: Compared with gastric cancer tissue, *$P < 0.05$.

Diagnostic Value of miR-4739 Expression Level in GC

The AUC of miR-4739 in the diagnosis of GC was 0.705. When the Youden index was 0.320 and the optimal cutoff value was 0.37, the sensitivity was 95.30% and the specificity was 36.70%. As shown in **Table 1** and **Figure 2**.

Relationship between miR-4739 and Clinical Pathological Characteristics

The cells were divided into high-expression (HE) group (>0.37) and low-expression (LE) group (≤0.37) with the best cutoff value of miR-4739 as the boundary. The expression level of miR-4739 in our patient was related to the differentiation degree, lymph node metastasis, tumor diameter, and TNM stage ($P < 0.05$). As shown in **Table 2**.

Relationship between miR-4739 Expression Level and Prognosis of Patients with GC

During the follow-up period, 26 of 96 patients died, and the survival rate was 72.92%(26/96). The median survival time was 29 months in the miR-4739 LE group, which was shorter than 39 months in the miR-4739 HE group ($P < 0.05$). As shown in **Figure 3**.

Univariate Analysis of Prognosis of Patients with GC

Univariate analysis showed that age, degree of differentiation, lymph node metastasis, tumor diameter, TNM staging, and

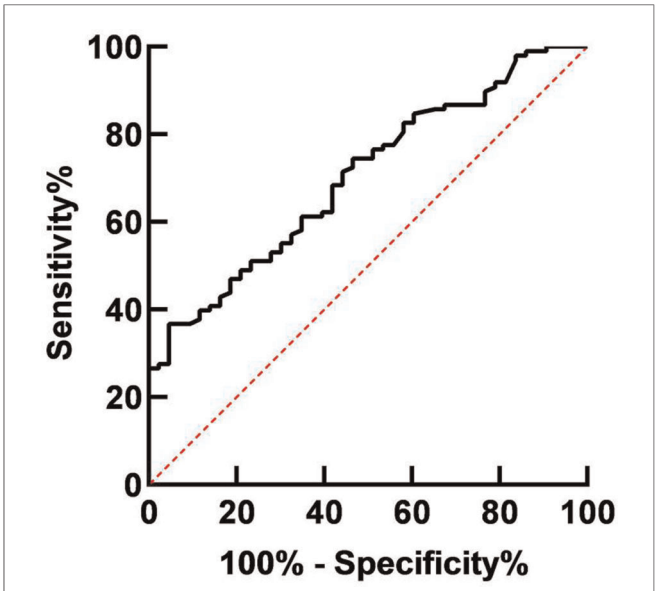

FIGURE 2 | Diagnostic value of miR-4739 expression level in GC.

TABLE 1 | Diagnostic value of miR-4739 expression level in GC.

Predictive indexes	AUC	95%CI	Youden index	Sensitivity (%)	Specificity (%)	Cut-off value
miR-4739	0.702	0.614–0.790	0.320	95.30%	36.70%	0.37

TABLE 2 | Relationship between miR-4739 expression level and clinical pathological features (n,%).

Clinical pathological features	*n*	miR-4739		χ^2	*P*
		HE group (*n* = 55)	LE group (*n* = 41)		
Age				1.336	0.248
≥60 years old	52	27 (49.09)	25 (60.98)		
<60 years old	44	28 (50.91)	16 (39.02)		
Gender				0.649	0.421
Man	54	29 (52.73)	25 (60.98)		
Woman	42	26 (47.27)	16 (39.02)		
Degree of differentiation				4.868	0.027
Low differentiation	58	28 (50.91)	30 (73.17)		
Moderate to high differentiation	38	27 (49.09)	11 (26.83)		
Lymph node metastasis				5.248	0.022
Yes	60	29 (52.73)	31 (75.61)		
No	36	26 (47.27)	10 (24.39)		
Tumor diameter				5.243	0.022
≥5 cm	41	18 (32.73)	23 (56.10)		
<5 cm	55	37 (67.27)	18 (43.90)		
TNM staging				4.234	0.040
Stages I–II	56	37 (67.27)	19 (46.34)		
Stages III–IV	40	18 (32.73)	22 (53.66)		

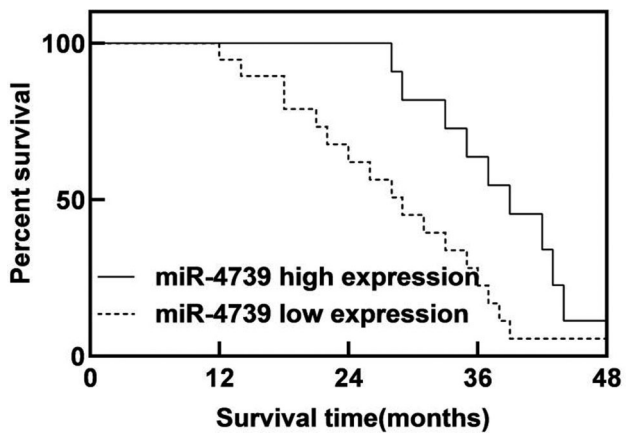

FIGURE 3 | Relationship between miR-4739 expression level and prognosis of patients with GC.

miR-4739 expression were all related to the prognosis of the patient ($P < 0.05$). As shown in **Table 3**.

Analysis of Multiple Factors Affecting the Prognosis of Patients with GC

Multivariate analysis showed that differentiation degree, lymph node metastasis, tumor diameter, TNM staging, and miR-4739 expression were all independent factors affecting the prognosis of the patients ($P < 0.05$). As shown in **Table 4** and **Table 5**.

DISCUSSION

At present, GC is generally confirmed by gastroscopy and biopsy of the lesion. Due to the invasive nature of gastroscopy operation, this examination method cannot be popularized as a routine physical examination item at present, so GC is still not able to achieve early detection and treatment (17, 18). For the treatment of GC, surgery, radiotherapy and chemotherapy are often used. Every GC patient has different responses to the same treatment. If we can timely understand the body characteristics of each patient and implement different treatment plans for different patients, namely personalized treatment, GC treatment will be further optimized (19, 20). In recent 20 years, the incidence and prevalence of GC in China have increased to varying degrees, especially the incidence of GC in young and middle-aged people in recent 10 years. With the continuous development of medical technology, the survival period of GC has been prolonged, but the mortality rate of GC patients is still high (21, 22). Therefore, it is very important to find tumor markers with high sensitivity and specificity for the diagnosis of GC. Studies have shown that miRNA has a specific expression spectrum in a variety of tumor tissues, and its overexpression may promote the growth and proliferation of tumor cells to a certain extent, thus promoting tumor progression (23, 24). Some studies have also pointed out that miRNA may play a role in promoting and inhibiting tumorigenesis (25). Abnormal regulation of miRNA is usually accompanied by epigenetic changes in genes, such as gene deletions, mutations and abnormal changes in DNA methylation level. MicroRNAs are a series of small, non-coding single-stranded RNA fragments in the body, which can regulate the translation and degradation of mRNA by ligating clip pairs in the untranslated region at the 3′ end of mRNAs, thereby affecting the proliferation and differentiation of histiocytes (26, 27). With the deepening of research on microRNAs, more and more research results show that in the process of occurrence and development of many tumors, the expression level of microRNAs is often abnormally increased or decreased (28). As a member of microRNAs, studies have found that Mir-4739 can play an inhibitory role in prostate cancer, and down-regulation of its expression can promote the proliferation. In GC, mir-4739 expression level was up-regulated in GC cells with down-regulated oncogene expression level.

The results of this study showed that the relative expression level of miR-4739 in GC tissues was (0.39 ± 0.06), lower than that in paracancerous tissues (1.18 ± 0.19). These results indicated that the miR-4739 was closely related to the occurrence of GC. The reason was analyzed as follows: overexpression of miR-4739 inhibited the expression of a variety of cell surface molecules, thus inhibiting the migration of tumor cells. The AUC of miR-4739 in the diagnosis of GC

TABLE 3 | Univariate analysis of prognosis of patients with GC (*n*,%).

Factor	n	Survival group (*n* = 70)	Death group (*n* = 26)	χ^2	*P*
Age				5.136	0.023
≥60 years old	52	33 (47.14)	19 (73.08)		
<60 years old	44	37 (52.86)	7 (26.92)		
Gender				0.405	0.524
Man	54	38 (54.29)	16 (61.54)		
Woman	42	32 (45.71)	10 (38.46)		
Degree of differentiation				6.176	0.013
Low differentiation	58	37 (52.86)	21 (80.77)		
Moderate to high differentiation	38	33 (47.14)	5 (19.23)		
Lymph node metastasis				7.441	0.006
Yes	60	38 (54.29)	22 (84.62)		
No	36	32 (45.71)	4 (15.38)		
Tumor diameter				5.167	0.023
≥5 cm	41	25 (35.71)	16 (61.54)		
<5 cm	55	45 (64.29)	10 (38.46)		
TNM staging				8.253	0.004
Stages I–II	56	47 (67.14)	9 (34.62)		
Stages III–IV	40	23 (32.86)	17 (65.38)		
Expression of miR-4739				7.494	0.006
High	55	46 (65.71)	9 (34.62)		
Low	41	24 (34.29)	17 (65.38)		

TABLE 4 | Multi-factor analysis assignment table.

Factors	Variable	Assignment
Age	X1	<60 = 0, ≥60 = 1
Degree of differentiation	X2	Medium to high differentiation = 0, low differentiation = 1
Lymph node metastasis	X3	No = 0, yes = 1
Tumor diameter	X4	<5 cm = 0, ≥5 cm = 1
TNM staging	X5	I–II = 0, III–IV = 1
Expression of miR-4739	X6	Hig = 0, low = 1

TABLE 5 | Multivariate analysis of prognosis of patients with GC.

Variables	B	S.E	Walds	P	OR	95%CI
Age	0.395	0.206	1.952	0.214	1.506	0.791–2.142
Degree of differentiation	1.191	0.436	4.508	0.038	3.284	1.715–6.822
Lymph node metastasis	1.293	0.511	5.106	0.025	3.704	1.992–5.846
Tumor diameter	1.336	0.694	5.708	0.019	3.809	1.278–7.328
TNM staging	0.741	0.319	5.582	0.021	1.592	1.105–2.086
Expression of miR-4739	0.663	0.312	6.428	0.009	1.905	1.069–3.158

was 0.705. When the Youden Index was 0.320 and the optimal cutoff value was 0.37, the sensitivity was 95.30% and specificity was 36.70%. These results indicated that miR-4739 had certain diagnostic value in patients with GC. Further analysis results in this study showed that abnormal expression of miR-4739 was related to tumor differentiation degree, lymph node metastasis, tumor diameter and TNM stage of patients. Patients with low differentiation degree, lymph node metastasis, large tumor diameter and high TNM stage had low expression level of miR-4739. During the follow-up period, 26 of 96 patients died, and the survival rate was 72.92%(26/96). The median survival time was 29 months in the miR-4739 LE group, which was horter than 39 months in the miR-4739 HE group. In addition, univariate and multivariate analyses showed that differentiation, lymph node metastasis, tumor diameter, TNM stage, and miR-4739 expression were all independent factors affecting the prognosis of the patient. Among them, patients with low differentiation, lymph node metastasis, large tumor diameter, high TNM staging and low expression level of miR-4739 have poor prognosis. All these have indicated that miR-4739 level can predict the prognosis of GC patients.

The deficiency of this study is that only the expression of Mir-4739 in GC tissues was detected, and analysis of Mir-4739 may be able to diagnose and predict the prognosis of GC patients. However, the specific mechanism of mir-4739 was not explored in this study, which needs to be further explored in the future.

CONCLUSION

The expression of miR-4739 in GC tissue was down-regulated, and its level was related to the degree of differentiation, lymph node metastasis, tumor diameter, and TNM stage. The expression level of miR-4739 has certain diagnostic value for patients with GC, and the prognosis of patients in LE group was worse than that in HE group.

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.

ETHIC STATEMENT

The studies involving human participants were reviewed and approved by The studies involving human participants were reviewed and approved by the Ethics Committee of our Hospital (2018012). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW and JL are co-first authors and the mainly responsible for the writing of the article. DG is mainly responsible for research design. YP is mainly responsible for data analysis. BY and HW are responsible for the guidance of the entire research. The corresponding author is Yun Zhou and she is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors may have contributed in multiple roles. JW and JL are the mainly responsible for the writing of the article. DG is mainly responsible for research design. YP is mainly responsible for data analysis. BY and HW are responsible for the guidance of the entire research. The corresponding author is Yun Zhou and she is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Efficacy of Xuebijing Combined with Ulinastatin in the Treatment of Traumatic Sepsis and Effects on Inflammatory Factors and Immune Function in Patients

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Objective: To investigate the efficacy of xuebijing combined with ulinastatin in the treatment of traumatic sepsis and analyze the effects on inflammatory factors and immune function of patients.

Methods: 182 patients with traumatic sepsis were selected from June 2017 to September 2021 in our hospital. The patients were divided into the control group and the observation group. Patients in both groups were given routine treatments such as initial resuscitation, blood transfusion, monitoring of lactic acid to guide fluid replacement, early control of infection source, selection of appropriate antibiotics, correction of acidosis, treatment of primary disease, prevention of hypothermia and stress ulcer, application of vasoactive drugs, application of glucocorticoid and nutritional support. The control group was treated with Xuebijing injection on the basis of routine treatment, and the observation group was given Xuebijing injection combined with ulinastatin treatment on the basis of routine treatment. The APACHE II score was applied to evaluate the patients before and after treatment, and the routine blood indicators, inflammatory factor indicators, immune function indicators and liver function indicators were tested.

Results: After the treatment, the APACHE II score of the observation group was (10.35 ± 3.04) lower than that of the control group (15.93 ± 4.52) ($P < 0.05$). After treatment, the WBC and neutrophils in the observation group (15.19 ± 2.91) and (0.65 ± 0.04) were lower than those in the control group (16.42 ± 3.44) and (0.79 ± 0.05), and the PLT (162.85 ± 43.92) was higher than that in the control group (122.68 ± 36.89) ($P < 0.05$). After treatment, the levels of serum PCT, IL-6, TNF-α in the observation group were (11.38 ± 3.05), (10.74 ± 3.82) and (9.82 ± 2.35) lower than those in the control groups (17.34 ± 3.29), (15.28 ± 4.05) and (13.24 ± 3.06) ($P < 0.05$). After treatment, the levels of CD3+, CD4+, CD8+, CD4+/CD8+ in the observation group were (50.64 ± 4.98), (40.56 ± 4.82), (27.22 ± 3.29), (1.49 ± 0.24) higher than those in the control groups (46.08 ± 4.75), (34.69 ± 4.08), (25.14 ± 3.18), (1.38 ± 0.19) ($P < 0.05$). After treatment, the levels of TBIL and AST in the observation group were (12.35 ± 3.82), (25.66 ± 4.49) lower than those in the control group (18.43 ± 4.06), (34.58 ± 5.06) ($P < 0.05$).

Conclusion: Xubijing combined with ulinastatin has a good effect in the treatment of patients with traumatic sepsis, which can effectively improve the condition, reduce the body's inflammatory response, and promote the recovery of patients' immune function and liver function.

Keywords: trauma, sepsis, Xuebijing, ulinastatin, inflammatory factors, immune function, liver function

INTRODUCTION

With the development of economy and modern transportation, the incidence of trauma increases year by year, and the injury condition is increasingly complex and serious. Sepsis is a syndrome caused by the body's malfunctioning response to an infection. The infection range can affect the whole body, and it is often the common complication after severe trauma, critical illness, infection and major surgery. It usually causes functional damage to important tissues and organs (liver, kidney, lung), and further deterioration will lead to tissue hypoperfusion and continuous hypotension, which in turn develops into severe sepsis and septic shock (1–4). Sepsis has a very important connection with trauma. Sepsis is one of the most serious complications in trauma patients, which easily leads to multiple organ dysfunction syndrome. Sepsis is not only an excessive inflammatory response, but also the result of immune dysfunction that interacts with the inflammatory and anti-inflammatory processes (5, 6). Studies have shown that the onset of traumatic sepsis is likely to lead to systemic organ function damage, and the liver is the most vulnerable organ to inflammatory injury. 0.6%∼50.0% of patients with traumatic sepsis will suffer from sepsis-related liver injury (7, 8). Therefore, effective prevention and treatment of liver function impairment plays an important role in the prognosis of patients with traumatic sepsis. At present, there is no very effective method for the treatment of sepsis, which is mainly based on the pathogenesis of sepsis, and comprehensive support treatments for its pathogenesis are mainly given, such as early fluid resuscitation, control of infection, mechanical ventilation, maintaining the stability of organ function, hormone therapy, but its mortality rate has not improved (9, 10). Xuebijing Injection has the effects of activating blood, resolving stasis, clearing heat, detoxicating, and strengthening the body resistance. It is currently commonly used for the treatment of patients with sepsis (11, 12). Ulinastatin is effective for alleviating inflammation and regulating immune function, and its role in the clinical treatment of sepsis has become increasingly prominent (13, 14). The purpose of this study was to investigate the efficacy of Xuebijing combined with ulinastatin in the treatment of traumatic sepsis and analyze its effects on the inflammatory factors and immune function of patients.

MATERIALS AND METHODS

Patients

Total of 182 patients with traumatic sepsis were selected from June 2017 to September 2021 in our hospital. Inclusion criteria: All the patients met the relevant diagnostic criteria for traumatic sepsis in the 2012 International Guidelines for the Diagnosis and Treatment of Severe Sepsis and Septic Shock (15); They were all the first confirmed cases of traumatic sepsis; There was no previous history of Xuebijing or ulinastatin treatment. Exclusion criteria: Patients with active bleeding and unable to stop bleeding or other serious diseases that cannot be controlled; Patients with diabetes, tumor and other basic diseases; Patients with contraindications to drugs in this study; Recent history of glucocorticoid treatment; People whose conditions can't be controlled. The patients were divided into the control group and the observation group, 91 cases in each group. There was no significant difference in general data between the two groups ($P < 0.05$). As shown in **Table 1**.

Treatment Methods

Patients in both groups were given routine treatments such as initial resuscitation, blood transfusion, monitoring of lactic acid to guide fluid replacement, early control of infection source, selection of appropriate antibiotics, correction of acidosis, treatment of primary disease, prevention of hypothermia and stress ulcer, application of vasoactive drugs, application of glucocorticoid and nutritional support. The control group was treated with Xuebijing injection (Produced by Tianjin Hongri Pharmaceutical Co., Ltd., Batch number: 20180317) on the basis of routine treatment. 50 mL of Xuebijing injection was added into 100 mL of sodium chloride injection, and intravenous infusion was completed, twice a

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

Groups	Gender		Age(years)	APACHE II score(points)	SOFA score(points)
	Male	Female			
Control group ($n = 91$)	53	38	53.08 ± 7.16	22.08 ± 5.92	12.49 ± 2.85
Observation group ($n = 91$)	50	41	52.76 ± 7.32	22.24 ± 5.86	12.68 ± 2.93
t/χ^2	0.201		0.298	0.183	0.443
P	0.654		0.766	0.855	0.658

day. For patients with severe disease, the treatment was given three times a day. On the basis of routine treatment, the observation group was treated with Xuebijing injection combined with ulinastatin (Produced by Guangdong Tianpu Biochemical Medicine Co., LTD., Batch Number: 20171019). The medication method of Xuebijing injection was the same as that of the control group. The ulinastatin for injection was added into 100 mL of sodium chloride injection at 300,000 units each time and given by intravenous infusion twice a day. The treatment lasted for seven days in both groups.

Observation indicators

Acute Physiological and Chronic Health Status Scoring System II(APACHE II) Score Detection

The APACHE II score was applied to evaluate patients before and after treatment, respectively (16). The scale totally included acute physiological score, age score and chronic health score. The higher the score was, the worse the prognosis was.

Detection of Blood Routine Indexes

5 mL of venous blood was collected from patients, and blood leukocytes (WBC), platelets (PLT) and neutrophils were detected using XFA automatic blood cell analyzer (Produced by Beijing Jiapukang Biotechnology Co., LTD.).

Detection of Inflammatory Factors

ELISA was used to detect the levels of procalcitonin (PCT), interleukin-6(IL-6) and tumor necrosis factor-α (TNF-α). The kit was purchased from Adlitteram Diagnostic Laboratories, and the microplate reader was Anthos 2010.

Detection of Immune Function Indicators

T-lymphocyte subsets (CD3+, CD4+, CD8+, CD4+/CD8+) were measured using FACSCount flow cytometer produced by BD Company in the United States and supporting reagents.

Detection of Liver Function Indicators

Total bilirubin (TBIL) was detected by thrombin method before and after treatment, and aspartate aminotransferase (AST) was detected by oxaloacetate dehydrogenase method.

Adverse Reactions

The incidence of adverse reactions during treatment was recorded.

Statistical Methods

The results of this experiment were statistically analyzed by SPSS 20.0 (SPSS Co., Ltd., Chicago, USA). 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 APACHE II Scores

After the treatment, the APACHE II score in the observation group was (10.35 ± 3.04) lower than that in the control group (15.93 ± 4.52) ($P < 0.05$). As shown in **Figure 1**.

Comparison of Blood Routine Indexes

After treatment, the WBC and neutrophils in the observation group were (15.19 ± 2.91) and (0.65 ± 0.04) lower than those in the control group (16.42 ± 3.44) and (0.79 ± 0.05), and the PLT(162.85 ± 43.92) was higher than that in the control group (122.68 ± 36.89) ($P < 0.05$). As shown in **Figure 2**.

Comparison of Inflammatory Factors

After treatment, the levels of serum PCT, IL-6, TNF-α in the observation group were (11.38 ± 3.05), (10.74 ± 3.82) and (9.82 ± 2.35) lower than those in the control groups (17.34 ± 3.29), (15.28 ± 4.05) and (13.24 ± 3.06) ($P < 0.05$). As shown in **Figure 3**.

Comparison of Immune Function Indicators

After treatment, the levels of serum CD3+, CD4+, CD8+, CD4+/CD8+ in the observation group were (50.64 ± 4.98), (40.56 ± 4.82), (27.22 ± 3.29), (1.49 ± 0.24) higher than those in the control groups (46.08 ± 4.75), (34.69 ± 4.08), (25.14 ± 3.18), (1.38 ± 0.19) ($P < 0.05$). As shown in **Figure 4**.

Comparison of Liver Function Indicators

After treatment, the levels of TBIL and AST in the observation group were (12.35 ± 3.82), (25.66 ± 4.49) lower than those in the

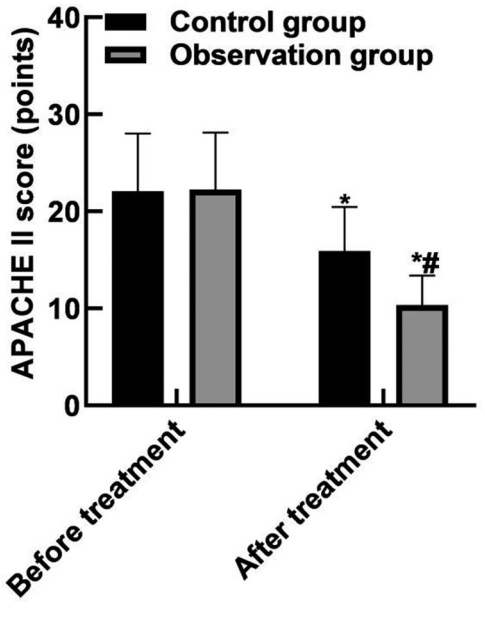

FIGURE 1 | Comparison of APACHE II scores. Note: Compared with before treatment, $^{*}P < 0.05$; Compared with the control group, $^{\#}P < 0.05$.

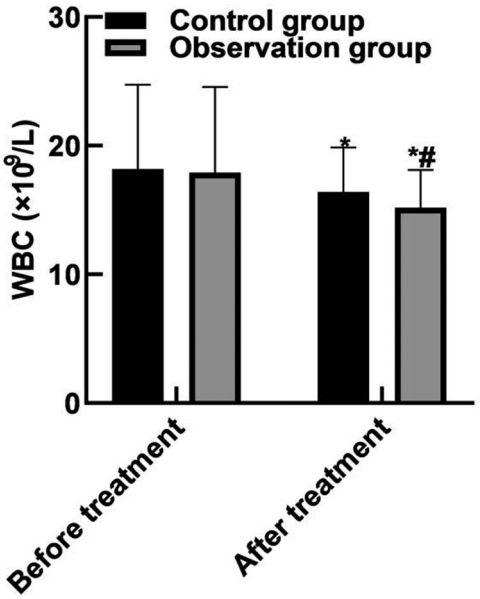

FIGURE 2 | Comparison of blood routine indexes. Note: Compared with before treatment, $^{*}P < 0.05$; Compared with the control group, $^{\#}P < 0.05$.

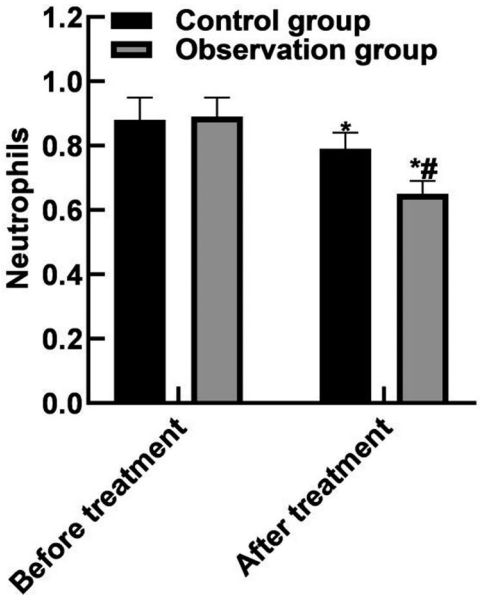

FIGURE 4 | Comparison of immune function indicators. Note: Compared with before treatment, $^{*}P < 0.05$; Compared with the control group, $^{\#}P < 0.05$.

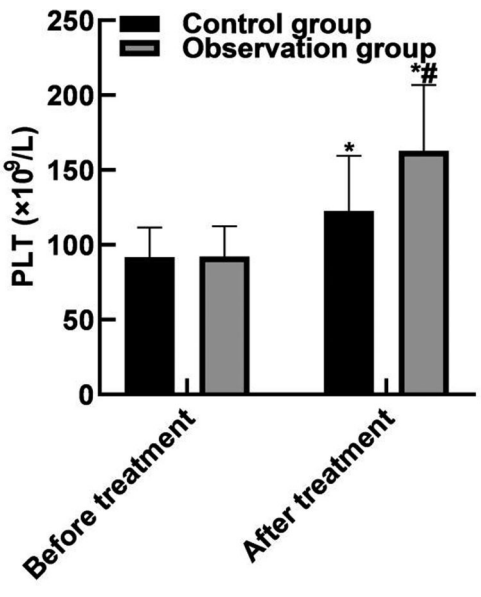

FIGURE 3 | Comparison of inflammatory factors. Note: Compared with before treatment, $^{*}P < 0.05$; Compared with the control group, $^{\#}P < 0.05$.

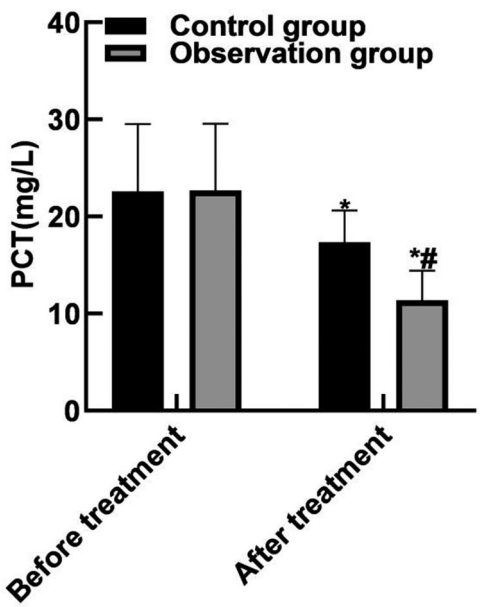

FIGURE 5 | Comparison of liver function indicators. Note: Compared with before treatment, $^{*}P < 0.05$; Compared with the control group, $^{\#}P < 0.05$.

control group (18.43 ± 4.06), (34.58 ± 5.06) ($P < 0.05$). As shown in **Figure 5**.

Comparison of Adverse Reactions

During the treatment, paroxysmal atrial fibrillation occurred in 1 case, gastrointestinal reaction in 2 cases and rash in 3 cases in the control group, and the incidence of adverse reactions was 5.49% (5/91). In the observation group, paroxysmal atrial fibrillation occurred in 2 cases, gastrointestinal reaction in 2 cases, rash in 4 cases, and the incidence of adverse reactions was 8.79% (8/91). There was no significant difference in the incidence of adverse reactions between the two groups ($P > 0.05$).

DISCUSSION

The infection of patients with traumatic sepsis can come from wounds, surgical sites, lungs, blood, urinary tract and other areas. Any open wound can easily become the source of bacterial colonization and infection, and the surgical incision and surgical site are also prone to occur, especially when there is contamination surgery such as internal fixation implantation or intestinal cavity opening (17, 18). Patients with severe trauma often have respiratory impairment, especially in patients with severe craniocerebral injury, chest trauma that cannot rule out airway secretions and the use of mechanical ventilation. Pulmonary infection has become the main source of traumatic sepsis (19, 20). Decreased immunity in trauma patients is an intrinsic cause of susceptibility to infection, including local and systemic defense deficits. Among them, much attention has been paid to the functional decline of neutrophils, mononuclear macrophages, lymphocytes, and dendritic cells, which are considered to be the factors occupying an important position in the pathogenesis of sepsis, manifested as decreased serum opsonin, decreased granulocyte generation, inhibition of neutrophil chemical tropism and bactericidal ability, and defects of specific immune responses, such as reduced lymphocyte formation (21, 22). Trauma induces inflammatory response and also produces a series of anti-inflammatory factors, which inhibit the binding of inflammatory factors to receptors on the cell membrane and down-regulate the immune response. Anti-inflammation and pro-inflammation interact, leading to immune regulation disorders or even low immunity (23, 24). Therefore, effective reduction of inflammatory response and recovery of immune function are the important basis for the treatment of sepsis. The occurrence of sepsis is directly related to the severity of trauma. Patients with severe trauma should be sent to medical institutions with corresponding treatment capacity as soon as possible and receive definitive treatment from professionals as soon as possible. This can reduce the occurrence of sepsis and organ dysfunction and reduce the mortality rate (25, 26). Xuebijing injection has the effects of promoting blood circulation, removing blood stasis, clearing away heat and detoxification and strengthening the root. Many pharmacological studies have shown that Xuebijing Injection has the effects of improving coagulation function, microcirculation and protecting vascular endothelial cells. At the same time, it can prevent secondary injury of liver and other organs by inhibiting the release of inflammatory factors and blocking the cascade waterfall reaction of inflammatory factors (27, 28). The defense system of the human body is mainly completed by nerve regulation and hormone. When the body is hit hard, it can stimulate the stress response and promote the release of inflammatory cell mediators, thus damaging tissue cells. Ulinastatin has the effects of stabilizing lysosomal enzymes and inhibiting the release of inflammatory cells, which can reduce inflammation, protect internal organs, fight infection and remove oxygen free radicals (29, 30).

The results of this study showed that after the treatment, the APACHE II score of the observation group was (10.35 ± 3.04) lower than that of the control group (15.93 ± 4.52), the WBC and neutrophils of the observation group were (15.19 ± 2.91) and (0.65 ± 0.04) lower than those of the control group (16.42 ± 3.44) and (0.79 ± 0.05), and the PLT was (162.85 ± 43.92) higher than that of the control group (122.68 ± 36.89). These results indicated that Xuebijing combined with ulinastatin could improve the condition and prognosis of patients with traumatic sepsis. Analysis of the reasons are as follows: Xubijing can effectively antagonize endotoxin and inflammatory mediators, protect vascular endothelial cells, improve coagulation function, dilate blood vessels, improve microcirculation and tissue perfusion, reduce capillary permeability, promote fiber tissue reabsorption and repair of tissue lesions, regulate immunity, and protect tissues and organs. And ulinastatin is a broad spectrum of protease inhibitors, can stabilize lysosomal membrane and membrane, restrain various proteolytic enzyme activity, inhibiting inflammatory factor, the production of oxygen free radical and release, also can protect the vascular endothelial cells, adjust the blood coagulation and immune function, improve microcirculation and tissue perfusion, thus reduce tissue damage. Chen (31) believed that TNF-α is the initiator of inflammatory response and the key mediator of the damaging effect of endotoxin. TNF-α induces the production of inflammatory cytokines such as IL-6, activates lymphocytes and a variety of inflammatory transduction pathways, participates in the immune response, and finally affects organ functions. Il-6 co-promotes T lymphocyte proliferation with TNF-α. Besides, the results of this study showed that the levels of serum PCT, IL-6, and TNF-α in the observation group after treatment were (11.38 ± 3.05), (10.74 ± 3.82), (9.82 ± 2.35) lower than those in the control groups (17.34 ± 3.29), (15.28 ± 4.05), (13.24 ± 3.06). These results indicated that Xuebijing combined with ulinastatin could reduce the inflammatory response in patients with traumatic sepsis. The reason was analyzed that the main components of Xuebijing Injection could improve microcirculation and increase blood flow. Reduce that inflammatory reaction and the permeability of capillaries, reduce inflammatory exudation, promoting the absorption of inflammation, and inhibiting the formation of inflammatory granulomas, thereby sufficiently reduce the inflammatory reaction. Ulinastatin can inhibit trypsin, kallikrein and neutrophil elastase, and has a significant blocking effect on the activation of inflammatory cells and cascade cascade reaction between inflammatory factors. In addition, ulinastatin can improve microcirculation and tissue perfusion, thereby further improving the inflammatory response of patients.

The results of this study showed that after treatment, the serum levels of CD3+, CD4+, CD8+, and CD4+/CD8+ in the observation group were (50.64 ± 4.98), (40.56 ± 4.82), (27.22 ± 3.29), (1.49 ± 0.24) higher than those in the control group (46.08 ± 4.75), (34.69 ± 4.08), (25.14 ± 3.18), (1.38 ± 0.19). These results indicated that Xuebijing combined with ulinastatin could restore the immune function of patients with traumatic sepsis. The reason was analyzed that Xuebijing Injection combined with ulinastatin could improve the

immune function decline, protein metabolism abnormalities and renal function decline induced by infection stimulation, prevent the organ and cell damage induced by endotoxin stimulation, and improve the microcirculation of patients during shock. The liver is the most vulnerable organ to inflammatory injury. The production of excessive free radicals and the ischemia and hypoxia of the body can lead to damaged membrane protein function and the destruction of mitochondrial membrane and liver membrane, thus causing damage to the secretion, uptake and transport of bilirubin by hepatocytes. Acute liver injury may be caused by sepsis at any stage, mainly manifested as elevated transaminases and TBIL and coagulation disorders. The results of this study also showed that after treatment, the levels of TBIL and AST in the observation group were (12.35 ± 3.82), (25.66 ± 4.49) lower than those in the control groups (18.43 ± 4.06), (34.58 ± 5.06). The reason was analyzed as follows: Xuebijing injection can inhibit the release of inflammatory factors and improve the synthesis ability of liver protein, thus reducing liver injury; Moreover, it has protective effect on liver, which may be related to regulating p-STAT3 signaling pathway and inhibiting the overexpression of pro-inflammatory factors. Ulinastatin can improve microcirculation and remove oxygen free radicals, fundamentally control cell damage and protect the liver function of patients.

CONCLUSION

Xubijing combined with ulinastatin has a good effect in the treatment of patients with traumatic sepsis, which can effectively improve the condition, reduce the body's inflammatory response, and promote the recovery of patients' immune function and liver 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.

ETHIC STATEMENT

The studies involving human participants were reviewed and approved by This study was approved by the ethics committee of Chongqing Qijiang District People's Hospital (2017008). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YS and YZ are co-first authors. YS is the mainly responsible for the writing, the research is completed by YZ and data analysis of the article is completed by Hongsheng Yuan. The corresponding author is Chuan Shen and he is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Explore the Value of Dual Source Computer Tomography Automatic Tube Current Regulation in Reducing the Radiation Dose of CTA in Lower Extremity Vessels

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Objective: To investigate the value of dual source computer tomography automatic tube current regulation in reducing the radiation dose of CTA in lower limb vessels.

Methods: From February 2020 to December 2021, 64 patients with lower limb artery CTA were selected in our hospital because of the symptoms of foot ischemia. According to the random number table, patients were divided into control group (treated with fixed tube current technology) and observation group (treated with automatic tube current regulation technology), with 32 cases in each group. All patients underwent a dual source computer tomography scan. Control group: tube voltage 120 kV, tube current 250 mA; Observation group: tube voltage was 80 kV, and reference tube current was 80–380 mA. Other scanning conditions of patients in the two groups were the same. CTDIvol, DLP and calculated SNR and CNR were recorded to obtain the ED.

Results: The values of CTDIvol, DLP and ED in the observation group were lower than those in the control group ($P < 0.05$). There was no significant difference in CT value, SD value, SNR value and CNR value of the femoral artery segment, popliteal artery segment and posterior tibial artery segment between the two groups ($P > 0.05$). The image quality scores of patients in the control group were slightly higher than those in the observation group, but there was no statistical difference between the two groups ($P > 0.05$).

Conclusion: The application of dual source computer tomography automatic tube current adjustment technology in CTA examination of lower limb vessels can automatically adjust the compensation output and realize the output of different tube currents in different thicknesses, densities and angles. On the premise of not affecting the image quality, the radiation dose in the scanning process to the maximum extent, and reasonably protect the examined patients.

Keywords: dual source computer tomography, automatic tube current regulation technology, CTA, radiation dosage, extremity vessels

INTRODUCTION

Arterial disease of the lower limbs is a kind of vascular disease that seriously harms human health, and it involves a wide range of asperts. In the later stage, it is mainly manifested as severe stenosis or occlusion of blood vessels, aneurysm formation, etc., which easily leads to ischemia or necrosis of the distal limbs, and often requires surgery or intervention therapy (1, 2). At present, the examination of lower limb arterial obstructive disease mainly diagnoses the cause, location, scope and degree of the disease when the disease occurs in the main artery or larger branch. Imaging examination is an important basis and prerequisite for identifying lesions and making treatment plans (3, 4). Although digital subtraction angiography is the gold standard of blood vessel examination, it has not been widely accepted as a routine blood vessel examination because of its invasiveness, high cost, and many complications.

With the rapid development of CT, the imaging speed of CT angiography is fast, relatively cheap, and there are few complications. Clinically, it is favored by doctors and patients, and it is a common means to diagnose vascular diseases at present. However, with its increasing clinical applications, the radiation dose has attracted more and more attention (5, 6). In many developed countries, CT is regarded as the most important cause of iatrogenic radiation. A wide range CTA scan of lower limb blood vessels using routine scanning will lead to an increase in the radiation dose of the subjects and the potential incidence of cancer in the exposed population (7). CTA scanning range of lower limbs is long, and there are obvious differences in thickness and density of each segment. If the current and voltage of the tube are fixed too high during the whole process, it will cause unnecessary radiation, or too low voltage will affect the image quality (8). Therefore, how to optimize the combination of tube voltage and tube current to reduce the scanning radiation dose and reduce the potential radiation damage is of paramount importance. In this study, the effective tube current was calculated based on the ray absorption by different parts of the human body and the shape of the scanned object to automatically adjust, and whether the automatic tube current adjustment technology could achieve the purpose of reducing the radiation dose while ensuring the image quality was discussed.

DATA AND METHODS

General Information

From February 2020 to December 2021, 64 patients with lower limb artery CTA were selected in our hospital because of the symptoms of foot ischemia. Inclusion criteria: Age ≥18 years old; BMI 20–30 kg/m^2; The patient cooperated well. Exclusion criteria: Allergy to iodine contrast agent; Severe cardiac and renal insufficiency; Hyperthyroidism; Pregnant or lactating women. The patients were divided into a control group and an observation group according to the random number table, with 32 cases in each group. The control group was treated with fixed tube current technology, while the observation group was treated with automatic tube current regulation technology. In the control group, there were 22 males and 10 females, with the average age of (54.81 ± 7.94) years old and body mass index (BMI) (24.84 ± 1.46) kg/m^2. In the observation group, there were 24 males and 8 females, with the average age of (55.17 ± 8.01) years old and BMI (24.73 ± 1.39) kg/m^2. This study was approved by the Hospital Ethics Committee and all patients signed informed consent forms before the examination.

Research Methods

Inspection Methods

All patients underwent a dual source computer tomography scan (SOMATOM Definition CT, DSCT). Scanning range: From the level of the third lumbar vertebra (including part of the abdominal aorta) to the foot end, to both soles of the feet. Supine position foot advanced, calm breathing. 120 mL of iopamidol (370 mgI/mL) was used as the contrast agent, and the injection was conducted in two consecutive times. The first injection was conducted with 80 mL, and the flow rate was 4.0 mL/s; A second injection of 40 mL was performed at a flow rate of 3.0 mL/s. After the injection of contrast agent, 50 mL normal saline was injected with a flow rate of 4.0 mL/s. A region of interest was selected at the popliteal fossa for monitoring using contrast tracking techniques. The trigger level was distal to the abdominal aorta, and the scan was manually triggered after the CT value reached the preset value (100 HU). Other scanning conditions of the patients in the two groups were the same: reconstruction layer thickness of 0.75 mm, reconstruction interval of 0.5 mm, pitch of 1.375, collimation of 64 mm × 0.6 mm, reconstruction matrix of 512 × 512, and reconstructed field of view of 185–200 mm. Control group: tube voltage 120 kV, tube current 250 mA; Observation group: tube voltage was 80 kV, and reference tube current was 80–380 mA.

Radiation Dose Assessment

The scan length after examination for each patient was calculated. The CT volume dose index (CTDIvol) and the dose length product (DLP) automatically calculated by the device were recorded in the image data column after the scan to obtain the effective dose (ED) $= \mathrm{DLP} \times \mathrm{W}$ ($\mathrm{W} = 0.019\ \mathrm{mSv \cdot mGy^{-1} \cdot cm^{-1}}$) (9).

Image Evaluation

The scanned data were transmitted to the workstation for volume rendering, multiplanar reconstruction, maximum intensity projection and curved surface reconstruction, followed by post-processing of the images.

The subjective 3-segment scoring was performed by two senior physicians in the cardiovascular group using a double-blind method. First segment: from the distal end of the abdominal aorta to the branch of the internal and external iliac arteries of the common iliac artery; Second segment: from the branch of internal and external iliac artery of the common iliac artery to the anterior and posterior tibial artery of the popliteal artery; Third segment: The popliteal artery runs from the anterior and posterior tibial arteries to the

following parts. According to the main points of lower extremity artery diagnosis, the scoring criteria were established as follows: 3 points: The lumens of arteries and their branches in the 3 groups were well filled with contrast agent, which could clearly show the calcification of the vessel wall, the degree and extent of stenosis, and the branches of arterioles. 2 points: The lumens of arteries and their branches in the three groups were better filled with contrast agent, which could better show the calcification of the vascular wall, and the degree and scope of stenosis. The branches of arterioles showed better. 1 points: The arteries and their branches in the three groups showed poor contrast, the vessel wall was rough, and the branches and segments of some arterioles were poor. 0 points: Only the morphology of the main blood vessels in the three groups could be displayed, and the distal vessels and branches were not fully displayed or could not be displayed.

Calculating a signal-to-noise ratio (SNR), wherein SNR = arterial CT enhanced scan value/image noise SD value; Contrast signal-to-noise ratio (CNR), CNR = (arterial CT enhancement scan value-muscle tissue CT value)/image noise SD value. Measure that CT values of the midpoint of the common iliac artery, the midpoint of the external iliac artery and the midpoint of the femoral artery and calculate the average CT value representing a target tissue signal; The standard deviation (SD) of the ambient air CT value measured at the midpoint of the bilateral common iliac arteries represented image noise; The measure mean CT values of that bilateral psoas muscle represent background signals.

Statistical Methods

SPSS22.0 software was used for processing. Measurement data such as CTDIvol, DLP, and ED values of the experimental data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and pairwise comparison of measurement data between groups was analyzed by t test. The test level was $\alpha = 0.05$, and $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of Radiation Doses Between the Two Goups

The values of CTDIvol, DLP and ED in the observation group were lower than those in the control group ($P < 0.05$). See **Figure 1**.

Comparison of Measured Values of Femoral Artery Segment Between the Two Groups

There was no significant difference in CT value, SD value, SNR value and CNR value of femoral artery segment between the two groups ($P > 0.05$). See **Figure 2**.

Comparison of Measured Values of Popliteal Artery Segment Between the Two Groups

There was no significant difference in CT value, SD value, SNR value and CNR value of popliteal artery segment between the two groups ($P > 0.05$). See **Figure 3**.

Comparison of Measured Values of Posterior Tibial Artery Segment Between the Two Groups

There was no significant difference in CT value, SD value, SNR value and CNR value of posterior tibial artery between the two groups ($P > 0.05$). See **Figure 4**.

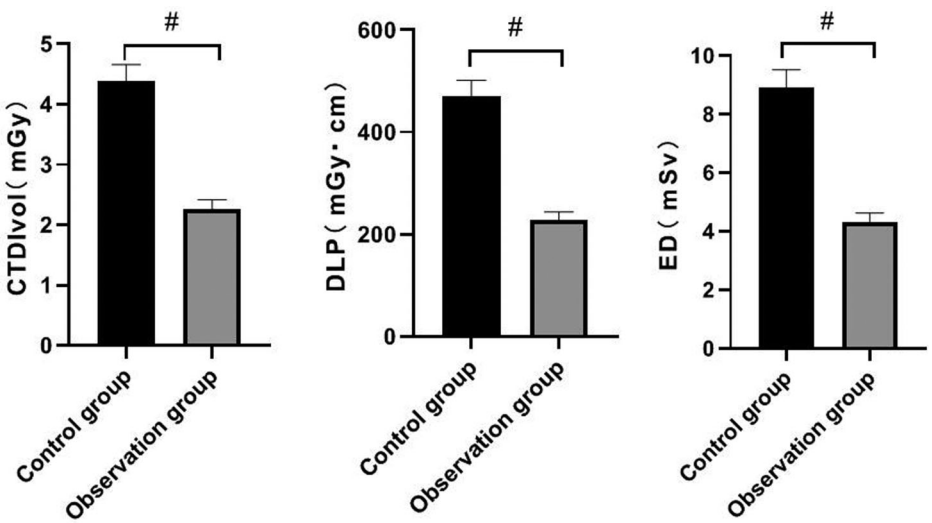

FIGURE 1 | Comparison of radiation doses between the two groups. Note: Compared with the control group, $^{\#}P < 0.05$.

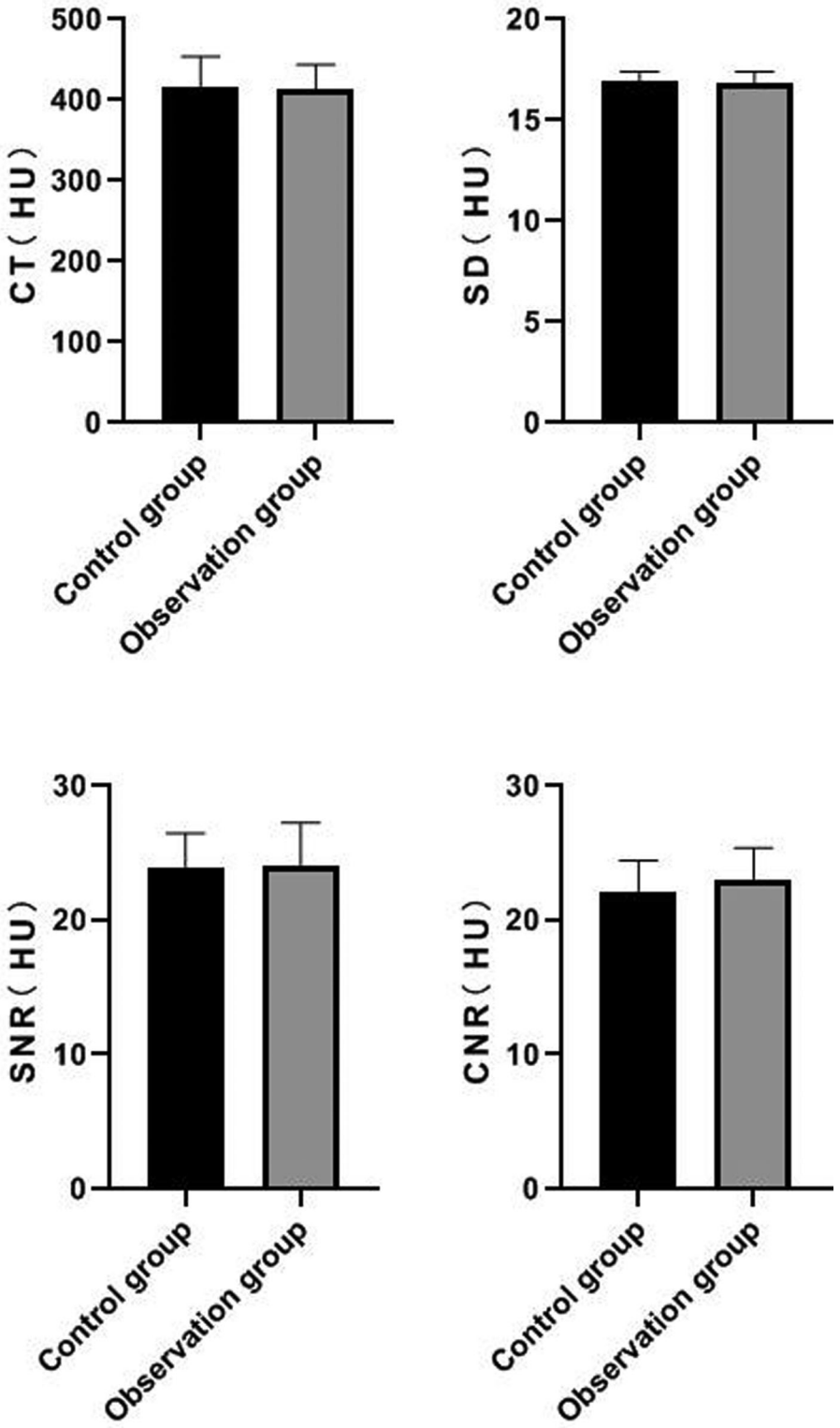

FIGURE 2 | Comparison of measured values of femoral artery segment between the two groups.

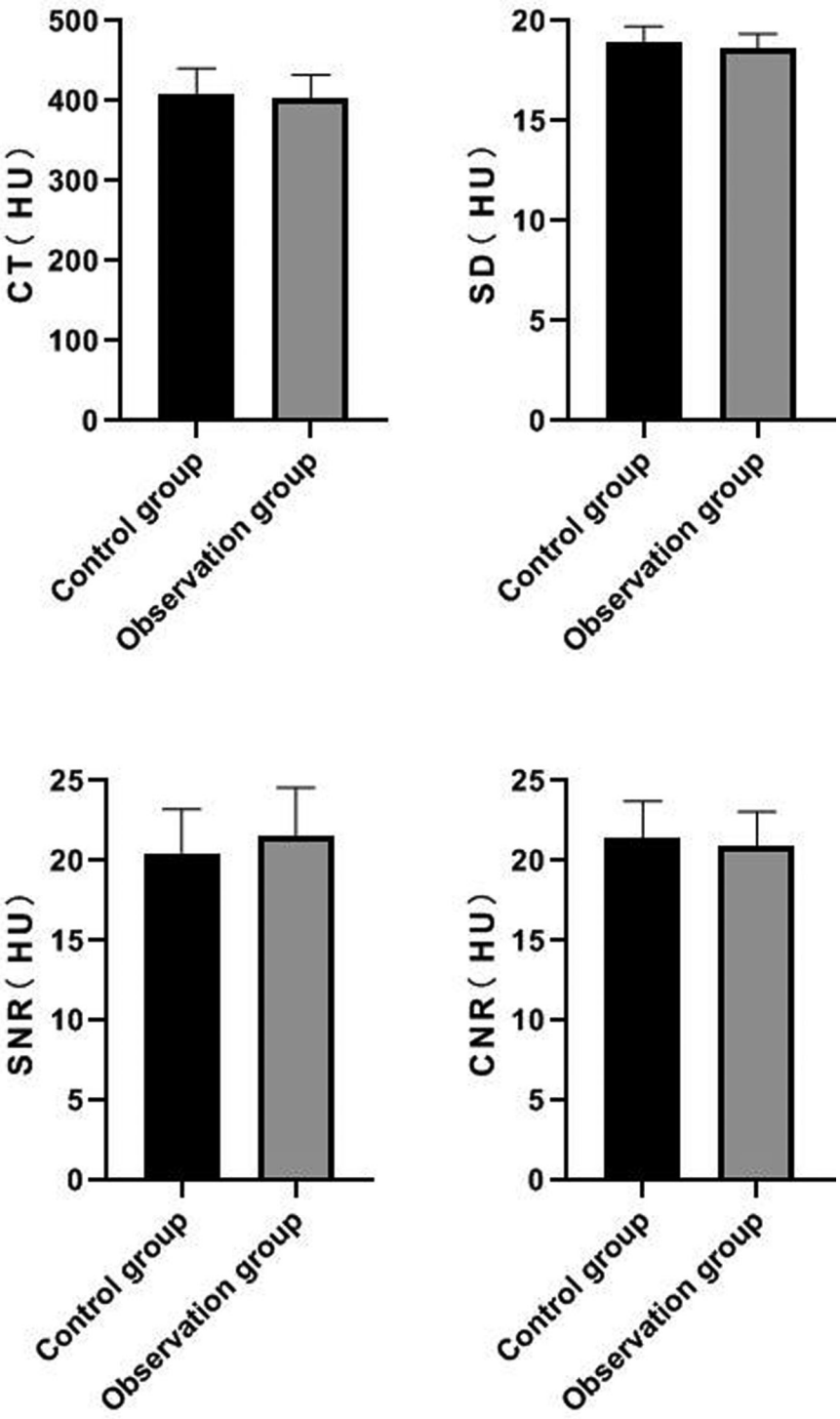

FIGURE 3 | Comparison of measured values of popliteal artery segment between the two groups.

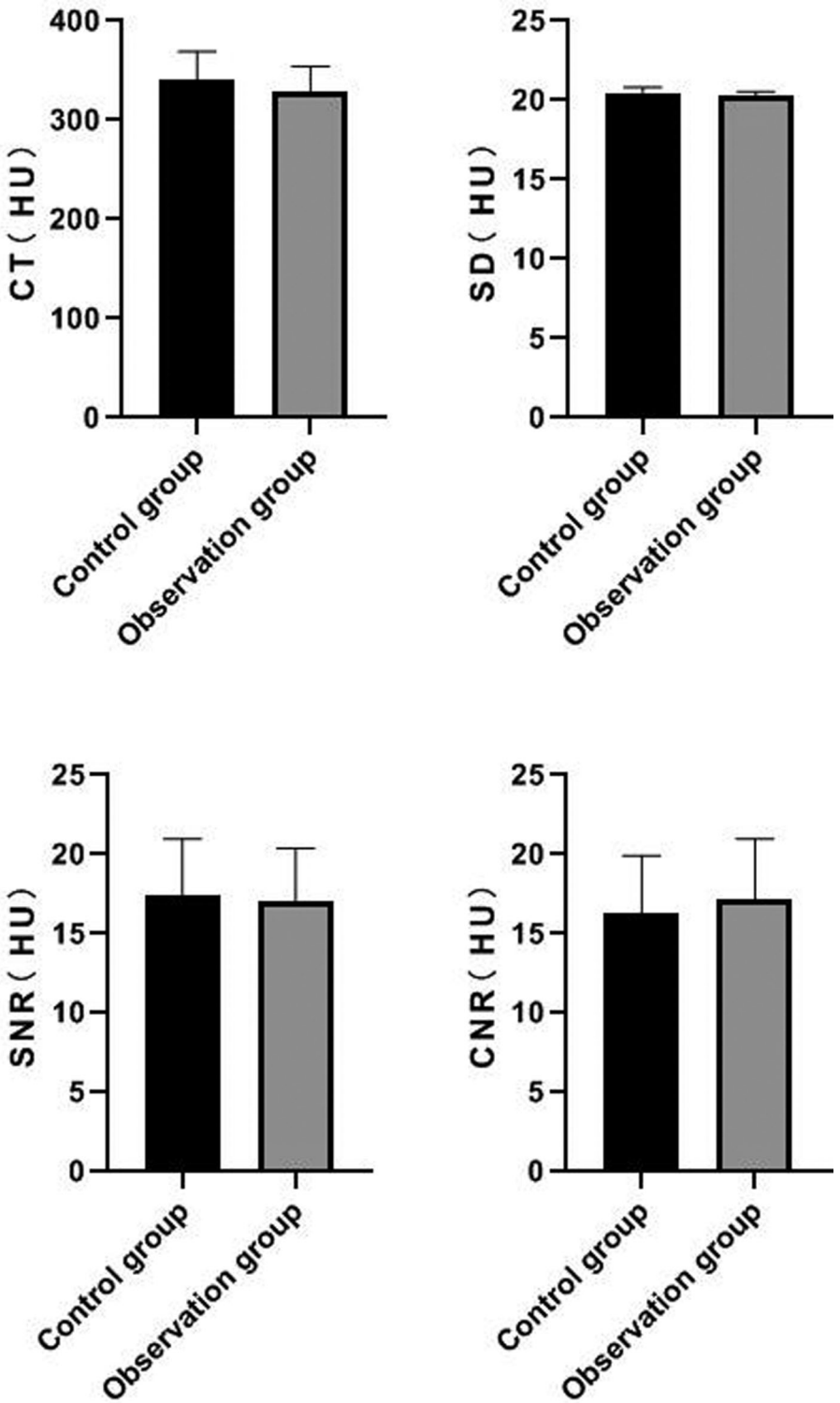

FIGURE 4 | Comparison of measured values of posterior tibial artery segment between the two groups.

Comparison of Image Quality Scores Between the Two Groups

The image quality scores of patients in the control group were slightly higher than those in the observation group, but there was no statistical difference between the two groups ($P > 0.05$). See **Figure 5**.

DISCUSSION

The harm of X-ray radiation used in medical diagnosis is mainly carcinogenic and teratogenic, and the harm degree is related to the absorbed dose. According to the estimation of the "Report of the Committee on the Biological Effects of Ionizing Radiation VII", for every 10,000 population in the United States, 1 case of radiation-induced cancer is added for every 1 mSv exposure (10). With the development of CT, the frequency of examination has doubled all over the world, and the radiation dose generated from CT examination accounts for about half of the total medical radiation dose. CT radiation dose is related to tube voltage, tube current, pitch, scanning range and collimator width. Other factors related to radiation dose are also closely related to image quality. Therefore, how to ensure the image quality while minimizing the radiation dose has become one of the research directions of CT (11–13).

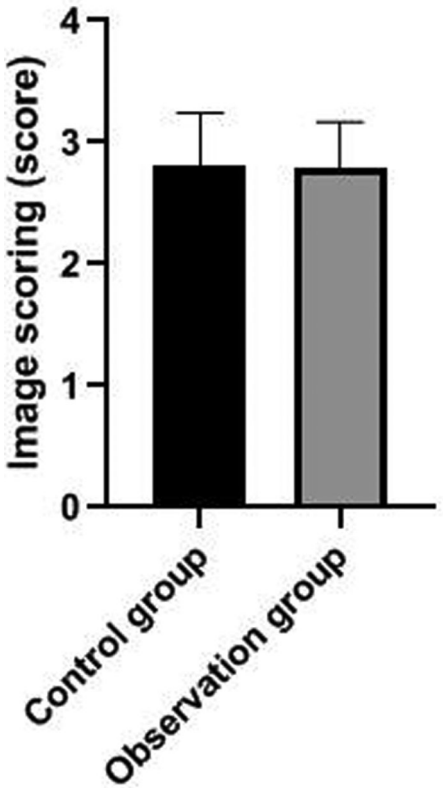

FIGURE 5 | Comparison of image quality scores between the two groups.

In the CTA examination of lower limb blood vessels, the CTA scanning range of the lower limb is long. After passing through the gonadal organs (radiation-sensitive organs), the thicknesses of tissues in each segment is quite different (such as the pelvic cavity, knee joint and ankle joint), and the distribution range of tissues in the whole segment is uneven (14, 15). Because the tube current needs to be multiplied by the downcomer voltage to ensure the image quality, if the tube voltage is greatly reduced and the tube current is doubled, the radiation dose may not be reduced, and the image quality may suffer (16–18). Therefore, in the process of reducing the radiation dose, it is difficult to grasp the adjustment of various parameters, and it is impossible to give considerations to the image quality and radiation dose. If we want to ensure the image quality and reduce the radiation dose, we must choose the best combination of tube voltage and current (19–21).

In this study, the automatic tube current regulation technology was used to make the tube current float up and down within a certain range. When the tube voltage at the thicker part was insufficient, the tube current is compensated to ensure the image quality. For the thinner part, the output of tube current is automatically reduced to reduce radiation dose, and the optimal combination of tube voltage and tube current can be realized according to different thicknesses and densities. The results showed that the values of CTDIvol, DLP and ED in the observation group were lower than those in the control group. It shows that the application of automatic tube current adjustment technology in CTA of lower limb, make accurate assessment of lower limb artery stenosis, display the location and degree of the lession from multiple angles and directions, and reduce the radiation dose on the premise of ensuring the image quality.

Applying the technique of automatic tube current adjustment, appropriately increase the tube current of iliac artery and appropriately decreasing the tube current of thigh and calf artery can ensure the noise consistency of the whole lower limb scanning range and reduce unnecessary radiation dose (22–24). The results of this study showed that there was no significant differences in CT, SD, SNR, and CNR values of femoral artery, popliteal artery and posterior tibial artery between the two groups. It could be seen that the automatic tube current regulation technology had little influence on the SD value of high-density tissue while ensuring the good filling of the contrast media in the vascular lumen. The results also showed that the image quality scores of the control group were slightly higher than those of patients in the observation group, but there was no statistical difference between the two groups. According to the international radiological examination, we should follow the principle of "rational use of low dose", carefully select scanning parameters, optimize all scanning procedures, and allow certain noise in according to different clinical requirements on the premise of meeting the requirementa of clinical diagnosis, so as to reduce the radiation dose as much as possible (25, 26). CTA of lower limb vessels mainly observes the arterial vessels, but does not require high image quality of other tissues. The filled high-

density blood vessels and surrounding tissues have high CNR, and the whole segment and important branches of the blood vessels can be clearly displayed through various post-processing methods, so there is no significant difference in quality score results of reconstructed blood vessel images (27, 28).

Limitations of this study: ① The radiation dose recorded by two groups of patients with fixed tube current and automatic tube current adjustmengt is not as accurate as that recoeded by the same group of patients with two different examination methods. ② The data of patients with BMI within the range of 20–30 kg/m^2 were only collected in the study, while patients with other BMI ranges were not included in the study. The cumulative number of case in follow-up research is needed to further support this conclusion.

In summary, the application of dual source computer tomography automatic tube current adjustment technology in CTA examination of lower limb vessels can automatically adjust the compensation output and realize the output of different tube currents in different thicknesses, densities and angles. On the premise of not affecting the image quality, the radiation dose in the scanning process to the maximum extent, and reasonably protect the examined patients.

DATA AVAILABILITY STATMEENT

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

ETHIC STATEMENT

The studies involving human participants were reviewed and approved by. This study was approved by the ethics committee of our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HX is mainly responsible for the writing, data analysis, and research design of the article. The corresponding author is YY, and she is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Effect of Oral Chinese Herbal Preparations Regulating Intestinal Flora on Lipid Metabolism Disorders in Patients: A Meta-Analysis of Controlled Clinical Studies

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Background: Lipid metabolism disorders can damage human health, and the changes in human intestinal flora are closely related to lipid metabolism disorders. Traditional Chinese medicine (TCM) can play a role in regulating intestinal flora and balancing intestinal microecology. In this meta-analysis, the role of oral preparations of TCM that regulate intestinal flora, in the prevention and treatment of lipid metabolism disorders, was systematically evaluated.

Methods: The databases CBM, Pubmed, Embase, CNKI, Wanfang, and Google Scholar were searched by rapid matching of keywords to obtain clinical controlled studies related to oral preparations of TCMs regulating intestinal flora. After screening and quality evaluation, meta-analysis was performed using Review Manager 5.3 software.

Results: Total of 835 patients were enrolled in the 10 articles included in this study. Meta-analysis showed that TCM intervention could reduce the level of total cholesterol (TC) in patients with abnormal lipid metabolism [*mean difference (MD)* = −0.61, 95% confidence interval (95%CI) (−0.80, −0.42), $p < 0.00001$], reduce triacylglycerol (TG) level [$MD = -0.46$, 95%CI (−0.60, −0.33), $p < 0.00001$], increase high-density lipoprotein (HDL) level [$MD = 0.25$, 95%CI (0.17, 0.34), $p < 0.00001$], reduce the number of intestinal enterobacteria [$MD = -0.64$, 95%CI (−0.79, −0.49), $p < 0.00001$], reduce the number of enterococci [$MD = -1.14$, 95%CI (−1.66, −0.63), $p < 0.00001$], increase the number of intestinal lactobacillus [$MD = 0.41$, 95%CI (0.09, 0.74), $p = 0.01$], and increase the number of intestinal bifidobacteria [$MD = 0.94$, 95%CI (0.20, 1.68), $p = 0.01$].

Conclusion: The application of oral preparations of TCMs that regulate intestinal flora, in the prevention and treatment of lipid metabolism disorders, can increase the colonization of beneficial bacteria in the intestine of patients, inhibit the growth of harmful bacteria, and restore the intestinal microecological balance, thus indirectly acting on the regulation of blood lipids in patients and contributing to the recovery of dyslipidemia.

Keywords: intestinal flora, traditional Chinese medicine, lipid metabolism disorders, oral Chinese herbal, meta-analysis

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INTRODUCTION

Lipid metabolism disorders, also known as dyslipidemia, refer to the abnormal increase of one or more of the indicators of triacylglycerol, total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) in human serum (1). With the gradual improvement of people's living standards and changes in dietary structure in China, dyslipidemia has become one of the major diseases threatening the health of middle-aged and elderly people, and is the main cause of atherosclerosis (AS) and coronary heart disease (CHD), damaging the health of patients (2). Lipid metabolism disorders often emerge with diseases such as obesity, diabetes, and ovarian syndrome, causing complex effects on the human body (3). Therefore, it is clinically important to seek treatments that effectively regulate the disorders of lipid metabolism and prevent the occurrence of dyslipidemia. Some studies (4) have found that the changes in intestinal flora in human body are closely related to lipid metabolism disorders. When lipid metabolism disorders occur, the intestinal flora in patients also undergo structural changes correspondingly, and the changes in intestinal flora structure can also synchronously affect the changes in blood lipids in patients. At present, Chinese medicine, which has accumulated long-term clinical practice, is gradually becoming a comprehensive treatment for lipid metabolism disorders, and some clinical studies have shown that regulating intestinal flora and balancing intestinal microecology are among the important ways for Chinese medicine to play a role (5). After oral preparation of traditional Chinese medicine (TCM), the unabsorbed components are in contact with intestinal flora, and a series of biotransformations, such as hydrolysis, oxidation, and reduction reactions, occur in the TCM components under the action of flora, making the components to be more easily absorbed and metabolized, and even produce new pharmacological activities. At the same time, the TCM components will have a certain effect on the diversity, richness, and bacterial structure of intestinal flora (6). At present, many studies (7, 8) have suggested that oral preparations of TCMs that regulate intestinal flora can prevent and treat lipid metabolism disorders, but there is no systematic evaluation of this intervention method, and this study searched recent clinical controlled studies to provide more exact evidence for oral preparations of TCMs to prevent and treat lipid metabolism disorders.

METHOD

Criteria for Inclusion of Literature in the Study

Literature Type

All studies were randomized controlled trials. We also excluded controlled clinical trials (CCTs), cohort study, case-control study, and case series. Other summaries of experience, reviews, case studies, and studies of heterogeneity were also excluded.

Inclusion, Exclusion Criteria

1. Inclusion criteria: The type of literature was domestic and foreign published clinical randomized controlled trials; the participants were adults aged >18 years, with abnormal lipid metabolism, including diabetic patients, obese patients, and patients with ovarian syndrome; the general data of patients such as gender, age, and weight were comparable; The included literature was able to provide sufficient data information for the study to perform calculations.

2. Exclusion criteria: use of probiotic preparations or statins or fibrate lipid-regulating drugs in the trial group; studies with inaccessible full text; studies with incomplete data results; those with duplicate data.

Description of Intervention

Since the included studies were randomized controlled studies, two randomized groups were included. The patients in both the groups were given the same basic treatment, aerobic exercise, resistance training, and diet control. The observation group took oral preparations of TCM (the TCM preparations were verified to regulate the number of intestinal flora), while the control group was not given additional measures or only given placebo. The intervention time was more than 3 weeks.

Outcome Indicators

In this study, the main outcome indicators included two categories: (a) post-treatment lipid levels, containing TC, triglycerides (TG), and HDL; (b) post-treatment number of intestinal flora, containing enterococcus, enterobacter, lactobacillus, and bifidobacterium.

Search Strategy

Search databases: CBM, Pubmed, Embase, CNKI, and Wanfang. We also searched relevant literatures by *google scholar* using the keywords "*Traditional Chinese Medicine*" or "*TCM*" or "*Intestinal flora*" or "*gut microbiota*" or "*Metabolic syndrome.*"

Literature Screening and Data Extraction

Two researchers independently screened the included studies and excluded duplicate articles, and obviously unqualified articles, by reading the titles and abstracts. If there was a conflict of opinion between the two researchers, a third researcher was consulted to resolve the difference of opinion.

Two researchers independently extracted the data, read each included study using a pre-prepared form, and obtained the data from the text, including author, journal name, publication time, number of participants, age, gender composition, weight, body mass index (BMI), disease duration, blood glucose level, four items of blood lipids before intervention, grouping method, number of cases in each group, intervention method, intervention time, and outcome indicators.

If there was no data in the literature for processing, the original author of the literature was contacted to obtain the data. If the data could not be obtained, the literature was discarded.

Literature Quality Evaluation

We used the Evidence-based Health Care Center of JBI (Joanna Briggs Institute) in Australia (9) to evaluate the evaluation criteria for randomized controlled trials. The evaluation criteria included six aspects: randomization, allocation concealment,

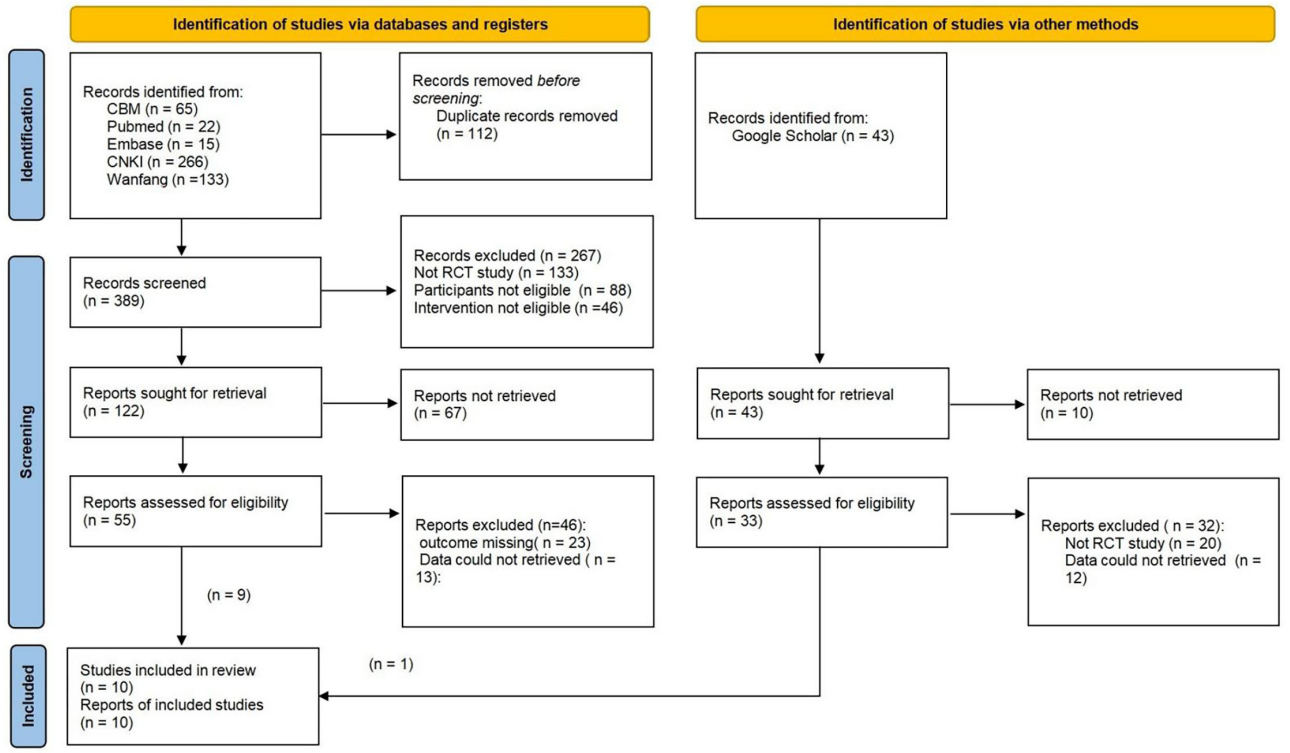

FIGURE 1 | Literature screening flow chart.

blind method, withdrawal and loss to follow-up, ITT (Intention-to-treat) analysis, and baseline comparison. The literatures were divided into three levels: Grade A: meeting the evaluation in the above six aspects, with less possibility of bias; Grade B: partially meeting the evaluation in the above six aspects, with certain possibility of bias; Grade C: most of them did not meet the evaluation, with greater possibility of bias. We only included studies with Grade A or B quality and excluded studies with Grade C quality.

Statistical Analysis

We used Review Manager 5.3 (released by The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) as an analytical tool in this study. The random effects inverse variance model was calculated, and the effect measure used mean difference (*MD*). We used Cochran *Q* test and I^2 to count the heterogeneity of the study, and $I^2 > 50\%$ or $p < 0.1$ indicated statistically significant heterogeneity. The heterogeneity was investigated by piecemeal exclusion method. If the source of heterogeneity was not obtained, only general descriptive analysis was performed. Funnel plots were used to represent publication bias.

RESULTS

Literature Search Results

Figure 1 shows the results of the literature search and the screening process.

Basic Characteristics of Included Literatures

A total of 10 articles (10–19) with a total of 835 patients were included in the study and published between 2015 and 2021, with an average intervention time between 1 and 6 months. Specific information is shown in **Table 1**. Only one study (10) used a single herb, while other studies used a variety of herbal formulas, which are shown in **Table 2**.

Risk of Bias Analysis and Quality Assessment

In this study, all literatures were randomized controlled trials, with descriptive blind method (single-blind or double-blind), but only literatures (10) had descriptive allocation hide, only literatures (14) recorded drop-out cases in detail, all literatures used ITT analysis, with descriptive baseline comparison.

1. Randomized allocation method: all literature in this study were randomized controlled trials.
2. Allocation concealment scheme: literature (10) used descriptive allocation concealment, and the allocation concealment scheme of the remaining 9 literatures was not described.
3. Blinding: all literature used descriptive blinding (single or double-blind).

TABLE 1 | Basic characteristics of included literatures, characteristics of study subjects, and quality evaluation scores.

References	Patient characteristics	Patient age (years)	BMI (kg/m^2)	Number of cases (E/C)	Experimental group intervention	Control group intervention	Intervention time (Median)	Outcome indicators
Song et al. (9)	Obese female	34.92 ± 6.46	29.99 ± 4.27	13/15	Schisandra chinensis fruit	Placebo	3 mo	(a–c)
Li et al. (10)	Obese patients with ovarian syndrome	20–40	27–29.9	50/50	Chinese herbs for kidney resolving phlegm+ acupuncture	Oral ethinylestradiol cyproterone tablets	3 mo	(a–g)
Chen et al. (11)	Patients with metabolic syndrome	30.5 ± 6.2	32.0 ± 6.58	30/30	Wendan Decoction	Placebo	1 mo	(a–g)
Zhang et al. (12)	Obesity 2 Patients with type 2 diabetes	41–68	19–33	52/54	Shenqi Compound Decoction	Placebo	2 mo	(a–c)
Li et al. (13)	Obese type 2 diabetic patients	51.09 ± 11.34	N/A	49/49	Wenyang Yiqi Huoxue Recipe+Metformin	Metformin	2 mo	(a–g)
Liu et al. (14)	Obese Patients	18–65	>28	24/24	Qi Wei Bai Zhu San	Placebo	3 mo	(b,c)
Du et al. (15)	Patients with glucose resistance	28–70	N/A	20/20	Jiangzhuo Mixture	Placebo	1 mo	(a–c)
Chen et al. (16)	Patients with type 2 diabetes	59.81 ± 5.44	N/A	40/40	Fuzi Lizhong Pills+Glichi	Gleetzil	1 mo	(a–g)
Zhang et al. (17)	Patients with metabolic syndrome	60.3 ± 6.7	28.64 ± 1.69	91/89	Lidan Huatan Huoxue Recipe	Placebo	6 mo	(b,c)
Liu et al. (18)	Spleen deficiency syndrome patients with type 2 diabetes	54.37 ± 6.45	25.01 ± 3.98	48/47	Yiqi Bupi Recipe	Placebo	2 mo	(a–g)

N/A, Not available; E/C, Experimental/Control group.
Outcomes: (a) TC; (b) TG; (c) HDL; (d) number of Enterobacteriaceae; (e) number of Enterococcus; (f) number of Lactobacillus; (g) number of Bifidobacterium.

4. The literature (14) recorded the withdrawal cases in detail, and the other literature studies had no withdrawal or lost visits.
5. ITT analysis: All literature used ITT analysis.
6. Baseline comparisons: All literature had descriptive baseline comparisons. The final assessment was that the overall quality of the literature was good. See **Table 3**.

Meta-Analysis Results

(A) Total cholesterol (mmol/l)

A total of eight literatures (10–14, 16, 17, 19) reported the comparison of TC indicators of patients after oral Chinese medicine intervention, with 302 cases in the experimental group and 305 cases in the control group, and the internal heterogeneity of the eight literatures was statistically significant ($I^2 = 85\%$, $p < 0.00001$). Using the random-effects model, it was shown that Chinese medicine intervention could reduce the TC level of patients with abnormal lipid metabolism [$MD = -0.61$, 95% confidence interval (95% CI) (-0.80, -0.42), $Z = 6.29$, $p < 0.00001$], as shown in **Figure 2**.

(B) Triacylglycerol (mmol/l)

A total of 9 literatures (11–17) reported the comparison of TG indicators after oral Chinese medicine intervention, with 404 cases in the experimental group and 403 cases in the control group. The internal heterogeneity of the nine literatures was statistically significant ($I^2 = 79\%$, $p < 0.00001$). The random-effects model was used to obtain that Chinese medicine intervention could reduce the triacylglycerol level in patients with abnormal lipid metabolism [$MD = -0.46$, 95% CI (-0.60, -0.33), $Z = 6.69$, $p < 0.00001$], as shown in **Figure 3**.

(C) High-Density lipoprotein (mmol/l)

All literatures (10–19) reported the comparison of HDL indicators after oral Chinese medicine intervention, with a total of 417 cases in the experimental group and 418 cases in the control group. The internal heterogeneity of the

TABLE 2 | Composition of Chinese herbal formulas.

Study	Name	Composition
Song et al. (9)	Schisandra chinensis	Schisandra chinensis
Li et al. (10)	Chinese herbs for treating kidney and resolving phlegm	Radix Bupleuri, Radix Paeoniae Alba, *Angelica sinensis*, Rhizoma Cyperi, *Fructus aurantii*, *Ligusticum chuanxiong*, licorice, Atractylodes, tangerine peel, *Poria cocos*, *Pinellia ternata*, coix seed, *Scutellaria baicalensis*
Chen et al. (11)	Wendan Decoction	Zhuru, *Fructus aurantii*, *Pinellia ternata*, tangerine peel, *Poria cocos*, roasted licorice, ginger, jujube
Zhang et al. (12)	Shenqi compound decoction	Ginseng, Astragalus membranaceus, *Cornus officinalis*, Chinese yam, *Rehmannia glutinosa*, *Salvia miltiorrhiza*, cooked rhubarb
Li et al. (13)	Wenyang Yiqi Huoxue Recipe	Rhizoma Aconiti, ginseng, roasted licorice, Atractylodes Macrocephalae, *Poria cocos*, *Fructus aurantii*, red peony, dogwood meat, bupleurum, Cinnamon Twig, dried ginger, *Salvia miltiorrhiza*
Liu et al. (14)	Qi Wei Bai Zhu San	Radix Pseudostellariae, Atractylodes Macrocephalae, *Poria cocos*, patchouli, wood incense, Pueraria, roasted licorice
Du et al. (15)	Jiangzhuo Mixture	Astragalus membranaceus, *Salvia miltiorrhiza*, *Atractylodes lancea*, raw coix seed, raw malt, raw lentils, *Gynostemma pentaphyllum*, chicken nuggets, *Pueraria lobata*
Chen et al. (16)	Fuzi Lizhong Pills	Aconite, *Astragalus membranaceus*, *Pinellia ternata*, ginseng, roasted licorice, tangerine peel, *Atractylodes macrocephala*, huangcen and dried ginger
Zhang et al. (17)	Lidan Huatan Huoxue Recipe	Corn whisker, *Polygonum cuspidatum*, *Pinellia ternata*, *Citrus sinensis*, *Salvia miltiorrhiza*
Liu et al. (18)	Yiqi Bupi Recipe	*Astragalus membranaceus*, *Codonopsis pilosula*, *Atractylodes macrocephala*, *Poria cocos*, licorice

TABLE 3 | Methodological quality assessment and risk of bias analysis based on JBI (Joanna Briggs Institute).

Study	Random sequence generation	Classification hiding	Blind method	Withdrawal and Lost to Follow-up	ITT analysis	Baseline comparison	Quality level
Song et al. (9)	Adopt	Described	Double-blind	Not described	Adopt	Described	Grade A
Li et al. (10)	Adopt	Not described	Single-blind	Not described	Adopt	Described	Grade B
Chen et al. (11)	Adopt	Not described	Single-blind	Not described	Adopt	Described	Grade B
Zhang et al. (12)	Adopt	Not described	Single-blind	Not described	Adopt	Described	Grade B
Li et al. (13)	Adopt	Not described	Single-blind	Described	Adopt	Described	Grade A
Liu et al. (14)	Adopt	Not described	Double-blind	Not described	Adopt	Described	Grade B
Du et al. (15)	Adopt	Not described	Single-blind	Not described	Adopt	Described	Grade B
Chen et al. (16)	Adopt	Not described	Single-blind	Not described	Adopt	Described	Grade B
Zhang et al. (17)	Adopt	Not described	Single-blind	Not described	Adopt	Described	Grade B
Liu et al. (18)	Adopt	Not described	Single-blind	Not described	Adopt	Described	Grade B

10 literatures was statistically significant ($I^2 = 82\%$, $p < 0.00001$). The random-effects model was used to obtain that Chinese medicine intervention could increase the HDL level in patients with abnormal lipid metabolism [$MD = 0.25$, 95% CI (0.17, 0.34), $Z = 5.84$, $p < 0.00001$], as shown in **Figure 4**.

(D) Number of Enterobacteriaceae

A total of four literatures (11, 12, 14, 19) reported the comparison of the number of intestinal enterobacteria in patients after oral Chinese medicine intervention, with 177 cases in the experimental group and 176 cases in the control group. The four literatures had no heterogeneity ($I^2 = 0\%$, $p = 0.92$). Using the fixed-effect model, it was obtained that Chinese medicine intervention could reduce the number of enterobacteria in patients with abnormal lipid metabolism [$MD = -0.64$, 95% CI (-0.79, -0.49), $Z = 8.24$, $p < 0.00001$], as shown in **Figure 5**.

(E) Number of Enterococci

A total of five literatures (11, 12, 14, 17, 19) reported the comparison of the intestinal cocci counts in patients after oral herbal intervention, with a total of 217 cases in the experimental

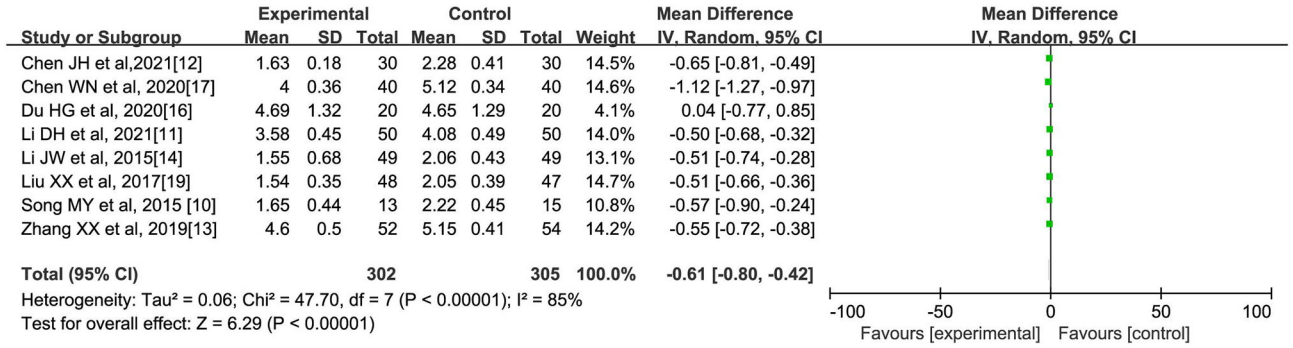

FIGURE 2 | Effect of oral Chinese herbs on total cholesterol (TC) in patients with dyslipidemia.

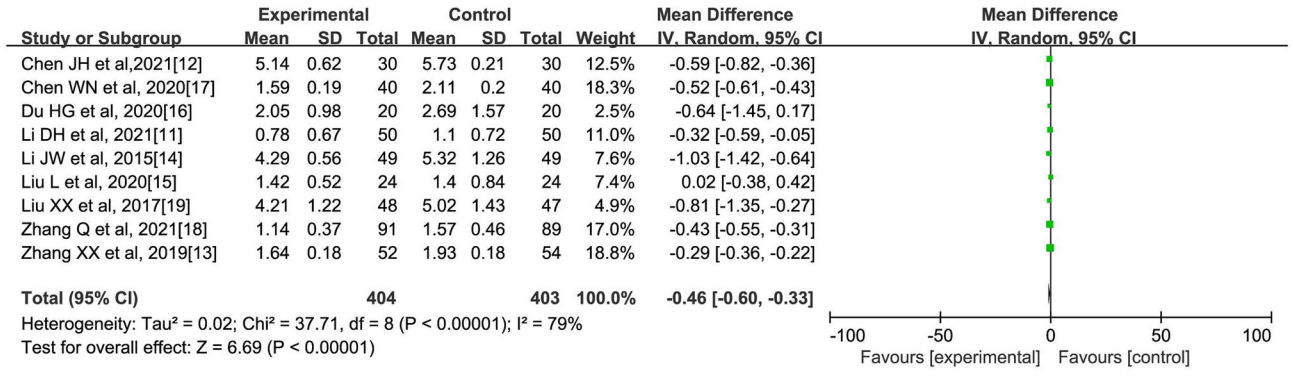

FIGURE 3 | Effect of oral Chinese herbs on triglycerides (TG) in patients with dyslipidemia.

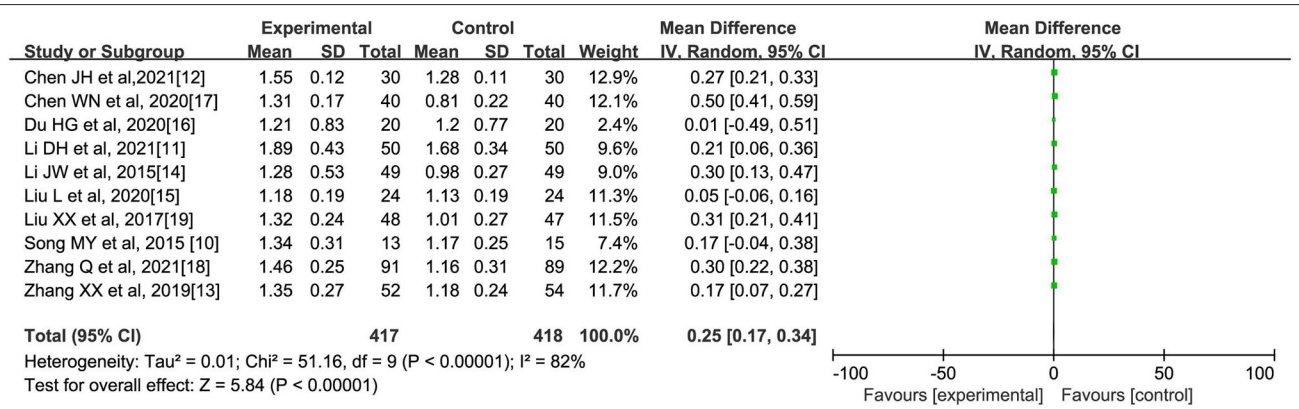

FIGURE 4 | Effect of oral Chinese herbs on high-density lipoprotein (HDL) in patients with dyslipidemia.

group and 216 cases in the control group. The analysis showed significant heterogeneity among the five studies (I2 = 87%, $p < 0.00001$). Meta-analysis using random-effects model showed that the number of enterococci in the experimental group was significantly lower than that in the control group [MD=-1.14, 95% CI (−1.66, −0.63), $Z = 4.34$, $p < 0.00001$], which suggested that herbal interventions could reduce the number of enterococci in patients with abnormal lipid metabolism, as shown in **Figure 6**.

(F) Number of Lactobacillus

A total of four literatures (11, 12, 14, 19) reported a comparison of intestinal lactic acid bacteria counts in patients after oral herbal interventions, with a total of 177 cases in the experimental group and 176 cases in the control group. The

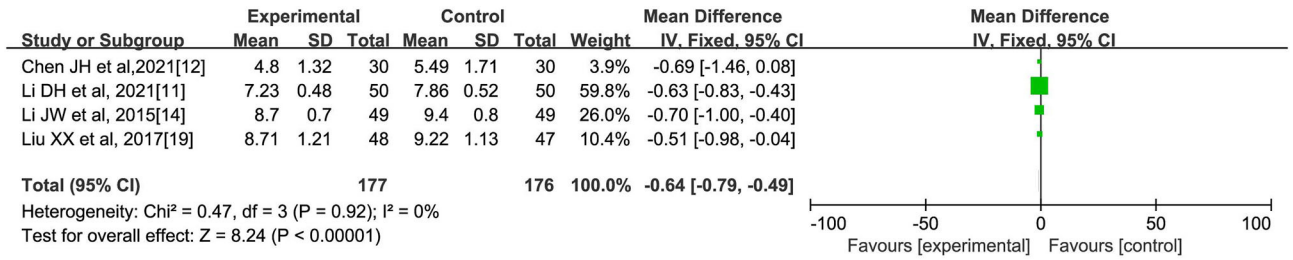

FIGURE 5 | Effect of oral Chinese medicine on the number of intestinal enterobacteria in patients with dyslipidemia.

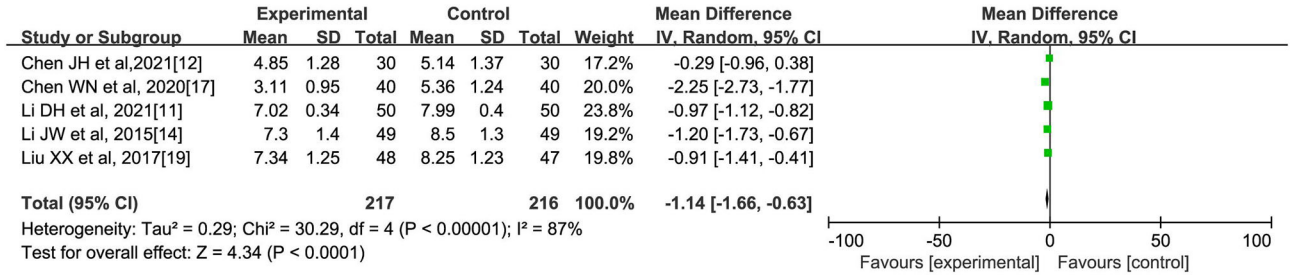

FIGURE 6 | Effect of oral Chinese herbs on the number of intestinal enterococci in patients with lipid abnormalities.

analysis showed significant heterogeneity among the four studies ($I^2 = 53\%$, $p = 0.09$). Meta-analysis using a random-effects model showed that the number of intestinal lactobacilli in the experimental group was significantly higher than that in the control group [$MD = 0.41$, 95% CI (0.09, 0.74), $Z = 2.48$, $p = 0.01$], which suggested that the herbal intervention could increase the number of intestinal lactobacilli in patients with abnormal lipid metabolism, as shown in **Figure 7**.

(G) Number of Bifidobacteria

A total of five literatures (11, 12, 14, 17, 19) reported a comparison of intestinal bifidobacteria counts in patients after oral herbal interventions, with a total of 217 cases in the experimental group and 216 cases in the control group. The analysis showed significant heterogeneity among the five studies ($I^2 = 94\%$, $p < 0.00001$). Meta-analysis using a random effects model showed that the number of intestinal bifidobacteria in the experimental group was significantly higher than that in the control group [$MD = 0.94$, 95% CI (0.20, 1.68), $Z = 2.50$, $p = 0.01$], which suggests that herbal interventions can increase the number of intestinal bifidobacteria in patients with abnormal lipid metabolism, as shown in **Figure 8**.

Heterogeneity Survey and Sensitivity Analysis

In the analysis of the effect of oral Chinese herbs on TC levels in patients, we adopted a case-by-case exclusion method to find the source of heterogeneity. However, after excluding any article, the remaining articles still had heterogeneity, and the heterogeneity between articles came from multiple aspects and may be related to factors such as different characteristics of patients, age, and different formulations of Chinese herbs.

Publication Bias Analysis

In the analysis of the effect of oral Chinese herbs on TG levels in patients, a funnel plot was drawn, and the left and right distributions of the 10 included articles were symmetrical, suggesting that there was no publication bias, as shown in **Figure 9**.

DISCUSSION

Lipid metabolism is regulated by genetics, neurohumoral, hormones, enzymes and tissues, and organs such as the liver. When these factors are abnormal, they can cause lipid metabolic disorders and pathophysiological changes in the related organs, hyperlipoproteinemia, lipidosis, and the resulting clinical syndromes, such as obesity, ketoacidosis, fatty liver, and neonatal scleredema (20). Statins are commonly used drugs for the treatment of dyslipidemia, but such drugs may bring many adverse effects, such as liver and kidney dysfunction, abnormal neuromuscular responses, increased risk of diabetes, and cognitive decline (21). Accumulating evidence suggests that gut flora structure is closely related to the development of lipid metabolism disorders (22). Intestinal flora are a unique microecosystem that depend on the host and affect each other, and when the structure of intestinal flora is disturbed, the dynamic ecological balance of the intestine is disrupted, which can affect bile acid metabolism, thereby changing lipid metabolism, which leads to dyslipidemia (23). Studies have shown (24) that TCM can indirectly regulate blood lipids by regulating intestinal flora. The polysaccharide components in Chinese medicine can promote the proliferation of probiotics

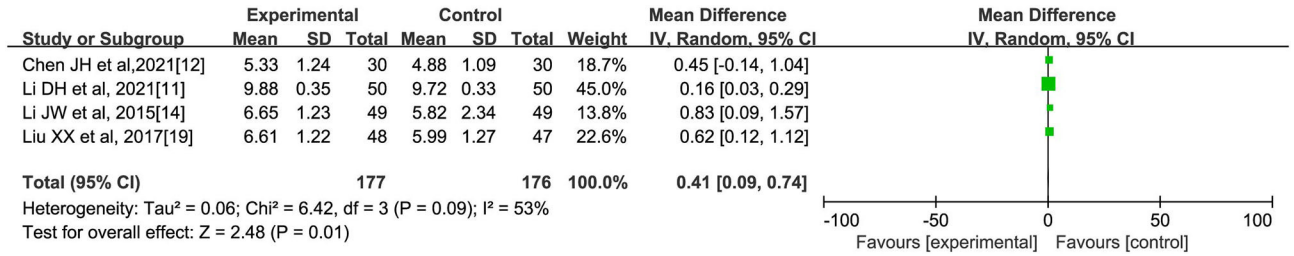

FIGURE 7 | Effect of oral Chinese herbs on the number of lactobacillus in patients with lipid abnormalities.

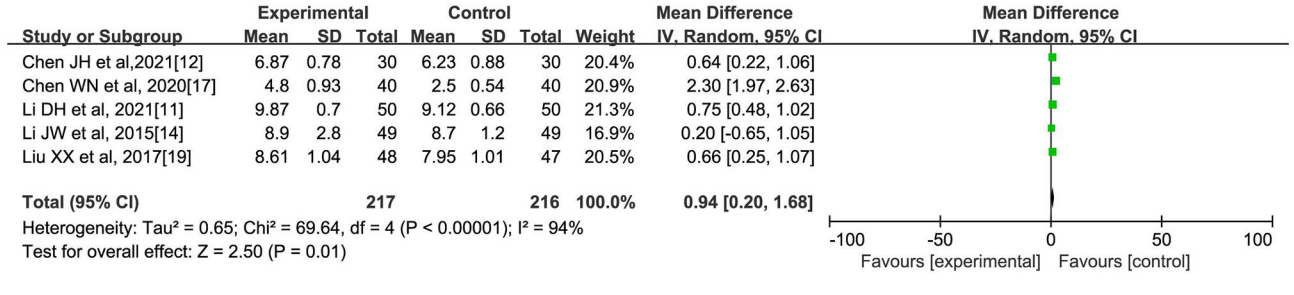

FIGURE 8 | Effect of oral Chinese herbs on the number of intestinal bifidobacteria in patients with lipid abnormalities.

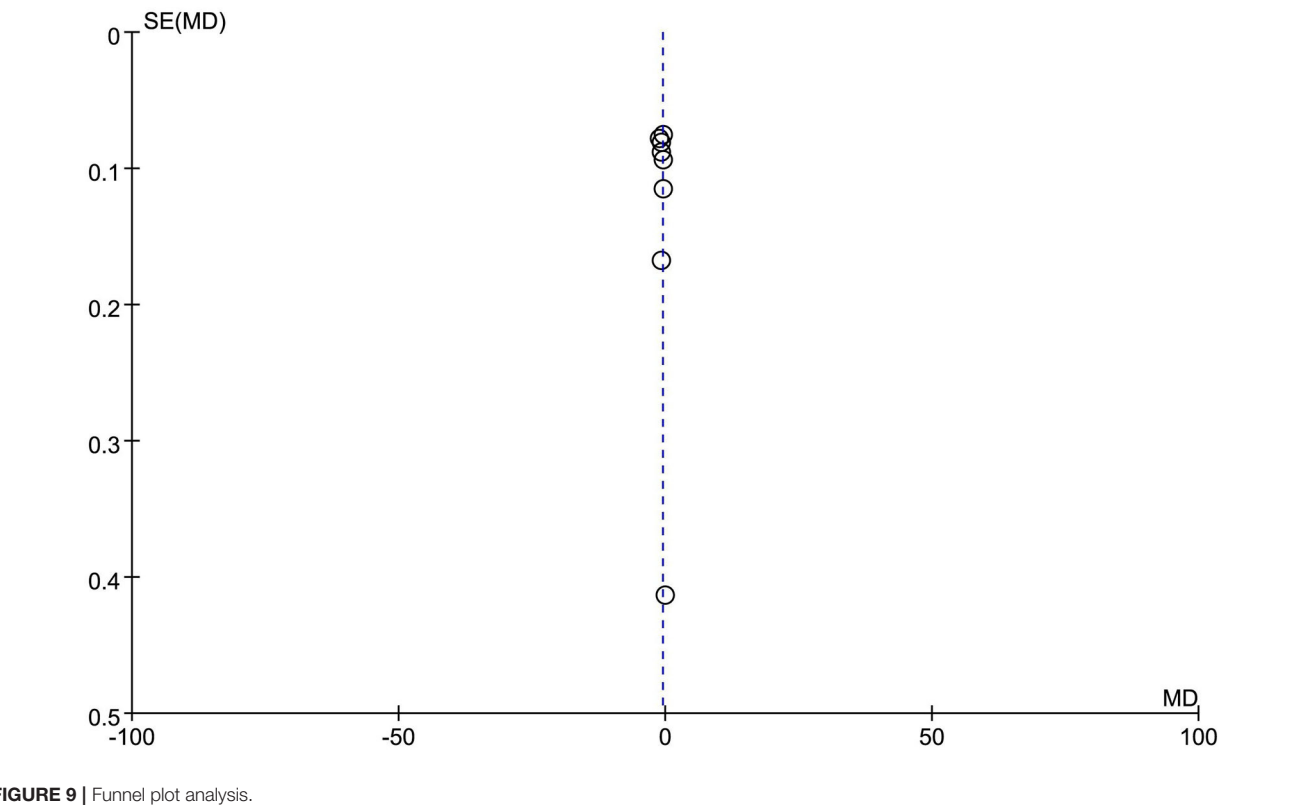

FIGURE 9 | Funnel plot analysis.

such as Bifidobacterium, Lactobacillus, and Haemophilus, and also indirectly inhibit the growth of harmful bacteria (24).

In this meta-analysis, 10 controlled clinical studies on TCMs that can regulate intestinal flora, for the prevention and treatment of dyslipidemia were included, and the results showed that after the intervention of TCM, the TC and triacylglycerol levels of the patients decreased compared with the control group, while the HDL level increased, which suggested that such TCM could contribute to the recovery of blood lipids in patients with abnormal lipid metabolism. On the other hand, after the intervention of TCM, the number of harmful bacteria in the intestinal flora of the patients decreased, and the number of beneficial bacteria such as lactobacillus and bifidobacterium increased, which indicated that the intervention of TCM helped the patients to restore the microecological balance in the intestine. The hydrolysis, oxidation, and reduction reactions of TCM components occur under the action of intestinal flora, and hence TCM components are more likely to absorb, metabolize, and even produce new active substances, and the efficacy of TCM will show enhanced activity, while intestinal flora will also be affected by TCM while biotransforming TCM, and the structure of intestinal flora will change under the action of TCM (25). Various herbal medicines have been found to be involved in this bacterial regulation, and studies (26) have shown that *Codonopsis pilosula* can increase the level of lactobacillus in the intestine of mice, while inhibiting *Escherichia coli*. *Atractylodes macrocephala* Koidz, *Astragalus membranaceus*, *Lycium barbarum*, and *Rehmannia glutinosa* can promote the proliferation of bifidobacteria, lactobacillus, *Lactobacillus acidophilus,* and other beneficial flora, and inhibit the growth of the large intestine (27).

In this study, the heterogeneity sources were investigated by excluding one by one. However, after excluding each article, the heterogeneity existed in the remaining literatures, which indicated that multiple aspects of heterogeneity sources might be related to different characteristics of patients, age, different formulations of TCMs and other factors. In this study, JBI's scale was used to evaluate the quality of the 10 included articles. The scores showed that the quality of the articles was good, but most of the articles did not describe the dropout cases, which may have a large implementation bias. Publication bias analysis showed a uniform distribution on both sides, suggesting the absence of publication bias. In future studies, more literatures with less heterogeneity and high quality can be selected for further analysis.

SUMMARY

In summary, the application of oral preparations of TCMs that regulate intestinal flora in the prevention and treatment of lipid metabolism disorders can increase the colonization of beneficial bacteria in the intestine of patients, inhibit the growth of harmful bacteria, and restore the intestinal microecological balance, thus indirectly acting on the blood lipid regulation of patients and contributing to the recovery of dyslipidemia. However, based on the heterogeneity and publication bias in the studies, the topic still needs to be further explored by including more controlled clinical studies with better quality 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 authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by this study was approved by the Ethics Committee of our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WG and WZ are the mainly responsible for the writing of the article. CC is mainly responsible for research design. WG is mainly responsible for data analysis. WZ and CC are responsible for the guidance of the entire research. The corresponding author is WG and she is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors may have contributed in multiple roles. All authors contributed to the article and approved the submitted version.

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Anesthetic Effect of the Fascia Iliaca Compartment Block with Different Approaches on Total Hip Arthroplasty and Its Effect on Postoperative Cognitive Dysfunction and Inflammation

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Objective: The objective of this article is to make a comparison of the anesthetic effects of the inside and outside fascia iliaca compartment block (FICB) in total hip arthroplasty (THA) and to study the effect of the different approaches of the FICB on postoperative cognitive dysfunction (POCD) and serum inflammatory cytokines in THA patients.

Methods: A total of 60 patients who received THA treatment from January 2021 to December 2021 were divided into two groups, namely, Inside group (inside approach of the FICB) and Outside group (outside approach of the FICB), according to the different approaches of the FICB. Forty-eight hours after surgery, we compared the use of ropacaine dosage, visual analogue scale (VAS) score, the use of patient-controlled analgesia (PCA), mini-mental state examination (MMSE) score, the incidence of POCD, and the serum levels of IL-1, IL-6. Secondary indicators include surgical indicators and the quality of anesthesia cannula.

Results: The ratio of re-fix the catheter, intubation time, and the use of ropacaine dosage at 48 h after surgery in the Outside group were significantly higher than that in the Inside group ($p < 0.05$), while the depth of cannulation in the Outside group was significantly lower than that in the Inside group ($p < 0.05$). VAS scores were comparable between the Inside and the Outside groups, except at 24 h after surgery. The use of PCA from 24 to 48 h after surgery in the Outside group was significantly higher than that in the Inside group ($p < 0.05$). The MMSE score and the incidence of POCD in the Outside group were higher than that in the Inside group. At the same time, the serum IL-1β levels at 1 and 6 h after surgery and the serum IL-6 levels at 1, 6, 24, and 48 h after surgery in the Outside group were significantly higher than that in the Inside group ($p < 0.05$).

Conclusion: Compared with the outside approach of the FICB, the inside approach of the FICB has better anesthetic effect, better postoperative analgesia, fewer postoperative analgesics, lower incidence of POCD, and lower serum cytokines during the treatment of THA patients.

Keywords: fascia iliaca compartment block, total hip arthroplasty, postoperative cognitive dysfunction, inflammation, anesthetic effect

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INTRODUCTION

With the aging of the population, the number of patients undergoing hip replacement surgery also increases. The number of patients requiring THA is expected to rise to 6.3 million by 2050 in the United States, and the number of patients in China will undoubtedly be higher (1, 2). THA is a common treatment for patients with hip fractures, but it is traumatic and painful, and the most severe pain occurs within 24 h after surgery (3, 4). Previous studies have shown that if postoperative pain cannot be effectively controlled at the initial stage, the risk of developing chronic pain will increase, which will not only affect the patient's postoperative recovery, but also have a serious impact on the patient's long-term quality of life (5, 6). Therefore, effective pain management after THA can not only promote patient recovery and reduce postoperative complications, but also improve patient satisfaction and prognosis. Due to the high proportion of middle-aged and elderly patients receiving THA, avoiding postoperative cognitive dysfunction (POCD) is also a major factor that impacts the choice of the anesthesia method used (7, 8). POCD is a disorder of postoperative brain function in patients without preoperative mental disorders affected by the perioperative period, resulting in different degrees of mental activities such as cognition, emotion, behavior, and will. It can be as high as 25%–50% in hospitalized patients (9, 10). Consistent with postoperative pain, anesthesia is an important factor impacting the occurrence of POCD in patients treated with THA.

Currently, general anesthesia, spinal anesthesia, and nerve block can all be used for THA treatment, and the disadvantages of different anesthesia methods vary (11, 12). General anesthesia can significantly affect the respiratory and circulatory systems, resulting in opioid-related adverse reactions. Severe nausea and vomiting will affect patients' early eating habit and reduce their levels of satisfaction, and patients with general anesthesia are at a higher risk for POCD (13). Intraspinal anesthesia is also a commonly used anesthesia scheme for THA patients in clinical practice, but the elderly often encounter many problems such as spinal degeneration, ligament calcification, and difficulty in placing the puncture position, which, in turn, increases the difficulty of the puncture condition (14). With the recent advancement of ultrasound visualization technology, nerve block technology is being increasingly used for surgical anesthesia and postoperative analgesia in fracture patients (15, 16). The advantage of nerve block technology is that it can not only help in good pain management during and after surgery, but also help avoid the impact of general anesthesia on cardiopulmonary function, maintain hemodynamic stability, and reduce the risk of POCD (17).

In this study, we compared the anesthetic effects of the inside and outside FICB in total hip arthroplasty (THA) and studied the effects of the different approaches of the FICB on POCD and serum inflammatory cytokines in THA patients. Twenty-four hours after surgery is the most obvious time point for THA patients to feel pain, and this period is a key time point to distinguish the effects of different anesthesia methods on postoperative analgesia.

MATERIALS AND METHODS

Patients and Ethics Statement

A total of 60 patients who received THA treatment from January 2021 to December 2021 were included in the present study. Inclusion criteria: age 18–80 years, American Society of Anesthesiologists (ASA) stages I–III, meeting surgical standards. At the same time, the following types of patients were excluded from this study: those allergic to local anesthetics, those who have peripheral neuropathy, deafness, or language impairment or inability to communicate effectively, those having neurological diseases, a history of alcoholism, and drug dependence, those whose operation time exceeds 3 h or surgical blood loss exceeds 800 mL, those with diabetes, chronic infectious diseases, malignant tumors, organ dysfunction, a mini-mental state examination (MMSE) score <27, and all those patients who are unwilling to participate in this study.

Anesthesia Protocol

All patients were monitored for vital signs. After the establishment of intravenous access, they were given atropine 0.3 mg and tropisetron 5 mg, and they inhaled pure oxygen by using a face mask, 6 L/min. Anesthesia induction protocol: dexmedetomidine 0.3 μg/kg, sufentanil 0.2–0.4 μg/kg, etomidate 0.1–0.3 mg/kg, cisatracurium 0.2 mg intravenously when the patient's bispect ral index (BIS) value drops to 55–45/kg, and mechanical ventilation through orotracheal intubation after jaw relaxation. During the operation, the patients underwent a continuous inhalation of 2%–4% sevoflurane, an intermittent bolus injection of cisatracurium, and a continuous pump injection of sufentanil 0.05–0.2 μg/kg/h to maintain the levels of anesthesia. Sevoflurane and sufentanil were discontinued at the start of the surgery.

Fascia Iliaca Compartment Block Protocol

After the patients were administered general anesthesia with endotracheal intubation, a persistent fascia iliacus space block procedure was performed with an ultrasound-guided inside approach (Inside group) or outside approach (Outside group). After the administration of anesthesia, the patients were placed in a supine position with both legs straight, with natural mild abduction and external rotation. The needle kit contains a 55- mm 18G nerve block catheter kit. The femoral artery, femoral nerve, fascia lata, and iliac fascia were observed under ultrasound guidance. The puncture needle was inserted from the inside or outside of the femur by the in-plane technique, avoiding the femoral artery, and the needle tip reached the fascia iliacus space. A diffusion of normal saline was observed. When the normal saline diffused in a fusiform shape, it indicated that the needle tip was indeed in the fascia iliacus space, and 30 mL of 0.3% ropivacaine was injected. After the iliac fascia space was expanded by the water separation technique, the steel needle was fixed, the trocar was inserted, the steel needle was withdrawn, 1 mL of normal saline was injected into the trocar to ensure the patency of the cannula, and finally, the catheter was inserted.

Data Collection

We recorded demographics including gender, age, body mass index (BMI), and ASA grade, surgical characteristics such as operation time, intraoperative blood loss, intraoperative urine volume, and intraoperative infusion volume, and nerve block–related indicators such as the ratio of re-fix the catheter, intubation time, the use of ropacaine dosage at 48 h after surgery, the depth of cannulation, and the time of ultrasound and puncture injection.

At 1, 6, 24, and 48 h after THA, the visual analogue scale (VAS) score was used to assess the postoperative pain of patients: VAS scores ranged from 0 to 10, with higher scores indicating greater pain (16, 17). At 6, 24, and 48 h, MMSE was used to assess the postoperative cognitive function of the patients: an MMSE score <27 indicated POCD.

Statistical Analysis

Data in this study were analyzed by using SPSS 20.0 (NIH, USA). Measurement data that conformed to normal distribution were presented as mean ± standard deviation, and the difference in the measurement data between the two groups was compared using an independent-sample *t*-test. Categorical data were presented as numbers and percentages and examined by using Chi-squared analysis or Fisher's exact-probability test. A score of $p < 0.05$ was considered statistically significant.

TABLE 1 | Comparison of demographic and surgical indicators between two groups.

Index	Inside group ($n = 30$)	Outside group ($n = 30$)	t/χ^2	p
Gender (*n*)				
Male	14/	15	0.067	0.796
Female	16	15		
Age (years)	59.3 ± 7.8	60.2 ± 9.4	0.503	0.602
BMI (kg/m^2)	24.5 ± 0.58	24.8 ± 0.74	1.777	0.081
ASA grade				
I + II	19	17	0.278	0.598
III	11	13		
Surgical indicators				
Time (min)	117.1 ± 4.7	116.6 ± 2.31	0.521	0.604
Bleeding volume (mL)	425.5 ± 157.7	427.5 ± 142.1	1.354	0.181
Urine (mL)	390.2 ± 38.9	376.8 ± 37.8	1.360	0.179
Infusion volume (mL)	1,672.6 ± 172.6	1,744.5 ± 215.2	1.426	0.159

RESULTS

Demographic and Surgical Characteristics

In the present study, we included 60 THA patients and divided them into two groups according to the anesthesia method used: Inside group and Outside group. The baseline data of gender, age, BMI, and ASA grade between the two groups were comparable ($p > 0.05$) (**Table 1**). At the same time, the surgical characteristics of operation time, intraoperative blood loss, intraoperative urine volume, and intraoperative infusion volume between the two groups were comparable ($p > 0.05$) (**Table 1**).

Anesthetic Effect

To compare the effect of anesthesia in the two groups, we found that the ratio of re-fix the catheter, intubation time, and the use of ropacaine dosage at 48 h after surgery in the Outside group were significantly higher than those in the Inside group ($p < 0.05$), while the cannulation depth in the Outside group was significantly lower than that in the Inside group ($p < 0.05$) (**Table 2**). In addition, there was no significant difference between the two groups in regard to the time of ultrasound and puncture injection ($p > 0.05$) (**Table 2**).

At 1, 6, 24, and 48 h after the operation, we evaluated the pain perception (VAS score) of the patients and recorded the number of times of patient-controlled analgesia (PCA) use within 48 h after the operation. As shown in **Figure 1**, the VAS scores were comparable between the Inside and the Outside groups, except at 1, 6, and 48 h after surgery, while the VAS score in the Inside group at 24 h after surgery was significantly lower than that in the Outside group. At the same time, the use of PCA from 0 to 6 h and from 6 h to 24 h after operation between the two groups was comparable ($p > 0.05$), while the use of PCA from 24 h to 48 h after surgery in the Outside group was significantly higher than that in the Inside group ($p < 0.05$) (**Figure 2**).

Postoperative cognitive dysfunction

Compared with the Inside group, the MMSE score of patients in the Outside group at 6 h (T1), 24 h (T2), and 48 h (T3) after surgery were significantly decreased ($p < 0.05$) (**Table 3**). At the same time, the incidence of POCD in the Outside group at 6 h, 24 h, and 48 h after surgery were higher than that in the Inside group, but there was no significant difference ($p > 0.05$) (**Table 3**).

TABLE 2 | Comparison of nerve block–related indicators between two groups.

Group	Inside group ($n = 30$)	Outside group ($n = 30$)	t/χ^2	p
Re-fix the catheter [*n* (%)]	2 (6.7)	11 (36.7)	7.954	0.005
Ultrasound time (s)	75.4 ± 5.9	77.5 ± 8.5	1.107	0.273
Puncture injection time (s)	95.5 ± 6.6	96.6 ± 10.2	0.479	0.621
Intubation time (s)	67.2 ± 4.6	159.0 ± 14.5	33.060	<0.001
Cannulation depth (cm)	11.2 ± 2.3	7.4 ± 2.2	6.613	<0.001
Ropacaine dosage (mL)	250.3 ± 51.8	279.4 ± 49.2	2.232	0.029

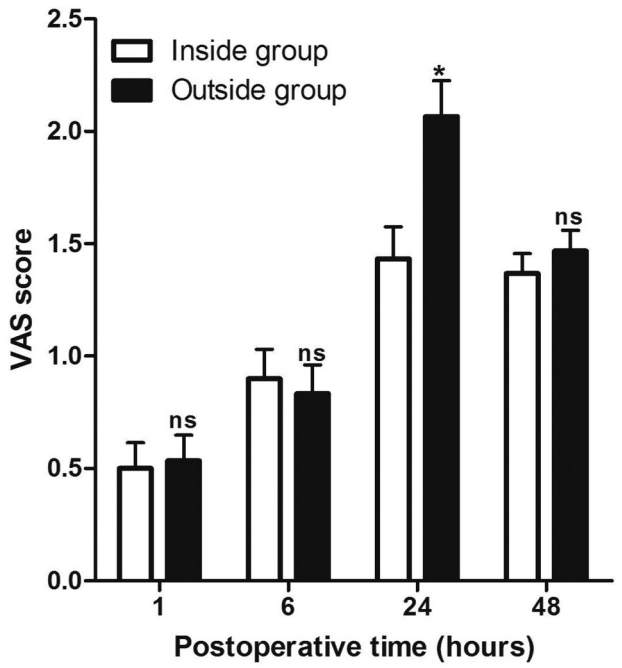

FIGURE 1 | Comparison of visual analogue scale scores at different postoperative times between two groups. Compared with the Inside group, ns $p > 0.05$ and $^*p < 0.05$.

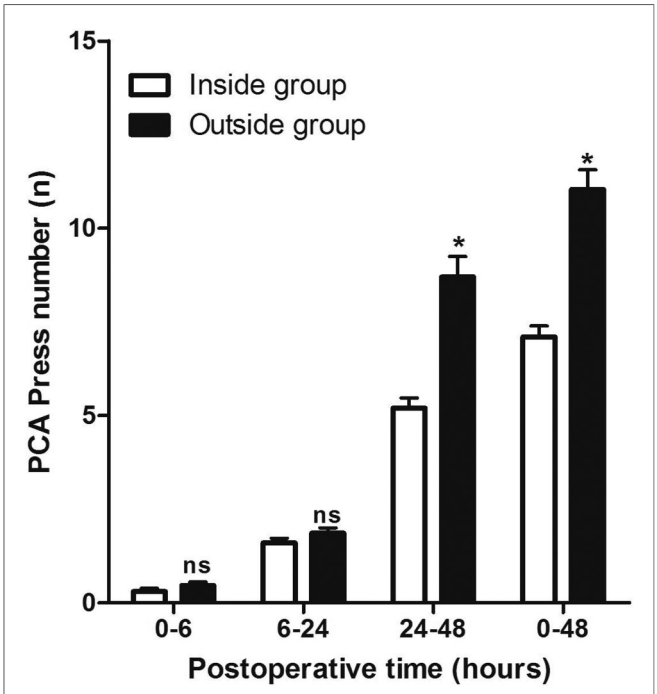

FIGURE 2 | Comparison of patient-controlled analgesia press number at different postoperative times between two groups. Compared with the Inside group, ns $p > 0.05$ and $^*p < 0.05$.

Serum inflammatory cytokines

As shown in **Figure 3**, the serum levels of IL-1β in patients of the Outside group at 1 and 6 h after surgery were significantly higher than those of the Inside group, while there was no significant difference at 24and 48 h after surgery. However, the serum levels of IL-6 in patients of the Outside group after surgery were all significantly higher than those in the Inside group ($p < 0.05$) (**Figure 4**).

DISCUSSION

THA is one of the common surgeries in clinical joint surgery. In the past, spinal anesthesia was commonly used, but its application was limited due to the blocking of the sympathetic nerve, the fluctuation of hemodynamics, and perioperative anticoagulation therapy (1, 2). At present, general anesthesia, combined with nerve block anesthesia, has been widely used in clinical practice, especially in THA, and its advantages are many, such as providing effective relief for perioperative pain, controlling and reducing the dosage of opioids, and promoting the rapid recovery of patients (13, 14). The iliac fascia is formed by the muscle fascia of the psoas major, iliacus, and pubis muscles, and the iliac fascia space is a potential gap in the anterior iliac fascia and the posterior iliopsoas and iliopsoas fascia (15–17). The three main nerves originating from the lumbar plexus—the femoral nerve, the lateral femoral cutaneous nerve, and the obturator nerve—run behind the fascia iliacus and are located together in the fascia iliacus space.

In this study, all 60 THA patients received general anesthesia, combined with the FICB, and all of them were in agreement with the fact that both the approaches of the FICB are different. We found that the ratio of re-fix the catheter, intubation time, and the use of ropacaine dosage at 48 h after surgery in the Outside group were significantly higher than that in the Inside group, while the cannulation depth in the Outside group was significantly lower than that in the Inside group, which suggested that the inside approach of the FICB was an easier and more effective one in anesthetizing the patients than the outside FICB approach. Needle insertion in the outside FICB approach is directed toward the inside, so that the direction of the inserted catheter is away from the lateral femoral cutaneous nerve, while the needle insertion direction of the inside FICB approach points to the outside, so that the indwelling catheter tip is closer to the lateral femoral cutaneous nerve (18, 19). The lateral femoral cutaneous nerve block ratio was higher with less postoperative analgesia (20–22). The lateral femoral cutaneous nerve divides into anterior and posterior branches at about 5 cm below the anterior superior iliac spine, and the posterior branch moves to the posterior and inferior ear, and distributes to the skin near the greater trochanter of the femur. Therefore, the block rate of the lateral femoral cutaneous nerve is higher, and there is lesser use of PCA and ropivacaine consumption at 48 h postoperatively (20–22).

In addition, we found that the VAS score of patients in the Outside group was significantly higher than that in the Inside group at 24 h postoperatively, and the use of PCA from 24 to

TABLE 3 | Comparison of mini-mental state examination (MMSE) score and postoperative cognitive dysfunction (POCD) incidence at different postoperative times between two groups.

Group	*n*	MMSE score			POCD [*n* (%)]		
		T1	T2	T3	T1	T2	T3
Inside group	30	29.4 ± 2.9	31.1 ± 2.9	31.3 ± 2.8	2 (6.7)	1 (3.33)	0 (0.0)
Outside group	30	26.8 ± 3.3	27.6 ± 3.5	28.2 ± 2.8	7 (23.3)	5 (16.7)	1 (3.3)
t/χ^2		3.195	2.900	5.348	3.268	2.963	1.017
p		0.002	0.005	<0.001	0.071	0.085	0.313

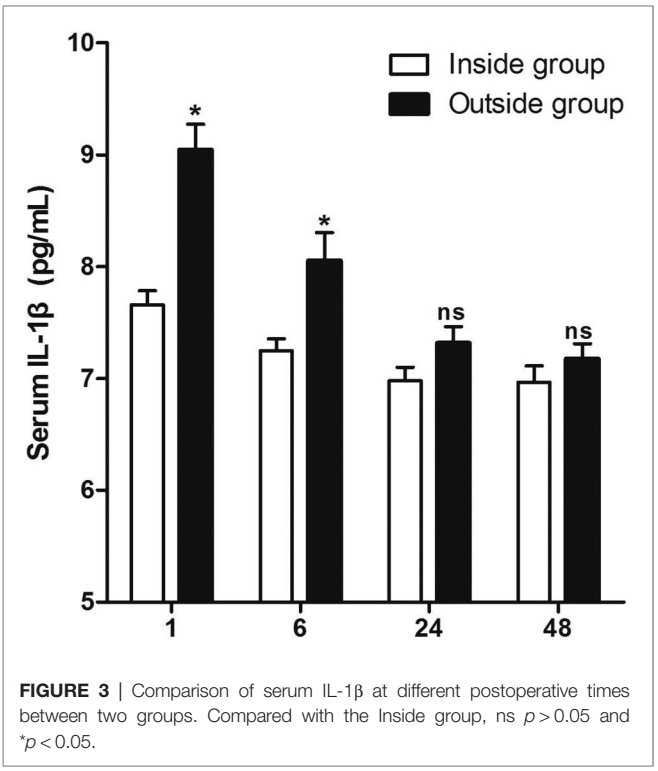

FIGURE 3 | Comparison of serum IL-1β at different postoperative times between two groups. Compared with the Inside group, ns $p > 0.05$ and $^*p < 0.05$.

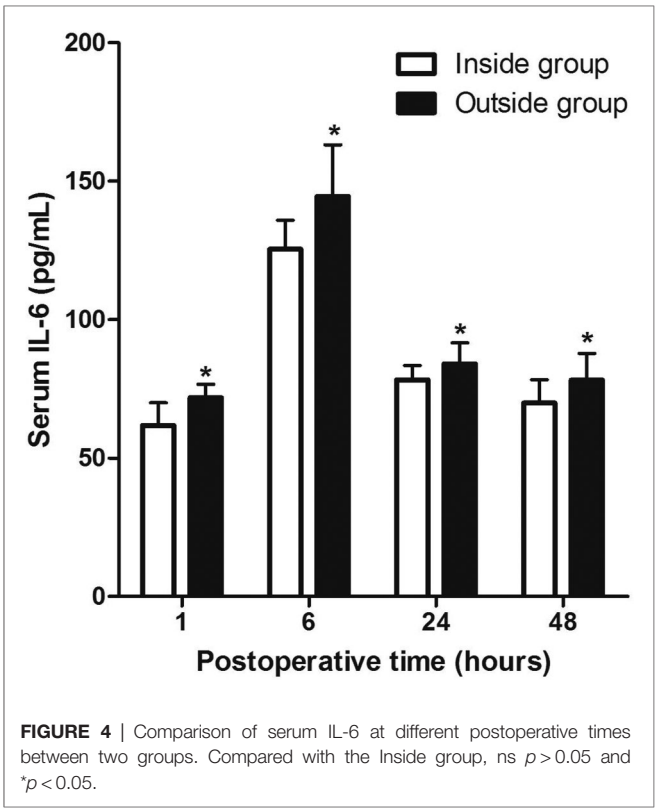

FIGURE 4 | Comparison of serum IL-6 at different postoperative times between two groups. Compared with the Inside group, ns $p > 0.05$ and $^*p < 0.05$.

48 h after surgery in the Outside group was significantly higher than that in the Inside group, which suggested that the postoperative analgesia effect of the inside FICB approach is better than the outside approach in THA patients. At the same time, we also found that the MMSE score in the Outside group was lower than that in the Inside group at 6, 24, and 48 h postoperatively, while the incidence of POCD in the Outside group was higher than that in the Inside group at 6, 24, and 48 h postoperatively. Anesthesia protocol is an important factor impacting postoperative pain and the incidence of POCD (23, 24). Our results have shown that the inside approach of the FICB was more effective in anesthetizing patients than the outside approach.

Surgery activates the immune system of patients to produce a strong peripheral inflammatory response. The type of surgery and surgical trauma will affect the level of serum inflammatory factors. Peripheral inflammatory factors can cause central nervous system (CNS) inflammatory response through direct or indirect pathways. When excessive CNS inflammatory response occurs, it can affect cognitive function by producing the following effects (25–30). First, inflammatory cytokines affect neural activity and synaptic connections (25). Second, high concentrations of inflammatory factors can produce neurotoxicity and cause neurodegeneration, resulting in impaired cognitive function (26, 27). Third, high levels of inflammatory cytokines cause nerve damage in the hippocampus (28). Last, inflammatory factors can stimulate actin in cells other than neurons in the brain, resulting in actin regeneration, a change that plays an important role in neurodegeneration (29, 30). Previous studies had showed that postoperative serum inflammatory cytokines were elevated in THA patients, and serum IL-1β and IL-6 levels were associated with the occurrence of POCD (31, 32). In the present study, the serum levels of IL-1β in patients of the Outside group at 1 and 6 h after surgery

are significantly higher than those in the Inside group, and the serum levels of IL-6 in patients of the Outside group after surgery are significantly higher than those in the Inside group.

However, there were several limitations to our study. First, this study focused only on the short-term pain and POCD of THA patients post surgery and lacked a comparison of the long-term efficacy of THA patients. Although we found differences in postoperative serum inflammatory cytokine levels in THA patients between the two approaches of the FICB, we could not further study their effects on POCD due to the inclusion of the limited sample size.

CONCLUSION

Compared with the outside approach of the FICB, the inside FICB approach has better anesthetic effect, better postoperative analgesia, fewer postoperative analgesics, lower incidence of POCD, and lower serum cytokines during the treatment of THA patients.

DATA AVAILABILITY STATEMENT

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

ETHIC STATEMENT

The studies involving human participants were reviewed and approved by the present study was authorized by the Ethics Committee of The First Affiliated Hospital of Hebei North University Hospital (2021002), and all patients participating in this study signed an informed consent form and voluntarily participated in this study. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TF and FL were primarily responsible for the writing and research of the article. JZ was mainly responsible for the research design. JW was mainly responsible for data analysis. XS and TJ were responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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Influence of Psychological Nursing Procedure on Negative Emotion, Stress State, Quality of Life and Nursing Satisfaction in Patients with Lung Cancer Radical Operation

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Objective: To discuss the influence of psychological nursing procedure on negative emotion, stress state, quality of life and nursing satisfaction in patients with lung cancer radical operation.

Methods: 106 patients with lung cancer who underwent radical resection in our hospital from September 2019 to September 2021 were selected. According to the intervention time, patients were divided into Group A and Group B, with 53 cases in each group. Group A received routine nursing, Group B used psychological nursing procedure on the basis of Group A. The negative emotions, stress state, quality of life and nursing satisfaction of patient were observed.

Results: Self-rating anxiety scale and self-rating depression scale scores of Group B were lower than Group A ($P < 0.05$). The levels of norepinephrine, epinephrine and cortisol in Group B were lower than Group A ($P < 0.05$). Generic quality of life inventory-74 scores of Group B were higher than Group A ($P < 0.05$). The nursing satisfaction of Group B (88.68%) was higher than Group A (73.58%) ($P < 0.05$).

Conclusion: Psychological nursing procedure is conducive to reducing the negative emotion, relieving stress reaction, improving the quality of life, increasing nursing satisfaction of patients with lung cancer radical operation.

Keywords: lung cancer radical operation, psychological nursing procedure, negative emotion, stress state, quality of life, nursing satisfaction

INTRODUCTION

With the deterioration of the environment and the increase of people's unhealthy living habits, the incidence of lung cancer has risen sharply. Because the symptoms of lung cancer in the early stage are concealed and lack of specific clinical symptoms, most of them are common symptoms, such as cough and chest tightness, so it is difficult to attract the attention of patients (1). By the time a

patient is diagnosed with lung cancer, the disease is often in the middle and late stage, and the 5-year survival rate of the patient is only 10%–15% (2). It is reported that in 2020, the most common cancer in China is lung cancer (820,000), and the death toll is far ahead, reaching 715,000 (3). In recent years, with the continuous development of medical technology, lung cancer resection has become the most effective method for the treatment of lung cancer. Surgery has improved the survival rate of patients with lung cancer to a certain extent, and brought hope to countless people suffering from cancer (4). However, after surgical resection of the lesion, the patient will have some trauma, and the the lung function of the patient will be damaged, thus triggering the body's stress response. Long-term severe stress will promote the abnormal release of histamine, catecholamine and other substances, and then affect the physical function (5, 6). At the same time, surgery, postoperative chemotherapy, pain of malignant tumor themselves and complications will cause double burdens on the patients' physiology and psychology, resulting in negative psychology such as irritability, anxiety and depression, which will affect the treatment effect of lung cancer and reduce the quality of life of patients (7). Therefore, it is very urgent to actively explore and improve the psychological status of patients during treatment. Psychological nursing procedure is a nursing method guided by psychological theory. It deals with various psychological problems by observing the law of patients' psychological activities, and then changes the patient's behavior and improves the outcome of the disease. We observed the changes of patients' negative emotions, stress state, quality of life and nursing satisfaction before and after the implementation of psychological nursing procedure for patients with lung cancer radical operation.

MATERIALS AND METHODS

Research Object

106 patients with lung cancer who underwent radical resection in our hospital from September 2019 to September 2021 were selected as the research object. Inclusion criteria: ① meeting the diagnostic criteria of lung cancer (8); ② There are indications for radical resection of lung cancer and no surgical contraindications; ③ No radiotherapy or chemotherapy before operation; ④ The expected survival time was >3 months; ⑤Cognitive, communication and writing skills are barrier-free. Exclusion criteria: ① suffering from autoimmune diseases; ② Complicated with functional diseases of important organs; ③ Other malignant tumors; ④ Complicated mental illness; ⑤ Have received similar mental health treatment in the past; ⑥ The patient was not the first to undergo surgery. According to the intervention time, patients were divided into Group A (from September 2019 to September 2020) and Group B (from September 2020 to September 2021), with 53 cases in each group.

Research Methods

Group A received routine nursing. Including: completed the health education work, introduced the current condition to patients, explained the operation plan, operation precautions and possible complications. Explained to patients the importance of maintaining good psychology, informed and supervised patients to quit smoking and drinking absolutely, and implement diet guidance.

Group B used psychological nursing procedure on the basis of Group A. ① Psychological nursing teams were established. All members team members were required to have at least 3 years of clinical work experience, and they must received training on psychological nursing related knowledge before joining the group. Only those who pass the examination can be enrolled into the group. The training content included the knowledge related to lung cancer disease, nursing measures and coping measures related to cancer radiotherapy and chemotherapy. ② Team members assessed the psychological status of patients, fully communicated with patients and established a good doctor-patient relationship. Through the results of psychological assessment to grasp the causes of patients' unhealthy psychology, and formulated corresponding psychological intervention programs. Focused on observing patients' psychological changes, communicated with patients who have negative emotions as soon as possible, and eased their unhealthy psychology. Patients were guided to establish self-management and psychological adjustment ability, explained the adverse effects of bad psychology to patients, and informed patients to keep a good state of mind. ③ The team members gave health education manuals to patients and their families, and taught the patients about lung cancer related knowledge, related effects of radiotherapy, adverse reactions of operation, etc., so as to help the patients understand their own diseases and relieve their fear. ④ The society and family were encouraged to provide emotional support to patients, and group activities such as communication meetings and outdoor outing were regularly organized, so that patients can realize their own value. Patients were encouraged to maintain communication with the outside world, so that patients could feel the meaning of life. Patient's family was instructed to spend more time with the patient, so that the patient could establish a positive and optimistic attitude and reduce negative emotions. ⑤ A supervisory group was established, consisting of head nurses and psychological counselors, and the supervisory group was supposed to oversee the implementation of the entire nursing process and the quality of care.

Observation Index

① Medical records were established for all patients when they were admitted to hospital, and personal information, disease information and other information were collected. ② Self-rating anxiety scale (SAS) and self-rating depression scale (SDS) were used to evaluate patients' negative emotions. The contents of SAS and SDS include 20 items, each of which was divided into 4 grades, and the demarcation values of standard scores were 50 points and 53 points respectively. The total score of SAS and SDS ranges from 20–80 points. The degree of anxiety and depression was directly proportional to the score. ③ The fasting venous blood of patients was collected, after centrifugation, the levels of norepinephrine (NE),

epinephrine (E) and cortisol by radioimmunoassay were measured. ④ Generic quality of life inventory-74 (GQOLI-74) was used to evaluate the patients' quality of life. Include 74 items, each of which was divided into 5 levels. They were 4 dimensions: psychological function, social function, material life and physical function. The total score for each dimension was 100 points. The quality of life is directly proportional to the score. ⑤ The self-made nursing satisfaction scale was used to evaluate patients' satisfaction. It include nurses' attention to patients, nurses' communicability, professional knowledge reserve, nursing accessibility and nursing service quality. Each item was divided into 5 grades, with a total score of 100 points, with >80 points as satisfied, 60–80 points as relatively satisfied and <60 points as dissatisfied. Total satisfaction = satisfied + relatively satisfied. The Cronbach's α of scale was 0.776. The scale has good reliability.

Statistical Methods

SPSS 22.0 software was used for analysis, measurement data were expressed as mean ± standard deviation, *t*-test was used to analyze the comparison. Count data was expressed as a ratio, χ^2-test was used to analyze the comparison. $P < 0.05$ was statistically significant.

RESULTS

Patients' Clinical Data

There was no significant difference in clinical data between the two groups ($P > 0.05$). (**Table 1**).

Patients' Negative Rmotions

SAS and SDS scores of Group B were lower than Group A ($P < 0.05$). (**Figure 1**).

Patients' Stress State

The levels of NE, E and cortisol in Group B were lower than Group A ($P < 0.05$). (**Figure 2**).

Patients' Quality of Life

GQOLI-74 scores of Group B were higher than Group A ($P < 0.05$). (**Figure 3**).

Patients' Nursing Satisfaction

The nursing satisfaction of Group B (88.68%) was higher than Group A(73.58%) ($P < 0.05$). (**Table 2**).

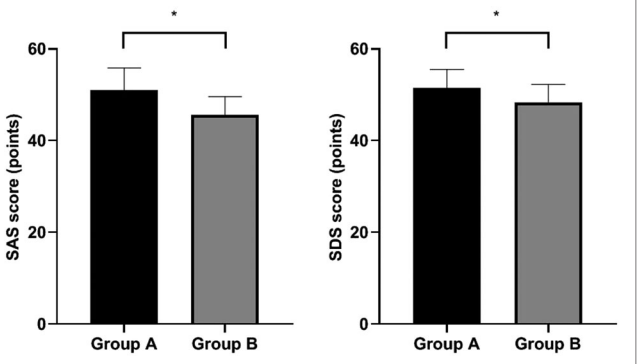

FIGURE 1 | Patients' negative emotions. Compared with Group A, *$P < 0.05$.

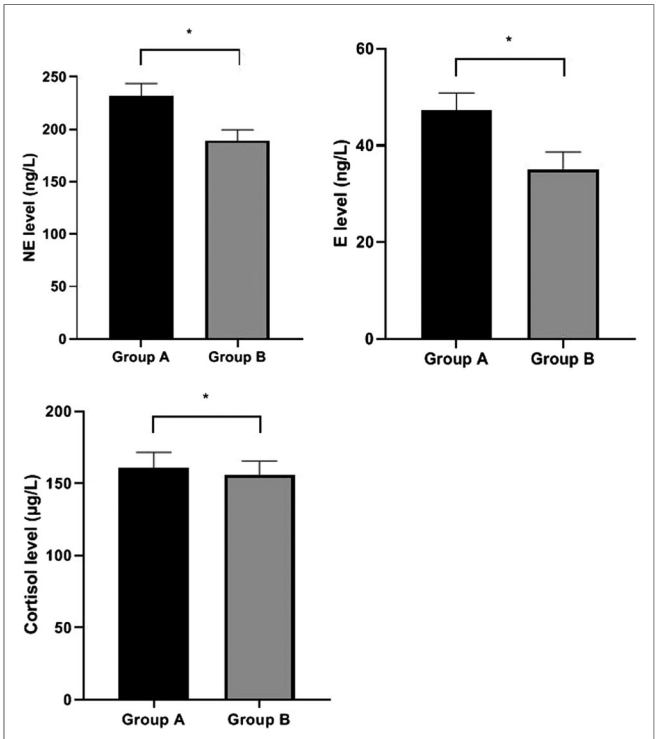

FIGURE 2 | Patients' stress state. Compared with Group A, *$P < 0.05$.

TABLE 1 | Patients' clinical data (*n*, %, $\bar{x} \pm s$).

Group	Gender		Age (years)	Pattern of organization		TNM staging		
	Male	Female		Squamous carcinoma	Glandular cancer	Stage I	Stage II	Stage III
Group A ($n = 53$)	30 (56.60%)	23 (43.40%)	63.82 ± 5.66	38 (71.70%)	15 (28.30%)	21 (39.62%)	29 (54.72%)	3 (5.66%)
Group B ($n = 53$)	34 (64.15%)	19 (35.85%)	62.95 ± 5.51	36 (67.92%)	17 (32.08%)	20 (37.74%)	31 (58.49%)	2 (3.77%)
χ^2/t value	0.631		0.802	0.179		0.291		
P value	0.427		0.424	0.672		0.865		

DISCUSSION

At present, surgical resection is often used in clinical treatment of lung cancer in China, and the survival time of patients is gradually prolonged. However, the disease of lung cancer itself and the long-term treatment process will cause patients to have different degrees of adverse reactions. Coupled with unbearable pain and high medical costs, patients are prone to negative attitudes, which seriously affects the quality of life of patients (9). At the same time, patients with lung cancer often have a strong psychological stress reaction due to the lack of disease-related knowledge, mainly manifested as emotional anxiety, depression and somatization, etc., which will have a great impact on the treatment effect (10, 11). At present, conventional nursing lacks targeted psychological counseling, and there are still some problems such as single personnel composition and incomplete nursing programs, so it cannot effectively reduce the stress reaction of patients, resulting in poor recovery of patients' body function after operation (12). In view of this, how to adopt effective psychological intervention methods to relieve patients' unhealthy psychology and improve the level of hope of patients has become an important topic in the treatment of lung cancer.

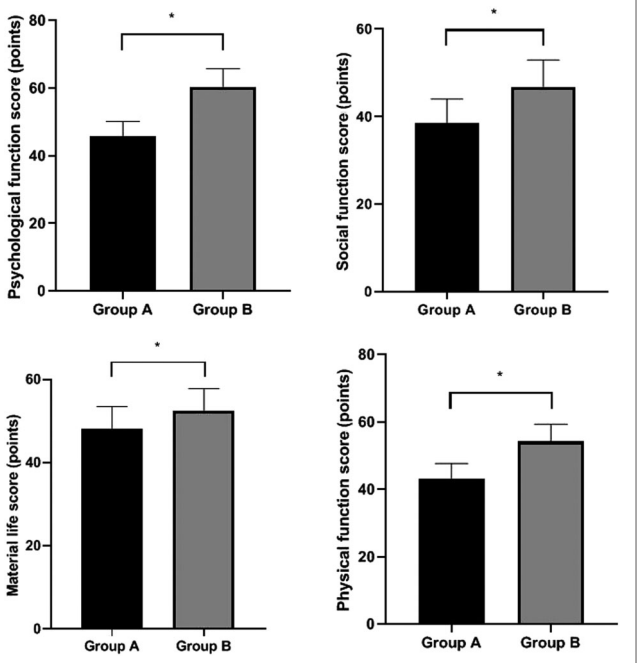

FIGURE 3 | Patients' quality of life. Compared with Group A, $^*P < 0.05$.

Due to the lack of understanding of the disease and the uncertainty of the operation results, patients with lung cancer undergoing radical resection are prone to negative emotions. Excessive negative emotions will affect the patient's multiple physiological systems and affect the patient's recovery, while poor recovery will aggravate the patient's negative emotions, thus forming a vicious circle (13, 14). We found that psychological nursing procedure for patients undergoing radical resection of lung cancer can reduce SAS and SDS scores. The psychological nursing procedure is aimed at the role of the patient, and applies the biological-psychological-social medical model to the treatment process of patients, so as to improve the patient's psychological condition and optimize the patient's self-emotional management ability (15). This method assesses the patient's psychological status, master the causes of unhealthy psychology and formulate corresponding psychological intervention programs, which can help patients reduce negative psychology, alleviate the pain caused by the tumor itself and treatment, and help patients face difficulties positively (16). Cetkin's team believed that health education is closely related to the clinical treatment effect of patients undergoing radical lung cancer surgery, but most patients lack knowledge about diseases, which often requires systematic popularization of science by medical staff (17). In the psychological nursing procedure, team members will explain the adverse effects of bad psychology on the body to the patients, and educate the patients about lung cancer-related knowledge, so as to help the patients understand their own diseases, reduce patients' anxiety about the diseases, and relieve patients' doubts (18). In addition, psychological nursing aims at the characteristics of psychological needs of patients undergoing radical lung cancer surgery, encourages patients to maintain communication with the outside world, enables patients to obtain social and family support, helps patients to eliminate psychological burden, increases their initiative to participate in disease treatment, and achieves the realization of psychological barriers (19).

As a stressor, surgery can excite the hypothalamus-pituitary-adrenal cortex system and locus coeruleus-sympathetic nerve-adrenal medulla system of patients, which can increase the secretion of catecholamine in the blood and cause patients to have psychological stress reaction (20). NE, E and cortisol are stress hormones secreted in large quantities by negative feedback of central nervous system under stress. When

TABLE 2 | Patients' nursing satisfaction (*n*, %).

Group	Satisfied	Relatively satisfied	Dissatisfied	Total satisfaction
Group A ($n = 53$)	18 (33.96%)	21 (39.62%)	14 (26.42%)	39 (73.58%)
Group B ($n = 53$)	23 (43.40%)	24 (45.28%)	6 (11.32%)	47 (88.68%)
χ^2 value				3.944
P value				0.047

patients have strong stress reaction, the levels of NE, E and cortisol in the blood can be increased several times, and the degree of increase is positively correlated with the intensity of stress reaction (21, 22). In this study, the levels of NE, E and cortisol in Group B are lower than those in Group A. This showed that psychological nursing procedure can alleviate the stress reaction of patients. Psychological nursing procedure is patient-centered, and reasonable psychological intervention plan is formulated according to its clinical characteristics. After implementing psychological counseling, health education, emotional support and other measures for patients, it is beneficial to improve patients' psychological resistance to face various problems and stimuli, so that they can still maintain a calm and good attitude in the face of stress, which is helpful to improve the mood of patients during treatment (23). At the same time, psychological intervention can make patients more aware of the disease and the operation process, reduce the damage to the body caused by emotional fluctuations, reduce the allowable effect of NE, E and cortisol alert reaction, and reduce the synthesis and release of endogenous opioid peptides in the brain, thereby alleviating the stress state (24). In addition, the research of van de Wiel's team and Long's team showed that psychological nursing can improve the quality of life and nursing satisfaction of patients undergoing radical lung cancer surgery (25, 26). It is basically consistent with the results of this study. Psychological nursing procedure can fully mobilize the subjective initiative of patients, improve the physical and psychological functions of patients, meet the needs of patients for knowledge related to diseases and operations, and finally achieve the purpose of improving patients' quality of life, and the nursing satisfaction will also increase accordingly.

CONCLUSION

To sum up, the psychological nursing procedure is conducive to reducing the negative emotion, relieving stress reaction, improving the quality of life, increasing nursing satisfaction of patients with lung cancer radical operation. This study only observed the physical and mental conditions of patients with lung cancer radical operation during the perioperative period, and it is necessary to further explore the long-term psychological state, long-term quality of life and long-term survival rate of patients in subsequent studies.

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 the ethics committee of our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YY and YX are the mainly responsible for the writing, research of the article. XF is mainly responsible for research design. YC is mainly responsible for data analysis. CL and JZ are responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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Analgesic and Sedative Effects of Different Doses of Dexmedetomidine Combined with Butorphanol in Continuous Analgesia after a Cesarean Section

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Objective: The present study is designed to study the analgesic and sedative effect of different doses of dexmedetomidine combined with butorphanol in continuous analgesia after a cesarean section.

Methods: A total of 60 puerperae undergoing a cesarean section recruited from a single center were divided into three groups according to the postoperative continuous analgesia protocol: control group (100 mL of normal saline containing 10 μg/kg fentanyl and 0.25 mg of palonosetron, 2 mL/h for continuous analgesia for 48 h), DB1 group (100 mL of normal saline containing 1.0 μg/kg dexmedetomidine, 4 mg of butorphanol, 10 μg/kg fentanyl, and 0.25 mg of palonosetron, 2 mL/h for continuous analgesia for 48 h), and DB2 group (100 mL normal saline containing 2.0 μg/kg dexmedetomidine, 4 mg of butorphanol, 10 μg/kg fentanyl, and 0.25 mg of palonosetron, 2 mL/h for continuous analgesia for 48 h). We compared the blood pressure, heart rate, oxygen saturation, VAS score, Ramsay score, and adverse reactions of puerperae among the three groups after surgery.

Results: The baseline data all have no significant difference in the three groups ($p > 0.05$). Compared with those in the control group, the systolic blood pressure, diastolic blood pressure, heart rate, and VAS score of the puerperae in the DB1 group and DB2 group were significantly decreased at 6, 24, and 48 h ($P < 0.05$), while the Ramsay scores of the puerperae in DB1 group and DB2 group were significantly increased at 6, 24, and 48 h ($p < 0.05$). At the same time, the systolic blood pressure, diastolic blood pressure, heart rate, and VAS score of the puerperae in the DB2 group were significantly lower than those in the DB1 group ($P < 0.05$), while the Ramsay scores of the puerperae in DB2 group were significantly higher than those in the DB1 group ($P < 0.05$). Also, there is no significant difference in oxygen saturation and adverse reactions of puerperae among the three groups after surgery ($p > 0.05$).

Conclusion: Dexmedetomidine combined with butorphanol can improve the analgesic and sedative effects in continuous analgesia after a cesarean section, and the analgesic and sedative effects of dexmedetomidine in the high-dose group are better than those in the low-dose group.

Keywords: dexmedetomidine, butorphanol, sedative, analgesic, cesarean section

INTRODUCTION

Postoperative pain-induced stress can lead to a series of changes in physiology, psychology, and behavior and adversely affect the normal endocrine and immune functions of humans (1, 2). Previous studies have shown that postoperative pain is closely related to the occurrence of postoperative complications, delays postoperative recovery, and affects patient prognosis (3, 4). In addition, severe postoperative pain is considered to be a high-risk factor for long-term chronic pain after surgery (5, 6). After a cesarean section, pain seriously affects the daily activities of the puerperium, and it is not conducive to early postpartum lactation and lactation and hinders the communication between the mother and the baby (7, 8). Therefore, it is of great significance to provide good, safe, and reliable analgesia to puerperae. Adequate postoperative analgesia can not only relieve postoperative fatigue and improve the comfort and satisfaction of puerperae but also help to improve the quality of postoperative recovery of puerperae (7, 8). However, there is currently no standard protocol for postcesarean section analgesia.

Dexmedetomidine is an α2 adrenergic receptor agonist with high selectivity and has sedative, analgesic, antisympathetic, anxiolytic, and stress-reducing effects, while it rarely causes respiratory depression (9–11). Butorphanol, an analgesic, exerts its analgesic effect mainly by agonizing κ receptors and partially antagonizing μ receptors (12). In addition, butorphanol is widely used in postoperative patient-controlled intravenous analgesia (PCIA), but it can cause many side effects when used alone (13). However, clinical studies suggest that dexmedetomidine can enhance the analgesic effect of butorphanol, and its combination can reduce its adverse effects (14, 15). In the present study, we designed to study the analgesic and sedative effect of different doses of dexmedetomidine combined with butorphanol in continuous analgesia after a cesarean section.

MATERIALS AND METHODS

Ethics Statement

This study complied with the principles of the Declaration of Helsinki and was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Northern College in Hebei Province. In addition, all volunteers who participated in this study were informed about the content of this study and signed an informed consent form.

Study Population

From January 2019 to December 2019, 60 puerperae undergoing a cesarean section were recruited in the present study. These puerperae must meet the following standards. Inclusion criteria are as follows: (1) undergoing a cesarean section under combined spinal–epidural anesthesia; (2) The American Society of Anesthesiologists (ASA) grades of grades I to II; (3) first birth, between 20 and 35 years old, with a height of 1.5–1.75 m; and (4) informed and agreed to participsate in this research. Exclusion criteria are as follows: (1) long-term use of nonsteroidal anti-inflammatory drugs, opioids, tranquilizers, and sedatives; (2) mental illness, intellectual disability, or other reasons for the maternal inability to complete the pain and sedation score; (3) preoperative heart rate below 50 bpm with abnormal cardiac conduction and rhythm; (4) neuromuscular endocrine diseases and allergic reactions to α2 adrenergic receptor agonists; (5) having a history of abdominal surgery in the past; and (6) anesthesia fails, the operation time is more than 2 h, the intraoperative blood loss is more than 500 mL, or a second operation is required to treat postpartum hemorrhage.

Anesthesia and Postoperative Analgesia Protocol

All participants received combined spinal–epidural anesthesia, with open venous access to infuse ringer sodium lactate (state approval no. H20044239; Shandong Weigao Pharmaceutical Co., Ltd., Shandong, China) and choosing the lumbar 3–4 space as the puncture point. Ephedrine hydrochloride injection (state approval no. H22020730; Tonghua Baishan Pharmaceutical Co., Ltd., Jilin, China) or phenylephrine (state approval no. H31021175; Shanghai Hefeng Pharmaceutical Co., Ltd., Shanhai, China) is given to maintain circulatory stability according to changes in the blood pressure and heart rate.

Sixty patients were divided into three groups according to the postoperative continuous analgesia protocol: control group, DB1 group, and DB2 group. The control group received 100 mL of normal saline containing 10 μg/kg fentanyl and 0.25 mg palonosetron, 2 mL/h for continuous analgesia for 48 h. The DB1 group received 100 mL of normal saline containing 1.0 μg/kg dexmedetomidine, 4 mg butorphanol, 10 μg/kg fentanyl, and 0.25 mg palonosetron, 2 mL/h for continuous analgesia for 48 h. The DB2 group received 100 mL of normal saline containing 2.0 μg/kg dexmedetomidine, 4 mg butorphanol, 10 μg/kg fentanyl, and 0.25 mg palonosetron, 2 mL/h for continuous analgesia for 48 h.

Data Collection

Herein, we used a visual analogue scale (VAS) score to assess pain at 6, 24, and 48 h after the cesarean section. Additionally, VAS scores range from 0 to 10, with higher scores indicating more severe pain. We used the Ramsay score to assess the level of sedation at 6, 24, and 48 h after the cesarean section, and the Ramsay scores range from 1 to 6, with higher scores indicating higher levels of sedation. We collected the clinical data of participants of age, height, weight, gestational week, onset time of operation, fetal delivery time, duration of surgery, and duration of anesthesia. At the same time, the blood pressure, heart rate, oxygen saturation, VAS score, and Ramsay score were also being determined at 1, 6, 24, and 48 h after the cesarean section. In addition, the adverse reactions including malignant vomiting, dizziness, itchy shin, bradycardia, and low blood pressure were also recorded immediately after surgery to 1 week after surgery.

Statistical Analysis

Data in the present study were analyzed by SPSS 19.0 software (SPSS Inc., Chicago, USA). Qualitative data are presented as counts (%), and *p*-values are calculated using chi-square or Fisher's exact test as appropriate. The Kolmogorov–Smirnov test was used to check whether quantitative data conformed to a normal distribution; data that conformed to a normal distribution were presented as mean ± standard deviation, and an unpaired Student's *t*-test was used to compare differences and calculate *p*-values. Quantitative data that did not conform to a normal distribution were presented as the median (interquartile range), and the Mann–Whitney *U*-test was used to compare differences and calculate *p*-values. $p < 0.05$ were considered statistically significant.

RESULTS

Demographic and Surgical Characteristics

The baseline data including characteristics including age, height, weight, and gestational week and surgical indicators including the onset time of operation, fetal delivery time, duration of surgery, and duration of anesthesia all have no significant difference in the three groups ($p > 0.05$) (**Table 1**).

Postoperative Blood Pressure, Heart Rate, and Oxygen Saturation

At 1, 6, 24, and 48 h after the cesarean section, the systolic blood pressure (**Table 2**), diastolic blood pressure (**Table 3**), and heart rate (**Table 4**) of puerperae in the DB1 group and DB2 group are all significantly lower than those in the control group ($p < 0.05$), and the systolic blood pressure, diastolic blood pressure, and heart rate of pirpera in the DB2 group are all significantly lower than those in the DB1 group ($p < 0.05$). However, there is no significant difference among these three groups in oxygen saturation of puerpera ($p > 0.05$) (**Table 5**).

VAS Score for the Analgesic Effect

The VAS scores of puerperae at 6, 24, and 48 h after the cesarean section in the DB1 group and DB2 group are all significantly lower than those in the control group ($P < 0.05$), and the VAS scores of puerperae at 6, 24, and 48 h after the cesarean section in the DB2 group are significantly lower than those in the DB1 group ($P < 0.05$) (**Table 6**).

Ramsay Score for the Calming Effect

The Ramsay scores of puerperae at 6, 24, and 48 h after the cesarean section in the DB1 group and DB2 group are all significantly higher than those in the control group ($p < 0.05$), and the Ramsay scores of puerperae at 6, 24, and 48 h after the cesarean section in the DB2 group are significantly higher than those in the DB1 group ($p < 0.05$) (**Table 7**).

TABLE 2 | Comparison of systolic blood pressure of puerperae at different times after surgery among three groups (mean ± SD, mmHg).

Group	*n*	Postoperative time (h)			
		1	6	24	48
Control group	20	126.9 ± 11.2	133.8 ± 8.9	123.6 ± 10.2	117.8 ± 8.9
DB1 group	20	120.5 ± 13.2*	123.8 ± 13.5*	117.4 ± 12.3*	114.7 ± 11.2*
DB2 group	20	110.3 ± 10.5*#	108.3 ± 8.7*#	110.2 ± 8.9*#	110.5 ± 10.8*#
F		7.628	13.125	8.127	4.326
p		<0.001	<0.001	<0.001	0.041

*Compared with the control group, *p < 0.05; compared with the DB1 group, #p < 0.05.*

TABLE 1 | Comparison of demographic and surgical indicators among three groups (mean ± SD).

Groups/variables	Control group (*n* = 20)	DB1 group (*n* = 20)	DB2 group (*n* = 20)	*p*-Value
Age (years)	29.4 ± 5.8	30.5 ± 6.2	30.7 ± 5.9	0.672
Height (cm)	161.8 ± 9.2	162.0 ± 10.5	161.7 ± 9.5	0.135
Weight (kg)	70.5 ± 10.8	68.9 ± 10.2	69.7 ± 10.2	0.415
Gestational week (weeks)	37.5 ± 1.9	38.3 ± 1.5	38.1 ± 1.8	0.223
Onset time of operation (min)	16.5 ± 3.8	16.3 ± 3.7	16.2 ± 3.5	0.527
Fetal delivery time (min)	23.8 ± 3.5	23.9 ± 5.1	23.7 ± 4.8	0.408
Duration of surgery (min)	63.5 ± 9.2	60.5 ± 10.2	62.3 ±	0.411
Duration of anesthesia (min)	80.5 ± 11.2	77.9 ± 13.2	79.8 ± 10.7	0.302

TABLE 3 | Comparison of diastolic blood pressure of puerperae at different times after surgery among three groups (mean ± SD, mmHg).

Group	*n*	Postoperative time (h)			
		1	6	24	48
Control group	20	72.3 ± 8.6	78.8 ± 9.3	71.8 ± 7.6	69.2 ± 5.3
DB1 group	20	68.3 ± 7.3*	69.2 ± 6.3*	69.5 ± 4.7*	69.2 ± 4.4*
DB2 group	20	67.8 ± 6.8*#	68.3 ± 6.7*#	67.1 ± 5.6*#	67.2 ± 5.5*#
F		4.932	7.921	5.031	3.729
p		0.038	<0.001	0.021	0.048

*Compared with the control group, *p < 0.05; compared with the DB1 group, #p < 0.05.*

TABLE 4 | Comparison of the heart rate of puerperae at different times after surgery among three groups (mean ± SD, *n*/min).

Group	*n*	Postoperative time (h)			
		1	6	24	48
Control group	20	73.6 ± 8.2	81.5 ± 9.2	80.4 ± 9.1	84.2 ± 7.5
DB1 group	20	70.3 ± 8.0*	76.6 ± 9.4*	76.8 ± 9.2*	76.6 ± 6.5*
DB2 group	20	67.8 ± 6.5*#	65.4 ± 5.8*#	66.9 ± 5.7*#	66.3 ± 6.2*#
F		8.159	9.426	13.082	10.328
p		<0.001	<0.001	<0.001	<0.001

*Compared with the control group, *p < 0.05; compared with the DB1 group, #p < 0.05.*

TABLE 5 | Comparison of oxygen saturation of puerperae at different times after surgery among three groups (mean ± SD, %).

Group	*n*	Postoperative time (h)			
		1	6	24	48
Control group	20	98.5 ± 1.4	97.8 ± 1.1	98.0 ± 0.9	98.2 ± 0.7
DB1 group	20	98.3 ± 1.3	97.5 ± 1.0	97.8 ± 0.9	98.0 ± 0.8
DB2 group	20	98.4 ± 1.5	97.8 ± 1.3	98.1 ± 1.1	98.0 ± 0.8
F		0.841	0.921	0.756	0.792
p		0.372	0.264	0.492	0.415

Adverse Reactions

There is no significant difference among the control group, DB1 group, and DB2 group in the adverse reactions at 48 h after surgery ($p > 0.05$) (**Table 8**).

TABLE 6 | Comparison of VAS scores of puerperae at different times after surgery among three groups (mean ± SD, score).

Group	*n*	Postoperative time (h)		
		6	24	48
Control group	20	3.1 ± 0.8	2.5 ± 0.4	1.9 ± 0.6
DB1 group	20	2.6 ± 0.6*	1.8 ± 0.6*	1.4 ± 0.7*
DB2 group	20	1.8 ± 1.0*#	1.4 ± 0.6*#	1.1 ± 0.4*#
F		6.829	13.218	10.081
p		<0.001	<0.001	<0.001

*Compared with the control group, *p < 0.05; compared with the DB1 group, #p < 0.05.*

TABLE 7 | Comparison of Ramsay scores of puerperae at different times after surgery among three groups (mean ± SD, score).

Group	*n*	Postoperative time (h)		
		6	24	48
Control group	20	2.1 ± 0.6	2.6 ± 0.5	2.3 ± 0.3
DB1 group	20	2.6 ± 0.6*	3.1 ± 0.4*	2.6 ± 0.5*
DB2 group	20	2.9 ± 0.0*#	3.4 ± 0.5*#	2.8 ± 0.3*#
F		4.439	8.942	4.908
p		0.039	<0.001	0.035

*Compared with the control group, *p < 0.05; compared with the DB1 group, #p < 0.05.*

DISCUSSION

In this study, we found that continuous intravenous infusion of dexmedetomidine along with butorphanol in PCIA after a cesarean section could lead not only to pain reduction and enhanced analgesic effect (according to VAS) but also improved sedative effects, while it did not affect the adverse reaction. At the same time, we also found that high-dose dexmedetomidine was more effective for analgesia and sedation than low-dose dexmedetomidine.

The use of opioids alone for sedation after a cesarean section has many disadvantages. On the one hand, the analgesic effect is insufficient (16). On the other hand, the application of high-dose opioid analgesics significantly increased the incidence of postoperative nausea, vomiting, and respiratory depression (17). In addition, the safety of many analgesics excreted in breast milk in newborns is uncertain (16, 17). Dexmedetomidine is a nonopioid drug with both peripheral and central analgesic effects, and it is a selective α2 adrenoceptor agonist, which can reduce sympathetic nerve activity, the release of catecholamines, and the harmful stimulation caused by surgery and has a certain protective effect on important organs. Results from a randomized and placebo-controlled study have shown that the combination of sufentanil and dexmedetomidine for PCA after a cesarean section can reduce sufentanil consumption and improve parturients' satisfaction compared with sufentanil PCA alone (18). In addition, a recent study indicated that adding dexmedetomidine to the postoperative analgesia regimen for a cesarean section could enhance postoperative analgesia and improve satisfaction (19). In previous studies (20–22), the doses of dexmedetomidine for sustained analgesia after a cesarean section included 0.08, 0.5, and 3 μg/kg/h, so we administered 1.0 and 2.0 μg/kg/h dexmedetomidine to determine the dose-dependent effect and optimal dose of analgesic management with PCIA in the present study.

TABLE 8 | Comparison of adverse reactions at 48 h after surgery among three groups (*n*, %).

Group	*N*	Malignant vomiting	Dizziness	Itchy shin	Bradycardia	Low blood pressure	Total
Control group	20	3 (15.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	5 (25.0)
DB1 group	20	1 (5.0)	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)	2 (10.0)
DB2 group	20	1 (5.0)	0 (0.0)	0 (0.0)	1 (5.0)	1 (5.0)	3 (15.0)

Furthermore, cesarean section-induced pain is not only from incision but also from uterine contraction during uterine involution, and there is no evidence suggesting that opioids are effective for uterine contraction pain (16). Butorphanol exerts an analgesic effect through the dual action of opioid receptor agonism-antagonism, and its single application has a definite effect on the treatment of severe and moderate pain (12, 13). More importantly, butorphanol can also relieve visceral pain, which can make up for the lack of opioid analgesics in postoperative analgesia for mothers (23, 24). In this study, we found that maternal addition of butorphanol for analgesia was effective in reducing uterine cramping pain, suggesting that butorphanol can relieve visceral pain in postcesarean section analgesia. Postoperative pain is the main factor leading to postoperative sleep deprivation, and patients with severe sleep deprivation are prone to postoperative hyperalgesia (25, 26). In addition, butorphanol has many advantages for PCIA after a cesarean section because of its unique pharmacological properties. First, the analgesic mechanism of butorphanol is mainly achieved by activating κ receptors, and the activation of κ receptors enables it to exert a more potent analgesic effect in the treatment of visceral pain (23, 24). Second, the milk secretion rate of butorphanol is low, and the drug concentration in maternal milk at therapeutic doses is extremely low, so there is almost no obvious adverse effect on the newborn (27).

Dexmedetomidine acts on the α2 adrenoceptor agonist in the nucleus locus coeruleus, reduces the release of norepinephrine, simulates natural sleep, and produces sedative, hypnotic, and anxiolytic effects (28, 29). In the present study, we found that dexmedetomidine combined with butorphanol can improve the sedative effects (according to the Ramsay score) in continuous analgesia after a cesarean section, and the analgesic and sedative effects of dexmedetomidine in the high-dose group are better than those in the low-dose group, which is consistent with the findings of Zhang et al. (30). Zhang et al. found that dexmedetomidine was more effective than sufentanil for maternal labor sedation, and the analgesic and sedative effects of dexmedetomidine in the high-dose group were better than those in the low-dose group (30).

Postoperative pain can induce adverse events, such as cardiovascular disease, respiratory depression, digestive and urinary system dysfunction, and neuroendocrine disorders, which bring great discomfort to patients and seriously affect the postoperative recovery of patients (31, 32). At the same time, although the use of unreasonable postoperative analgesics can effectively control pain, it can also cause adverse reactions, such as malignant vomiting, dizziness, itchy skin, bradycardia, and low blood pressure (33, 34). Therefore, to date, there is still no accepted and optimal analgesic regimen for postoperative pain. In our study, we found that the addition of dexmedetomidine combined with butorphanol to the basic postoperative analgesia regimen enhanced the analgesic effect without increasing the adverse reactions in patients, which suggested that dexmedetomidine combined with butorphanol is not only effective in postoperative analgesia and sedation but also safe in puerperae after a cesarean section.

There were several limitations to our study. First, we only studied the effect of dexmedetomidine combined with butorphanol on mothers and did not study the content of dexmedetomidine and butorphanol in maternal milk and whether they affected neonates. Second, the sample size included in this study is small, so the results may be biased to a certain extent. The results of this study need to be further verified by a systematic study with large sample size. At last, we only analyzed two doses of dexmedetomidine, and more doses of dexmedetomidine need to be studied to further explore the optimal dose for clinical application.

CONCLUSION

Dexmedetomidine combined with butorphanol can improve the analgesic and sedative effects in continuous analgesia after a cesarean section, and the analgesic and sedative effects of dexmedetomidine in the high-dose group are better than those in the low-dose group.

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 our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HL and YW are mainly responsible for the writing of the article. FL is mainly responsible for research design. YW is mainly responsible for data analysis. WR and LY are responsible for

the guidance of the entire research. The corresponding author is Hui Liu, and she is responsible for ensuring that the descriptions are accurate and agreed upon by all authors. All authors contributed to the article and approved the submitted version.

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Clinicopathological Characteristics of Primary Appendiceal Mucinous Neoplasm and Recurrence After Radical Resection

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Objective: Appendiceal mucinous neoplasm (AMN) is a rare obstructive dilatation of the appendix caused by an intraluminal accumulation of mucoid material, showing an insidious onset and few specific clinical manifestations. The purpose of the study is to analyze clinicopathological characteristics of primary AMN and recurrence after radical resection.

Methods: A total of 50 patients were included in the retrospective cohort study of AMN. Patient data, such as demographics, tumor characteristics, surgical management, preoperative serum carcinoembryonic antigen (CEA), and carcinoembryonic antigen 19-9 (CA19-9) levels, were collected. All patients were followed-up with interval CT scans until the end of December 2021, with overall survival (OS) and progression-free survival (PFS) being calculated.

Results: All patients were confirmed as AMN by pathological diagnosis after surgery, including 28 cases (56.00%) of low-grade AMN (LAMN) and 22 cases (44.00%) of non-LAMN. Among 50 patients with AMN, there were 12 cases (24.00%) complicated with pseudomyxoma peritonei (PMP). Higher proportions of patients with pTis, pT3, pT4a, ruptured at presentation, and PMP were found in patients with non-LAMN patients than LAMN ($p < 0.05$). There was a remarkable difference about preoperative serum CA19-9 levels between patients with LAMN and non-LAMN ($p = 0.044$). Patients complicated with PMP had a higher proportion of patients with ruptured at presentation than those who were not ($p < 0.001$). The patients with PMP had increased tumor size compared with those without PMP ($p = 0.031$). Remarkable differences were observed in terms of preoperative serum CA19-9 ($p = 0.009$) levels between patients with PMP and without PMP. We performed a multivariate analysis of the presence or absence of PMP and found that ruptured at presentation was found to be a risk factor for PMP in patients with AMN ($p = 0.003$). The PFS in the patients with PMP and those without was 33.33% (4/12) and 2.63% (1/38), showing a significant difference ($P = 0.002$).

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Conclusion: The study demonstrates that ruptured at presentation and PMP may influence the prognosis and survival of patients with AMN.

Keywords: appendiceal mucinous neoplasm, low-grade appendiceal mucinous neoplasm, PMP, rupture, non-LAMN

INTRODUCTION

Appendectomy is a common surgical intervention. It is reported that about 1% of the appendectomy specimens are diagnosed with appendiceal tumors after pathological analysis (1), and appendiceal mucinous neoplasms (AMNs) are responsible for 0.2–0.3% of appendectomy specimens (2).

Appendiceal mucinous neoplasm is an uncommon disease and its prevalence is less than 1% of all cancers (3). Early criteria for simple mucocele considered AMN as a benign disease, also known as appendiceal mucocele (4), cystadenoma, and cystadenocarcinoma (5). The fifth edition of the World Health Organization (WHO) Classification of Tumors of the Digestive System divides AMN into low-grade and high-grade from morphological characteristics, such as structure, cytology, the presence of signet ring cells, and mitotic activity (6). Although this classification simplifies the diagnostic terminology of AMN, the ninth edition of the American Joint Committee on Cancer proposes descriptive terminology, such as well-differentiated (G1), moderately differentiated (G2), and poorly differentiated (G3), to classify AMN. Low-grade AMN (LAMN) is classified as G1, while high-grade AMN is classified as G2 or G3 (7). Studies have indicated that there are AMNs with relatively slow growth but high recurrence rate and high mortality, as well as AMNs with high invasiveness and an increased risk of early death (8, 9). AMN can lead to an increased risk of pseudomyxoma peritonei (PMP). LAMN with potential malignancy is significantly correlated with the presence of PMP. Furthermore, the increase of synchronous or metachronous colorectal cancer is associated with AMN (10, 11). PMP is a rare disease with a 1-per-million incidence rate (2), and is most frequently seen among women aged 50–70 years (12). PMP was first mentioned in the study of mucinous tumors of the ovary in 1884 (13). It is characterized by obvious diffuse intra-abdominal mucinous ascites on the surface of the peritoneum in clinical (14). This situation can be fatal if the patients with PMP are not treated.

Delayed diagnosis of appendiceal tumors often occurs due to their nonspecific clinical manifestations. In early-stage disease, the clinical manifestation presents pain in the right lower abdomen, commonly seen in acute appendicitis. A clinicopathological study of 184 patients with appendiceal tumors found that 32% of patients were misdiagnosed with acute appendicitis before the operation, and the proportion of patients accidentally diagnosed with appendiceal tumor was 23% (15).

Generally, these rare tumors are usually identified after surgery. More and more such tumors are diagnosed before any surgical operation, which benefits from the improvement of the availability and accuracy of medical imaging. The affecting factors, such as the stage at diagnosis and histological characteristics reflecting cell differentiation, are relevant to the clinical course of AMN (8, 9). In our retrospective report, we enrolled the clinical data of 50 patients with AMN and summarized the clinical characteristics of the disease and the factors affecting the prognosis, thus providing a reference for clinical diagnosis and treatment.

METHODS

Patients and Data Collection

We retrospectively reviewed data of patients with a final pathological diagnosis of AMN who underwent primary surgical treatment at the Bozhou Hospital Affiliated with Anhui Medical University between January 2017 and October 2021. Those receiving neoadjuvant chemotherapy and those with a preoperative pathological diagnosis before the primary surgery were excluded from the retrospective analysis. The diagnosis of AMN was made according to the WHO classification and the Peritoneal Surface Oncology Group (PSOGI) consensus classification (16) with our routine practice by two pathologists. A third pathologist was invited to advise if there were significant differences between the two pathologists concerning the diagnosis, and we adopted the diagnosis of the third pathologist. We reviewed clinical information, physical examination notes, surgery, and pathological records of all included patients with the approval of the Institutional Review Board of the Bozhou Hospital Affiliated with Anhui Medical University.

Biochemical Detection and Imaging Evaluation

Blood samples were collected from each patient before surgery for the detection of tumor biomarker, carcinoembryonic antigen (CEA), and carcinoembryonic antigen 19-9 (CA19-9). All patients had undergone at least one imaging evaluation (color Doppler ultrasound and CT).

Variables

Patient data, such as demographics, tumor characteristics, and surgical management, were collected. Demographic variables included age, sex, and body mass index (BMI). Surgical modality included open or laparoscopic appendectomy. On pathological review, tumor characteristics included pT stage, tumor size, resection margin, and ruptured or non-ruptured appendix. Based on the American Joint Committee on Cancer (AJCC) Staging Standard (8th edition), the pT stage was classified into pTis, pT3, pT4a, and pT4b. pTis is defined as AMNs confined to the appendix (defined as involvement by acellular mucin or mucinous epithelium that may extend into the muscularis propria), pT3 is defined as tumor penetrating the muscularis propria or fibrotic appendix wall and invading the subserosa or mesoappendix, pT4a is defined as tumor perforating the

visceral peritoneum, such as mucinous peritoneal tumors or acellular mucinous tumors on the serosa of the appendix or mesoappendix, and pT4b is defined as tumor directly invading other organs or structures. Tumor size was calculated according to either the pathology report, operative note, or radiological report of preoperative imaging. The ruptured status, which was defined as complete penetration of mucin from the lumen to the serosal surface with evidence of discontinuity of the appendiceal wall, was evaluated according to the final pathology report (17).

Follow-Up

All patients were followed-up with interval CT scans until the end of December 2021. Overall survival (OS) was calculated from the date of surgery to the last date of follow-up or date of death. Progression-free survival (PFS) was calculated from the time of surgery to the date of disease progression confirmed by imaging motility.

Statistical Analysis

Data processing and analysis were performed using SPSS software version 13.0 (IBM Inc., Armonk, NY, USA). Median and ranges were used to report continuous variables when non-normally distributed and mean ± standard deviation (SD) to report continuous variables when normally distributed. Frequencies and percentages were reported for categorical values. Multivariate analysis was employed to evaluate prognostic factors. A value of $p < 0.05$ reflects a statistically significant difference by the *t*-test, Mann–Whitney *U*-test, or the chi-square test.

RESULTS

Patient Demographics

A total of 50 patients were included in the retrospective cohort study of AMN, among whom there were 19 men and 31 women. Patient age ranged from 21 to 81 years, with a mean age of (56.04 ± 17.13) years. There were 12 patients (24.00%) aged <44 years, 11 patients (22.00%) aged from 45 to 59 years, and 27 patients (54.00%) aged more than 60 years. The BMI of patients was 27.84 ± 5.35. The interval between the first symptoms and surgery of 50 patients was (25.5 [3.25, 120]) days.

Clinical Characteristics of Patients With AMN

Among 50 patients, 15 cases (30.00%) showed acute abdominal diseases at the visit, such as right lower abdominal pain ($n = 12$), total abdominal pain ($n = 2$), and upper abdominal pain ($n = 1$); the majority of cases presented no acute abdominal disease at visit (70.00%). There were 13 cases (26%) that had a history of right lower abdominal mass. About preoperative detection of an inflammatory response, 9 cases (18.00%) of 50 patients were found to have increased white blood cell and neutrophil counts. All patients had undergone color Doppler ultrasound ($n = 37$) and/or CT ($n = 29$). Before surgery, 43 cases (86.00%) were diagnosed as AMN, while 5 cases were misdiagnosed as acute appendicitis due to no evident cystic lesion on the appendix or surrounding tissues on preoperative color Doppler ultrasound or CT and 2 cases as digestive tract perforation due to perihepatic gas effusion. There were 37 patients (74.00%) undergoing open appendectomy and 13 patients (26.00%) undergoing laparoscopic appendectomy. Ruptured at presentation was found in 10 patients. The tumor size was (6.85 ± 3.39) mm. All patients were confirmed as AMN by pathological diagnosis after surgery, including 34 cases (68.00%) of appendiceal mucocele, 14 cases (28.00%) of mucinous cystadenoma of the appendix, 2 cases (4%) of mucinous adenocarcinoma of appendix; 28 cases (56.00%) of LAMN and 22 cases (44.00%) of non-LAMN. Among 50 patients with AMN, there were 12 cases (24.00%) complicated with PMP.

Surgical Management of Patients With AMN

All patients underwent complete surgical resection. During surgery, 20 patients (40.00%) who found their tumors in the middle-distal appendix were given appendectomy, 23 patients (46.00%) who had a whole appendix involved by the tumor or found their tumors at the end of the appendix were given appendectomy with partial cecectomy, and 7 patients (14.00%) who found their tumors involving the cecum and colon were given appendectomy with right hemicolectomy. Among 50 patients, 33 patients (66.00%) were defined as pTis stage, 10 patients (20.00%) were defined as pT3, and 7 patients (14.00%) were defined as pT4a; 5 patients (10.00%) had a positive resection margin and 45 patients (90.00%) had a negative resection margin. As for those with tumors ruptured at presentation, additional lymph node dissection was performed.

Association Between Clinical Characteristics and LAMN

Demographics, surgical management, and tumor characteristics of patients stratified by LAMN and non-LAMN classification are listed in **Table 1**. No significant difference was found regarding age, gender distribution, BMI, surgical modality, tumor size, and preoperative serum CEA levels between patients with LAMN and non-LAMN ($p > 0.05$). Of note, there were remarkable differences in pTis, pT3, and pT4a between patients with LAMN and non-LAMN ($p < 0.001$; $p = 0.015$; and $p = 0.035$). A higher proportion of patients with ruptured at presentation was found in patients with non-LAMN than LAMN ($p = 0.010$). In addition, we found a higher proportion of patients complicated with PMP in patients with non-LAMN than LAMN ($p = 0.013$). There was a remarkable difference in preoperative serum CA19-9 levels between patients with LAMN and non-LAMN ($p = 0.044$). It was revealed that pTis, ruptured at presentation, the presence of PMP, and CA19-9 levels may contribute to the aggressiveness of AMN.

Risk Factors of PMP in Patients With AMN

Demographics, surgical management, and tumor characteristics of patients stratified by the presence and absence of PMP are shown in **Table 2**. It was found that the patients complicated with PMP were older than those who were not ($p = 0.007$). Patients complicated by PMP had a higher proportion of patients with ruptured at presentation than those who were not ($p < 0.001$). The patients with PMP had increased tumor size compared with those without ($p = 0.031$). Remarkable

TABLE 1 | Demographics, surgical management, tumor characteristics of patients stratified by LAMN and non-LAMN classification.

Variables	LAMN ($n = 28$)	Non-LAMN ($n = 22$)	*P*
Age (year)	55.05 ± 16.39	58.04 ± 17.94	0.542
Female, n (%)	18 (64.29%)	13 (59.09%)	0.774
BMI	27.83 ± 5.75	27.86 ± 4.94	0.985
Open appendectomy, *n* (%)	20 (71.43%)	17 (77.27%)	0.751
pT stage, *n* (%)			
pTis ($n = 33$)	25 (89.29%)	8 (36.36%)	< 0.001
pT3 ($n = 10$)	2 (7.14%)	8 (36.36%)	0.015
pT4a ($n = 7$)	1 (3.57%)	6 (27.27%)	0.035
Ruptured at presentation, *n* (%)	2 (14.29%)	8 (27.27%)	0.010
Tumor size (mm)	6.55 ± 3.48	7.23 ± 3.32	0.488
PMP, *n* (%)	3 (17.86%)	9 (31.82%)	0.013
Preoperative serum CEA levels (ng/mL), median (range)	3.12 (0–438.59)	4.00 (0–2,536)	0.172
Preoperative serum CA19-9 levels (ng/mL), median (range)	9.34 (0–1,524.55)	15.31 (0–8824.33)	0.044

Median and ranges were compared using Mann-Whitney test; Mean ± standard deviation were compared using t test. Frequencies and percentages were compared using chi-square test.

TABLE 2 | Demographics, surgical management, tumor characteristics of patients stratified by the presence and absence of PMP.

Variables	Presence ($n = 12$)	Absence ($n = 38$)	*P*
Age (year)	67.42 ± 11.00	52.45 ± 17.24	0.007
Age ≥ 65 years, *n* (%)	8 (66.67%)	14 (36.84%)	0.099
Female, *n* (%)	9 (75.00%)	22 (57.89%)	0.332
BMI	27.51 ± 5.02	27.95 ± 5.52	0.807
Open appendectomy, *n* (%)	9 (75.00%)	28 (73.68%)	0.928
Ruptured at presentation, *n* (%)	8 (66.67%)	1 (2.63%)	< 0.001
Tumor size (mm)	8.38 ± 4.34	6.37 ± 2.94	0.031
Preoperative serum CEA levels (ng/mL), median (range)	7.98 (0–2,904.56)	2.42 (0–357.46)	0.208
Preoperative serum CA19-9 levels (ng/mL), median (range)	16.27 (0–9,264)	7.55 (0–1,280.43)	0.009

Median and ranges were compared using Mann-Whitney test; Mean ± standard deviation were compared using t-test. Frequencies and percentages were compared using chi-square test.

differences were observed in terms of preoperative serum CA19-9 ($p = 0.009$) levels between patients with PMP and without. There was no significant difference in gender distribution, age-stratification of 65-year-old BMI, surgical modality, and preoperative serum CEA levels between patients with PMP and without ($p > 0.05$). These observations suggested age, rupture at presentation, tumor size, and CA19-9 levels may contribute to the progression of PMP. We performed a multivariate analysis of the presence or absence of PMP by including age (assigned as actual values), ruptured at presentation (assigned as 1 = yes; 0 = no), and tumor size (assigned as actual values). It was revealed that ruptures at presentation were found as risk factors of PMP in patients with AMN ($p = 0.003$, **Table 3**).

TABLE 3 | Multivariate analysis of the presence or absence of PMP.

Variables	Exp	95%CI	*P*
Age (year)	1.087	0.992–1.191	0.075
Ruptured at presentation, n (%)	51.793	3.713–722.477	< 0.001
Tumor size (mm)	1.124	0.826–1.530	0.455

Follow-Up Analysis

All patients were followed-up with interval CT scans until the end of December 2021. The median follow-up time was 19 months, ranging from 2 to 47.5 months. The OS did not exhibit a significant difference between patients with non-LAMN and LAMN, between patients with PMP and without due to nobody dying. CT scans showed 4 patients with PMP who had been diagnosed with PMP and had tumors ruptured at a presentation during surgery. There was a case of strangulated hernia. The PFS was 90.00% (5/50). The PFS in the patients with non-LAMN and LAMN was 13.64% (3/22) and 7.14% (2/28), respectively, showing no significant difference ($p > 0.05$). The PFS in the patients

with PMP and those without was 33.33% (4/12) and 2.63% (1/38), respectively, showing a significant difference ($p = 0.002$). These data indicate that PFS of patients with AMN is more closely associated with PMP than primary appendiceal pathological grade.

DISCUSSION

Appendiceal tumors are uncommon and often manifest as appendicitis, which is usually accidentally found in an acute situation (18). Neuroendocrine-related appendiceal tumors account for ∼65% of histological classification of appendiceal tumors, and 20% of these tumors are adenocarcinoma which is defined as the most prevalent malignant histological subtype (19). In all subtypes, more than 50% of populations were subjective to adenocarcinoma (20). Most appendiceal tumors are not malignant and can be treated by appendectomy. AMN is a rare clinical disease, but the incidence rate is rising, accounting for 58% of all appendiceal tumors (21).

The nomenclature and diagnostic criteria of AMN have not been well identified for a long time. According to cytology, AMN is classified into low-grade and high-grade by the WHO Classification of Tumors of the Digestive System (2019), which is defined as a tumor with appendiceal mucinous epithelial hyperplasia, accompanied by extracellular mucus and "pushing" tumor border (6). Some studies demonstrated that KRAS and GNAS gene mutations occurred in LAMN (22, 23), and patients with high-grade AMN manifested mutations of KRAS and GNAS, along with TP53, as well as ATM (24). The pathogenesis needs to be further studied. At present, AMN is regarded as a disease of cystic expansion of the appendix caused by obstruction of the appendiceal cavity, leading to failure in the discharge of mucus secreted by the appendix mucosa. AMN can be classified into 4 types, such as retention cyst, epithelial hyperplasia cyst, mucinous cystadenoma, and mucinous cystadenocarcinoma, based on causes of obstruction of the appendix (25). It is difficult to judge whether AMN is benign or malignant simply. The initial affecting factors of AMN can be the same, but different evolution can occur, resulting in the existence of PMP (2) in the absence of hematogenic or lymphatic metastasis (26). Therefore, it is necessary to analyze AMN in combination with the biological characteristics of malignant tumors.

Appendiceal mucinous neoplasm exhibits non-specificity clinical features. In this study, 15 cases (30.00%) showed acute abdominal diseases, such as right lower abdominal pain (12 cases), total abdominal pain (2 cases), and upper abdominal pain (1 case). The majority of patients presented no acute abdominal disease (70.00%), suggesting that patients with an acute abdominal disease might be associated with AMN. In recent years, with the development of imaging technology, the accuracy of preoperative diagnosis of AMN has improved. AMN presents some ultrasound characteristics, such as location in the right lower abdomen, the anatomical position closing to the right psoas major muscle or iliac blood vessel, shaped like a tube or a circle, cystic or solid lesions, non-thick cystic wall, and the presence of calcification (27, 28). Ultrasound detection reveals a false negative rate to a certain extent due to the effect induced by intestinal gas. It is necessary to perform an abdominal CT examination for those with an unknown diagnosis. The CT examination assists in judging the correlation between the tumors and surrounding tissues, contributing to improvements in the preoperative diagnosis rate (29). In this study, all patients underwent abdominal color Doppler ultrasound or CT before surgery. We found that 43 cases (86.00%) were diagnosed with AMN before surgery. Then, 7 cases (14.00%) were misdiagnosed with other diseases, including acute appendicitis (5 cases) and digestive tract perforation caused by perihepatic gas effusion (2 cases). In the 5 patients with acute appendicitis, there was no evident cystic lesion on the appendix or surroundings before surgery.

Surgical intervention is still the only possible radical method for the treatment of AMN. Specific interventions must be determined based on the size of tumor, location of the tumor, and its invasion and adhesion with abdominal organs (30). The present study followed the following principles: (a) appendectomy is carried out to the tumors located in the middle and distal end of the appendix and without invasion at the root of the appendix (applying to 20 cases); (b) if the tumor is located in the whole segment of the appendix or invades the root of the appendix, the appendectomy combined with partial cecectomy shall be performed (applying to 23 cases); (c) the appendectomy combined with right hemicolectomy is applied to those tumors that invade the cecum or the lower segment of the ascending colon (applying to 7 cases). In addition to the above principles, additional lymph node dissection was performed for those with tumor rupture during the intervention. Open appendectomy and laparoscopic appendectomy were applied to 37 patients (74.00%) and 13 patients (26.00%), respectively. In addition, 10 patients showed tumor rupture at presentation, and the tumor size was (6.85 ± 3.39) mm. Moreover, 12 cases of 50 patients with AMN were complicated with PMP. It suggested that the presence of PMP was associated with AMN. Ning et al. indicated that the occurrence of PMP was induced by LAMN accompanied by rectal cancer (31), and Reiter et al. revealed that the progression of PMP was related to LAMN (32). In this study, all patients were confirmed as AMN by pathological diagnosis after surgery, and LAMN accounted for 56.00%, and non-LAMN occupied 44.00%. Furthermore, we found that the incidence of tumor rupture and PMP in patients with non-LAMN was higher than that in patients with LAMN. CA19-9 is a tumor marker of pancreatic, gastric, and hepatobiliary malignancies. The high level of CA19-9 indicates that the lesion develops into malignancy, which is related to a poor prognosis (33). In our study, patients with non-LAMN presented a much higher level of preoperative serum CA19-9 than the patients with LAMN. These results showed that pTis, tumor rupture at presentation, the presence of PMP, and CA19-9 levels may be associated with the aggressiveness of AMN. To further analyze the risk factors of PMP in patients with AMN, we analyzed demographics, surgical management, and tumor characteristics

of patients stratified by the presence and absence of PMP. It was revealed that age, tumor rupture at presentation, tumor size, and CA19-9 levels might be associated with the progression of PMP. We found that tumor rupture was a risk factor leading to PMP in patients with AMN, which was supported by other studies (34) indicating tumor rupture at presentation was the only factor significantly associated with PMP. The follow-up data (median: 19 months, ranging from 2 to 47.5 months) showed no significant difference in the OS between patients with non-LAMN and LAMN, and between patients with PMP and without PMP. However, the long-term effect needs to be further studied. It has been reported that no matter how benign or malignant AMN, once the tumor ruptures, it will significantly increase the postoperative recurrence rate and the risk of peritoneal implantation and metastasis, and affect the prognosis of patients (35). The present study found that 4 patients with previous PMP were diagnosed with PMP again and showed tumor rupture.

In conclusion, AMN is rare in clinics and lacks specific clinical manifestations. Clinicians should consider the possibility of AMN when the patient presents right lower abdominal pain, total abdominal pain, and upper abdominal pain. Abdominal color Doppler ultrasound and CT examination are helpful in making a clear diagnosis and guiding the treatment of AMN. Tumor rupture in AMN is a risk factor affecting the progression of PMP. However, further investigations with a large-scale sample size should be performed to provide a full understanding of the pathogenesis and progression of AMN.

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 Bozhou Hospital Affiliated to Anhui Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ZBW conceived and designed the study and contributed to the writing of initial draft, and as well as review and editing. MMY contributed to study design, study validation, along with experimental resources, and software preparation. JYS assisted in writing, performed data analysis, and interpretation. ZPY was responsible for data verification and visualization. JP assisted in data analysis and verification. ZML contributed to funding acquisition and manuscript revision. All authors approved final manuscript.

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Application of Salvage Autologous Blood Transfusion for treating Massive Hemorrhage during Ectopic Pregnancy

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Purpose: To explore the application value of salvage autologous blood transfusion for massive hemorrhage occurring during ectopic pregnancy.

Methods: A retrospective analysis was performed on the basis of the clinical data of patients in our hospital for the period January 2019 to December 2021. These patients were confirmed to have suffered massive hemorrhage from an ectopic pregnancy during surgery and were treated with blood transfusion. The patients were divided according to their blood transfusion method into three groups: an autologous group ($n = 46$) treated with salvage autologous blood transfusion, a mixed group ($n = 28$) treated with salvage autologous + allogeneic blood transfusion, and an allogeneic group ($n = 41$) treated with allogeneic blood transfusion. The volume of intra-abdominal bleeding, the volume of autologous and allogeneic blood transfusion, postoperative fever and blood transfusion reaction, hemodynamic indices [systolic blood pressure (SBP), diastolic blood pressure (DBP), oxygen saturation (SpO2), and heart rate (HR)] before and after blood transfusion; 24-h postoperative blood routine [hematocrit (HCT), hemoglobin (Hb), platelets (PLT), red blood cells (RBCs)], and electrolyte indices (Na^+, K^+, Cl^-) were all compared among the three groups.

Results: It was found that intra-abdominal bleeding volume in the autologous and mixed groups was higher than that in the allogeneic group ($p < 0.05$), and there was no statistical difference between the autologous and the mixed groups ($p > 0.05$). Autologous blood transfusion volume in the autologous group was higher than that in the mixed group ($p < 0.05$). Allogeneic blood transfusion volume in the allogeneic group was higher than that in the mixed group ($p < 0.05$). After blood transfusion treatment, the postoperative fever rates were 4.35%, 10.71%, and 19.51% in the autologous, mixed, and allogeneic groups, respectively, and the blood transfusion reaction rates were 0.00%, 3.57%, and 9.76%, respectively, which were lower in the autologous group than in the allogeneic group ($p < 0.05$). At 30 min after blood transfusion, SBP, DBP, and SpO_2 were higher in all three groups than before blood transfusion ($p < 0.05$), and HR was lower than before blood transfusion ($p < 0.05$), but

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there was no statistically significant difference between the groups at 30 min after blood transfusion ($p > 0.05$). At the 24- h postoperative period, no statistical difference was found when HCT, Hb, PLT, RBC, Na^+, K^+, and Cl^- were compared among the three groups ($p > 0.05$).

Conclusion: The use of salvage autologous blood transfusion for treating massive hemorrhage occurring during ectopic pregnancy is a safe and feasible method for rescuing patients with such condition because it can rapidly replenish the patient's blood volume and save blood resources without causing postoperative hemodynamic, blood routine, and electrolyte abnormalities.

Keywords: ectopic pregnancy, massive bleeding, salvage autologous blood transfusion, allogeneic blood transfusion, application value

INTRODUCTION

Delayed rescue of patients who have suffered massive hemorrhage during ectopic pregnancy can cause shock even death. Timely surgical hemostasis and rapid blood transfusion are the key to successful rescue. However, blood source tension and the spread of AIDS, hepatitis, and other infectious diseases caused by blood transfusion are the two major problems that plague blood transfusion medicine. Internationally, autologous blood transfusion is recommended to address this issue (1, 2). At present, there are three main methods of autologous blood transfusion, namely, prestorage type, dilution type, and recovery type (3). The first two methods are mainly suitable for patients undergoing elective surgery; that is, bloodletting is performed before surgery to prepare for intraoperative or postoperative reinfusion (4, 5). In the third method, the blood that is accumulated in the body cavity or the blood that leaks from the operative area is used as a blood source, which is recovered and processed for transfusion back to the patient (6). It is suitable for patients with acute internal hemorrhage, especially those with massive intra-abdominal hemorrhage who cannot use prestored and diluted autologous blood transfusions due to acute onset and severe condition requiring rapid rescue. It not only saves clinical blood allocation, blood collection, and blood resources and gains resuscitation time for patients, but more importantly, reduces the risk of immune blood transfusion and infectious blood transfusion associated with allogeneic transfusion, which can provide a safer guarantee for patients (7, 8). This study summarizes the experience of the application of intraoperative salvage autologous blood transfusion in patients who suffered massive hemorrhage during ectopic pregnancy in our hospital during the January 2019 to December 2021 period and compares the results with those with the same condition treated with autologous + allogeneic blood transfusion and allogeneic blood transfusion during the same period. The aim of this exercise is to explore the value of salvage autologous blood transfusion in patients who have had massive hemorrhage during ectopic pregnancy. The investigation is reported below.

MATERIALS AND METHODS

Research Object

A retrospective analysis was performed on the basis of the clinical data of patients in our hospital during January 2019 to December 2021. These patients were confirmed to have suffered massive hemorrhage from an ectopic pregnancy during surgery and were treated with blood transfusion. The inclusion criteria were as follows: all patients were diagnosed to have intra-abdominal hemorrhage caused by ectopic pregnancy rupture before operation, all were confirmed to have suffered tubal pregnancy rupture during operation, and postoperative pathological diagnosis confirmed tubal pregnancy; age 18–40 years old; menopause days 35–70 days; urine β-HCG positive; abdominal puncture or vaginal fornix puncture was positive; liver and kidney function and biochemical test results were normal; preoperative blood routine and coagulation function tests were performed; preoperative patients or their relatives signed the "informed consent form for blood transfusion"; case data were complete. The blood transfusion criteria were as follows: the intra-abdominal bleeding time was <24 h, blood was not contaminated, blood was bright red or dark red in color, ectopic pregnancy was <12 weeks, and the fetal membranes were not broken. The exclusion criteria were as follows: hydatidiform mole and choriocarcinoma were excluded, as also the following: previous cardiac, hepatic, renal, hematologic, or immunologic diseases; combined acute and chronic infectious diseases or a recent history of infections; combined severe anemia or coagulation factor deficiency; combined contraindications to blood transfusion; open wound hemorrhage with a duration of more than 4 h; the case data were incomplete. The patients were divided according to their blood transfusion method into three groups: an autologous group ($n = 46$) treated with salvage autologous blood transfusion, a mixed group ($n = 28$) treated with salvage autologous + allogeneic blood transfusion, and an allogeneic group ($n = 41$) treated with allogeneic blood transfusion. There was no statistical difference between the three groups of general data ($p > 0.05$), and they were comparable. See **Table 1**.

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

Group	Autologous group ($n = 46$)	Mixed group ($n = 28$)	Allogeneic group ($n = 41$)	t	p
Age (years old)	27.59 ± 3.88	26.82 ± 3.77	26.92 ± 3.50	0.509	0.602
BMI (kg/m^2)	23.08 ± 2.21	23.11 ± 2.19	22.85 ± 1.89	0.177	0.838
Preoperative Hb (g/L)	135.28 ± 6.11	136.25 ± 5.97	136.81 ± 6.12	1.047	0.355
Menopause time (d)	48.39 ± 3.81	49.11 ± 3.86	48.93 ± 4.00	0.510	0.602
Abdominal pain duration (h)	4.74 ± 1.41	4.68 ± 1.44	4.73 ± 1.36	0.012	0.987

Treatment Method

After a clear diagnosis of intra-abdominal hemorrhage for ectopic pregnancy, treatment such as infusion (crystalloid and colloid) and oxygen inhalation was immediately given, and the necessary preoperative preparations were actively made. After the three parties confirmed the identity of the patient and the surgical site, an emergency surgery was performed under general anesthesia conditions. The patient was placed in a supine position, the surgical field was disinfected with iodophor, a sterile towel was laid on them, which was connected to various parts of the laparoscope, a 10- mm-long skin incision was made on the upper edge of the umbilicus, a pneumoperitoneum needle was punctured, and CO2 gas was charged to make the intra-abdominal pressure reach 13 mmHg, a Trocar with a diameter of 10 mm was placed on them, and a laparoscope was inserted into the abdominal cavity. A 105- mm-diameter Trocar was placed in the left and right lower abdomen under laparoscopic direct vision. An investigation of intra-abdominal hemorrhage and blood clots was done, surgical excision of the lesions was performed, and a suture repair of the bleeding lesions and hemostasis was done.

On this basis, the autologous group adopted salvage autologous blood transfusion: the instrument used was Cell Saver 5+ (National Food and Drug Administration (Jin) Zi 2009 No. 3542073). Anticoagulant (500 mL of saline with 25,000 U of heparin), blood reservoir, suction device, connecting tube, centrifugal pump, and flushing solution were made ready just before the operation. Blood was collected at the beginning of the surgery by using an aspirator to draw blood into the blood reservoir, and blood resulting from traumatic bleeding, intra-abdominal bleeding, and intraoperative irrigation fluid was also collected. The blood was filtered through multiple layers of the blood storage tank. When the blood storage volume reached 500–600 mL, the automatic processing system of centrifugation, cleaning, and purification was activated. After cleaning, the anticoagulant, tissue debris, free hemoglobin, and anticoagulant were dispensed into the waste bag, and the concentrated red blood cells were drained into the blood bag and directly returned to the patient for use. Allogeneic group transfusion of allogeneic stock blood is explained as supplementation with the appropriate concentrated red blood cell suspension and plasma according to the patient's blood loss and vital signs. The mixed group was treated with combined autologous + allogeneic blood transfusion.

Observation Indicator

The volume of intra-abdominal bleeding, autologous and allogeneic blood transfusion, postoperative fever, and blood transfusion reaction were counted in the three groups. The hemodynamic indices of systolic blood pressure (SBP), diastolic blood pressure (DBP), blood oxygen saturation (SpO_2), and heart rate (HR) were recorded before and 30 min after blood transfusion in the three groups. Blood routine consisting of hematocrit (HCT), hemoglobin (Hb), platelets (PLT), and red blood cells (RBC) was recorded for the 24- h postoperative period in the groups. The electrolyte indices of Na^+, K^+, and Cl^- were also recorded for the same period.

Statistical Methods

SPSS 25.0 statistical software package was used to analyze the research data. The normally distributed measurement data were expressed as mean ± standard deviation, the intragroup comparison was performed by using the paired t-test, and the multigroup comparison was performed by using variance analysis. Enumeration data were expressed as rates, and comparisons were performed by using χ^2 analysis. A score of $p < 0.05$ indicates that the difference is statistically significant.

RESULTS

Comparison of the Volume of Intra-Abdominal Bleeding and Autologous and Allogeneic Blood Transfusion in Three Groups

The results revealed that intra-abdominal bleeding volume in the autologous and mixed groups was higher than that in the allogeneic group ($p < 0.05$), and there was no statistical difference between the autologous and the mixed groups ($p > 0.05$). Autologous blood transfusion volume in the autologous group was higher than that in the mixed group ($p < 0.05$). Allogeneic blood transfusion volume in the allogeneic group was higher than that in the mixed group ($p < 0.05$). See **Figure 1**.

Comparison of Postoperative Fever and Blood Transfusion Reaction in Three Groups

After blood transfusion treatment, the postoperative fever rates were 4.35%, 10.71%, and 19.51% in the autologous, mixed, and allogeneic groups, respectively, and the blood transfusion reaction rates were 0.00%, 3.57%, and 9.76%, respectively, which were lower in the autologous group than in the allogeneic group ($p < 0.05$). See **Figure 2**.

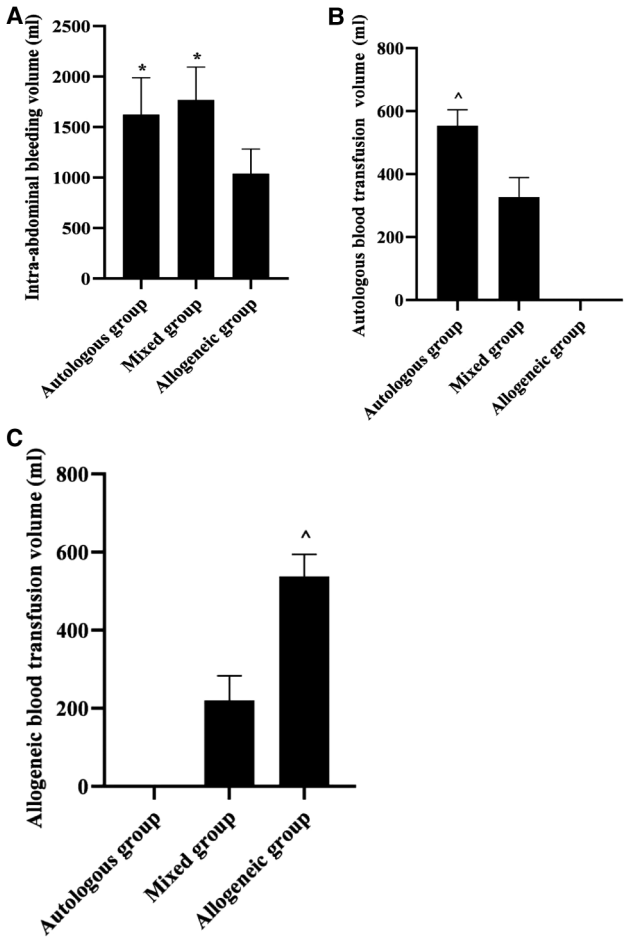

FIGURE 1 | Comparison of the volume of intra-abdominal bleeding and autologous and allogeneic blood transfusion in three groups ($\bar{x} \pm s$, mL). Note: (**A**) Intra-abdominal bleeding volume (mL). (**B**) Autologous blood transfusion volume (mL). (**C**) Allogeneic blood transfusion volume (mL). $^{*}p < 0.05$ compared with the allogeneic group; $^{\wedge}p < 0.05$ compared with the mixed group.

Comparison of Hemodynamic Indices Before and After Blood Transfusion in Three Groups

At 30 min after blood transfusion, SBP, DBP, and SpO_2 were higher in all three groups than before blood transfusion ($p < 0.05$), and HR was lower than before blood transfusion ($p < 0.05$), but there was no statistically significant difference between groups at 30 min after blood transfusion ($p > 0.05$). See **Figure 3**.

Comparison of 24 h Postoperative Blood Routine in Three Groups

At the 24- h postoperative period, no statistical difference was noted during the comparison of HCT, Hb, PLT, and RBC among the three groups ($p > 0.05$). See **Figure 4**.

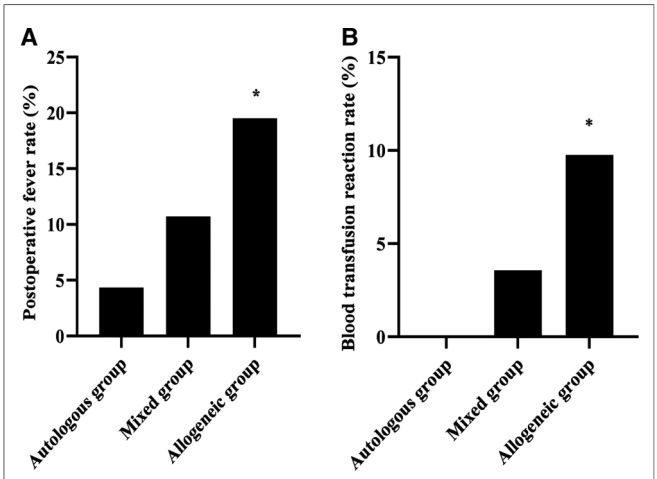

FIGURE 2 | Comparison of postoperative fever and blood transfusion reaction in three groups (*n*, %). Note: (**A**) Postoperative fever rate (%). (**B**) Blood transfusion reaction rate (%). $^{*}p < 0.05$ compared with the autologous group.

Comparison of 24 h Postoperative Electrolyte Indices in Three Groups

At the 24- h postoperative period, no statistical difference was found during the comparison of Na^+, K^+, and Cl^- among the three groups ($p > 0.05$). See **Figure 5**.

DISCUSSION

Ectopic pregnancy is a common emergency abdominal condition in obstetrics and gynecology but is an emergency with an acute condition and a lot of bleeding, with an incidence of about 2% to 3% (9). It refers to the implantation of a fertilized egg outside the uterine cavity, which, if not treated promptly, can lead to hemorrhagic shock, accounting for about 9% to 13% of pregnancy-related deaths, and requiring surgical hemostasis and blood volume replenishment in the first instance. Blood transfusion is an effective means of treatment for this condition (10). The current blood sources are allogeneic blood and autologous blood. Of these, the transfusion of allogeneic blood requires tedious steps such as matching and transport, which may easily lead to patients missing the golden period of rescue. In addition, the transfusion of allogeneic blood poses risks that are difficult to eliminate, such as allogeneic immunosuppression, transfusion-transmitted diseases, hemolytic reactions to transfusion, and technical errors that may occur during operations such as blood matching, histocompatibility, and disease testing when blood sources are tight and cannot be supplied in sufficient quantities in a timely manner. Autologous blood transfusion has become an important measure in the treatment of ectopic pregnancy bleeding.

Our data showed that intra-abdominal bleeding volume was higher in the autologous and mixed groups than in the allogeneic group ($p < 0.05$), and there was no statistical difference between the autologous and the mixed groups

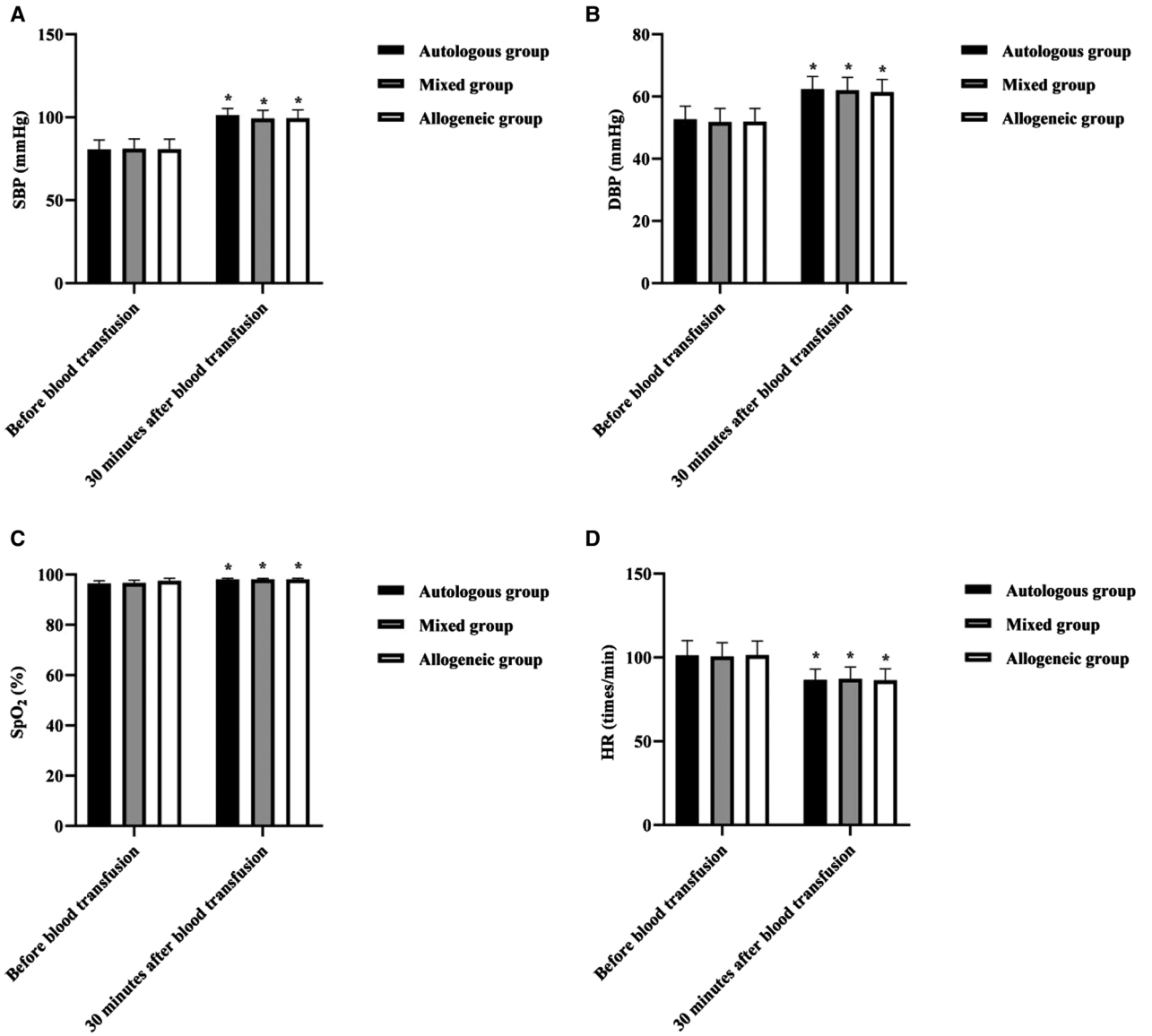

FIGURE 3 | Comparison of hemodynamic indices before and after blood transfusion in three groups (n, $\bar{x} \pm s$). Note: (**A**) SBP (mmHg). (**B**) DBP (mmHg). (**C**) SpO_2 (%). (**D**) HR (beats/min). *$p > 0.05$ when comparing before and 30 min after blood transfusion in the same group.

($p > 0.05$); autologous blood transfusion volume in the autologous group was higher than that in the mixed group ($p < 0.05$); allogeneic blood transfusion volume in the allogeneic group was higher than that in the mixed group ($p < 0.05$). These show that the method of salvage autologous blood transfusion achieves the purpose of reducing blood loss and saving blood resources through the utilization of "waste blood". According to the briefing, the average blood donation rate per 1,000 people in China has increased from 4.8% in 1998 to 11.1% in 2020, but it is still lower than the average blood donation rate per 1,000 people in high-income countries in the world, which is 45.4%, and meets only the 10% rate recommended by the World Health Organization. Also, the foundation of blood supply, especially non-remunerated blood donation, is still relatively weak in China (11). In contrast, a salvage autologous blood transfusion is a transfusion method that uses a blood recycling machine to return blood accumulated in the body cavity after trauma or blood lost during surgery to the patient themselves after anticoagulation and filtration (12). Concentrated red blood cells with a hematocrit of 50%–65% can be obtained after automatic processing by the blood recovery machine (13). It is efficient and fast, without depending on the blood type and cross-matching results, and requires only a simultaneous recovery of the patient's intraoperative blood loss at the beginning of the procedure, so that the processed final

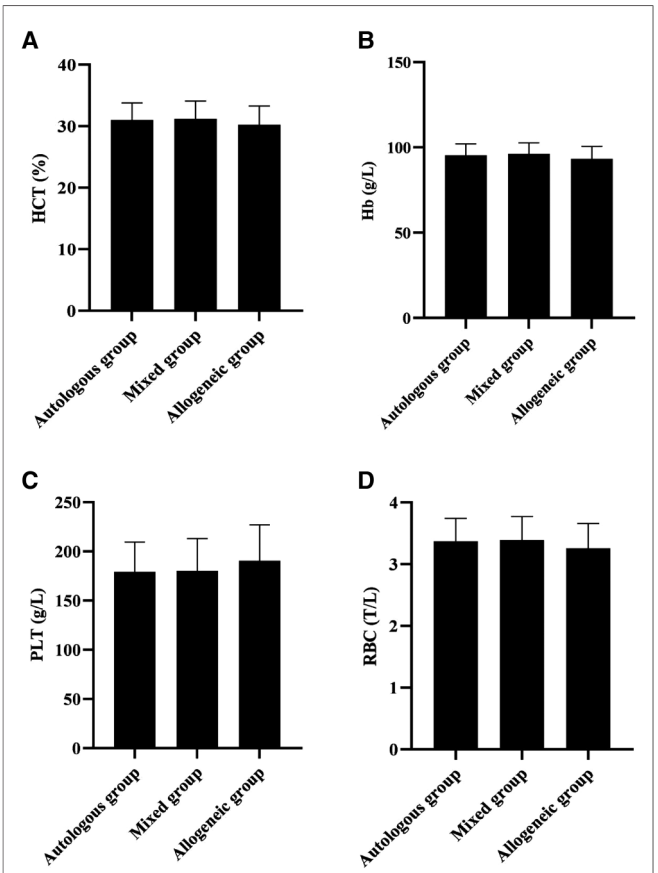

FIGURE 4 | Comparison of 24 h postoperative blood routine in three groups (n, $\bar{x} \pm s$). Note: (**A**) HCT (%). (**B**) Hb (g/L). (**C**) PLT (g/L). (**D**) RBC (T/L).

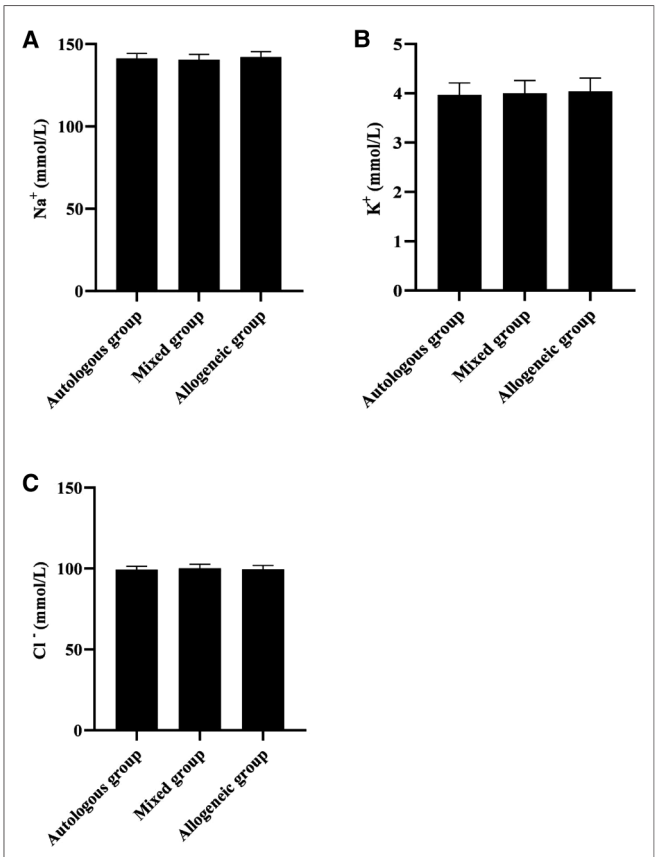

FIGURE 5 | Comparison of 24- h postoperative electrolyte indices in three groups ($\bar{x} \pm s$, mmol/L). Note: (**A**) Na^+ (mmol/L). (**B**) K^+ (mmol/L). (**C**) Cl^- (mmol/L).

concentrated red blood cells can be directly transfused back to the intraoperative patient, thus gradually becoming an important blood protection technique for patients with emergency hemorrhage.

Allogeneic blood transfusion has risk factors affecting blood quality and safety in all aspects of blood collection, preparation, testing, storage, transportation, and clinical transfusion. Up to a dozen diseases have been clinically confirmed to be transmitted through blood, and four infectious agents are mainly detected in China: hepatitis B, hepatitis C, syphilis, and AIDS (14). Other unknown blood-borne viruses may also be present in human blood, which can exacerbate the risk of allogeneic transfusions. Transfusion transmission of HIV is currently reported in various countries (15, 16). Due to limited medical technology, the problem of window periods for infectious diseases still plagues the detection of blood-related pathogens. Our data showed that after transfusion therapy, the postoperative fever rates were 4.35%, 10.71%, and 19.51% in the autologous, mixed, and allogeneic groups, respectively, and the transfusion reaction rates were 0.00%, 3.57%, and 9.76%, respectively, all of which were lower in the autologous group than in the allogeneic group ($p < 0.05$). Transfusion reactions mainly manifest as immune transfusion reactions such as chills, itchy facial sensation, and rubella (17, 18). This shows that the salvage autologous blood transfusion effectively avoids the risk of allogeneic blood transfusion to the patient. This may be due to the fact that the blood recovered from autologous blood transfusion is separated by filtration, washing, and centrifugation, which removes villi and embryonic tissue, traumatic tissue debris, clots, contaminants, and destroyed blood cells, plasma viable fractions, free Hb, plasma, fatty acids, and anticoagulants, resulting in concentrated red blood cells (19). Although this method causes some damage to the red blood cells and discards the plasma components, it removes the harmful cell debris and free Hb, and the final red blood cells obtained are of high quality, so there are few adverse reactions after the return transfusion.

The cause of hemorrhagic shock in patients with hemorrhagic ectopic pregnancy is the rapid loss of circulating blood volume resulting in a sharp drop in blood pressure, tissue hypoxia, and increased heart rate (20). Rapid blood volume replacement is the primary measure to correct hemorrhagic shock. Our data showed that 30 min after blood transfusion, SBP, DBP, and SpO2 in all three groups were higher than before blood transfusion ($p < 0.05$), and HR was lower than before blood transfusion ($p < 0.05$), but the difference between groups 30 min after blood transfusion was

not statistically significant ($p > 0.05$); at the 24- h postoperative period, no statistical difference was found during the comparison of HCT, Hb, PLT, and RBC in all three groups ($p > 0.05$). This shows that both autologous and allogeneic blood transfusion can effectively replenish blood volume and promote the body's circulatory function to return to normal. The data also showed that SpO_2 was essentially within the normal range before and after transfusion in all three groups of patients. This may be related to the fact that none of the patients included in this group had Hb below 80 g/L, despite the presence of hemorrhage, and, therefore, did not result in significant tissue hypoxia (21). Our data also showed that there was no statistical difference when Na^+, K^+, and Cl^- were compared among the three groups at the 24- h postoperative period ($p > 0.05$). This may be related to the fact that most of the blood transfusions in this group were component transfusions in smaller amounts, which did not cause electrolyte disturbances.

CONCLUSION

In conclusion, the salvage autologous blood transfusion technique for treating ectopic pregnancy hemorrhage is a safe and feasible method to rescue patients with such condition. Although it cannot completely replace the allogeneic blood transfusion technique, it can rapidly replenish the patient's blood volume and save blood resources without causing postoperative hemodynamic, routine blood, and electrolyte abnormalities.

DATA AVAILABILITY STATEMENT

All data in the submitted article used or analyzed can be obtained from the respective authors.

ETHIC STATEMENT

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

AUTHOR CONTRIBUTIONS

HJ and ZH are mainly responsible for writing this article, performing data analysis, and conceptualizing the research design. The corresponding author is JL, and she is responsible for ensuring that the descriptions in this article are accurate and are agreed upon by all authors. All authors contributed equally to the article and approved the submitted version. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Effect Observation of Electro-Acupuncture Anesthesia Combined with General Anesthesia in Elderly Patients Undergoing Gastrointestinal Tumor Resection

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Objective: To investigate the anesthetic effect of electro-acupuncture (EA) anesthesia combined with general anesthesia in elderly patients undergoing gastrointestinal tumor resection, and to analyze the effects of EA anesthesia on inflammatory factors, stress state and T lymphocyte subsets in elderly patients.

Methods: Total of 118 elderly patients who underwent gastrointestinal tumor resection in our hospital from June 2018 to March 2021 were selected and divided into the control group (59 cases) and the observation group (59 cases) according to the random number method. General anesthesia was adopted in the control group and EA anesthesia combined with general anesthesia was adopted in the observation group. The anesthesia effect, stress state, levels of inflammatory factors, T-lymphocyte subsets and adverse reactions were compared.

Results: The VAS score, agitation score and respiratory normalization time in the observation group were lower than those in the control group ($p < 0.05$). After surgery, the levels of serum Cor, ET, NE and DA in the observation group were lower than those in the control group ($p < 0.05$). At 24 h after surgery, the levels of serum TNF-α, IL-6 and IL-1β in the observation group were lower than those in the control group ($p < 0.05$). At 24 h after surgery, the levels of CD_3^+, CD_4^+, and CD_4^+/CD_8^+ in the two groups were lower than those before surgery, and the levels of CD_3^+, CD_4^+, and CD_4^+/CD_8^+ in the observation group were higher than those in the control group ($p < 0.05$). During the hospitalization, the total incidence rate of adverse reactions after anesthesia in the observation group was lower than that in the control group ($p < 0.05$).

Conclusion: EA anesthesia combined with general anesthesia has good anesthesia effect when used for gastrointestinal tumor resection in the elderly. It can stabilize the internal environment of patients, alleviate postoperative stress response and inflammatory response, and regulate the body immune function. Moreover, it has high safety and can significantly reduce the occurrence of postoperative adverse reactions.

Keywords: anesthesia, acupuncture, gastrointestinal tumor resection, inflammatory factors, stress state, T lymphocyte subsets

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INTRODUCTION

Resection of gastrointestinal tumors in elderly patients is a common treatment option in abdominal surgery and is performed under general anesthesia. Traumatic surgery often leads to stress state in patients and stimulates the immune system to release a large number of pro-inflammatory factors, damage vascular endothelial cells, and inhibit normal immune function (1, 2). Elderly patients are more likely to suffer from hemodynamic disorders, aggravate surgical stress trauma, cognitive impairment, intestinal adhesion and other postoperative adverse conditions due to the decline of basic organ function and poor tolerance to surgery, as well as the application of general anesthesia drugs.

Acupuncture has a long history of application in the field of analgesia. With the development of acupuncture technology and the emergence of electro-acupuncture (EA) apparatus, its analgesic effect is stronger. At the same time, it has the advantages of convenience, economy, and little body interference (3, 4). It is generally believed that the analgesic and therapeutic effects of EA are superior to those of conventional acupuncture. In recent years, some studies (5, 6) have shown that application of EA anesthesia can strengthen sedation and analgesia, stabilize the internal environment of the body, enhance immunity, and promote body recovery during the perioperative period, and can appropriately reduce the use of local anesthetics. The analgesic effects of EA are mainly manifested as alleviation of diabetic neuropathic pain, postherpetic neuralgia, tactile sensation-induced pain, paclitaxel chemotherapy pain, reduction of cold and heat sensitive pain threshold, and other various types of pain. Based on the above viewpoints, it is of great research significance to explore the effect of EA on tumor resection in elderly patients.

Therefore, this study explores the effect of EA anesthesia combined with general anesthesia in elderly patients with gastrointestinal tumor resection, and analyzes its influence on inflammatory factors, stress state and immune function.

METHODS

Subjects of Observation

Total of 118 elderly patients who underwent gastrointestinal tumor resection in our hospital from June 2018 to March 2021 were selected and divided into the control group (59 cases) and the observation group (59 cases) according to the random number method. Inclusion criteria: 1. Age ≥60 years old; 2. Have the indications of gastrointestinal tumor resection; 3. Preoperative vital signs were stable; 4. Be tolerated with EA; 5. American Society of Anesthesiologists (ASA) anesthesia classification II–III; 6. The patient or his/her family member have signed informed consent form. Exclusion criteria: 1. Combined with other tumors or important organ dysfunction; 2. There are preoperative cognitive impairment; 3. There are contraindications for general anesthesia. Control group: 32 males and 27 females; Age ranged from 60 to 81 years, with an average of (68.36 ± 5.72) years; The body weight was 52–73 kg, and the average body weight was (62.36 ± 7.95) kg. Observation group: 30 males and 29 females; Age ranged from 60 to 82 years old, and the average age was (69.15 ± 7.99) years old; The body weight was 54–74 kg, and the average body weight was (63.72 ± 9.45) kg. There was no statistical difference between the two groups in general information.

Treatment Methods

All patients underwent gastrointestinal tumor resection. Relevant signs were monitored, and symptomatic intervention was taken to maintain the stability of vital signs during the operation. There were no significant abnormalities in vital signs such as operation center rate and blood pressure in all patients.

In the control group patients were anesthetized and induced by intravenous midazolam injection (50 μg/kg), phenolphthalein citrate injection (4 μg/kg), propofol emulsion injection (1.5 mg/kg) and vecuronium bromide injection (0.1 mg/kg) before operation. After tracheal intubation, anesthesia was maintained with remifentanil hydrochloride for injection (continuous pumping) and sevoflurane (mask semi-closed inhalation, concentration of 4%, and oxygen flow of 3 L/min).

In the observation group the patients were treated with acupuncture at Baihui (GV20), Hegu (LI 4), Neiguan (PC 6), Shenmen (HT 7) and Zusanli (ST 36) at both sides 20 min before anesthesia induction. After twirling to Deqi, they were connected to the electroacupuncture therapeutic apparatus. The stimulation intensity was adjusted from small to large to the maximum tolerance intensity according to the slow tolerance of the patients, and the density wave was maintained for 20 min. After that, anesthesia induction and anesthesia maintenance were performed, the specific operations were the same as those in the control group.

Observation Indicators

The anesthesia effects of the two groups were evaluated. Six hours after surgery, the pain was assessed using visual analogue scale scale (VAS) with a total score of 0–10. A higher score indicated more severe pain. The patients' agitation during the surgery was assessed and divided into 0–3 grades, as shown in **Table 1**. Record the patient's respiratory normalization time.

Fasting venous blood was collected before surgery, at the end of surgery and 24 h after surgery. The stress state indicators of patients after surgery were detected, including serum cortisol (Cor) by chemiluminescent analyzer, endothelin (ET) by

TABLE 1 | Agitation scoring classification.

0 grade	Quiet cooperation, no restlessness
1 grade	Mild irritability, stimulated surgery patients limbs restlessness, occasional moaning
2 grade	Continuous restlessness and moaning, need to fix the patient's upper limb
3 grade	Severe agitation, shouting, need to be fixed in patients with upper and lower limbs

radioimmunoassay, and norepinephrine, (NE) and dopamine (DA) by high-pressure liquid chromatography (HPLC). Enzyme-linked immunosorbent assay was used to detect the serum levels of inflammatory factors 24 h after surgery, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-1β. The levels of T lymphocyte subsets including CD_3^+, CD_4^+ and CD_4^+/CD_8^+ before and 24 h after surgery were determined by direct immunolabeling with flow cytometry.

Record the number of adverse reactions such as cognitive impairment, nausea, vomiting, intestinal obstruction, intestinal adhesion and so on.

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 (M ± SD), 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. $p < 0.05$ was taken as statistically significant.

RESULTS

Comparison of Anesthesia Effects Between Two Groups

The VAS score, agitation score and respiratory normalization time in the observation group were lower than those in the control group, and the differences were statistically significant ($p < 0.05$). See **Figure 1** for details**.**

Comparison of Stress State Index After Surgery Between Two Groups

After surgery, the levels of serum Cor, ET, NE and DA in the observation group were lower than those in the control group, and the differences were statistically significant ($p < 0.05$). See **Figure 2.**

Comparison of Postoperative Inflammatory Factor Level Between Two Groups

At 24 h after surgery, the levels of serum TNF-α, IL-6 and IL-1β in the observation group were lower than those in the control group, and the differences were statistically significant ($p < 0.05$). See **Figure 3.**

Comparison of T Lymphocyte Subsets Between Two Groups

At 24 h after surgery, the levels of CD_3^+, CD_4^+ and CD_4^+/CD_8^+ in the two groups were lower than those before surgery, and the levels of CD_3^+, CD_4^+ and CD_4^+/CD_8^+ in the observation group were higher than those in the control group. The differences were statistically significant ($p < 0.05$). See **Figure 4**.

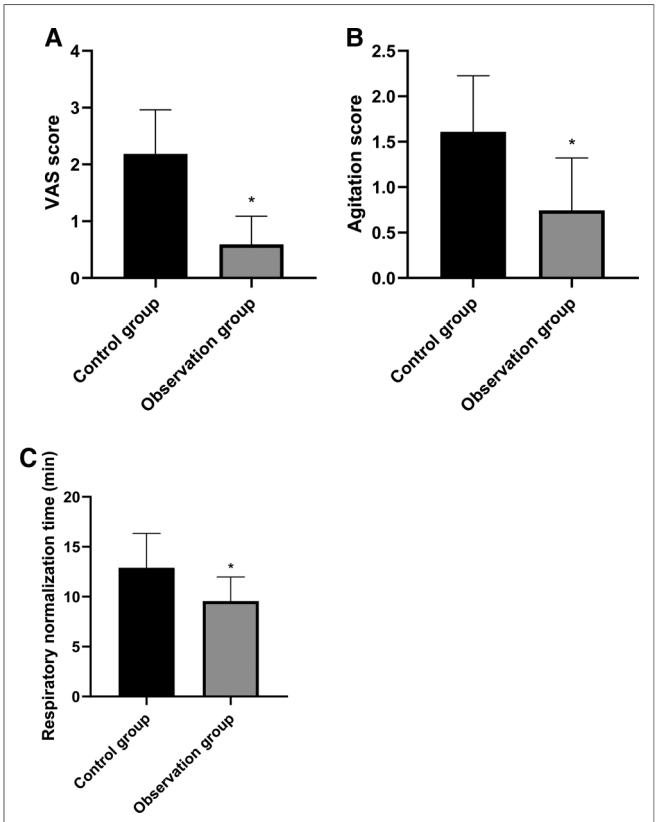

FIGURE 1 | Comparison of anesthesia effects between two groups. Note: Compared with the control group, *$p < 0.05$.

Comparison of Adverse Drug Reactions Between the Two Groups During Treatment

During the hospitalization, the total incidence rate of adverse reactions in the observation group after anesthesia was lower than that in the control group, and the difference was statistically significant ($p < 0.05$). See **Table 2**.

DISCUSSION

Elderly patients have low tolerance to narcotic drugs, but general anesthesia is often needed when tumor resection is performed. During this period, severe hemodynamic abnormalities, severe stress response, obvious postoperative anesthesia side effects and high incidence of adverse reactions easily occur (7, 8). Therefore, how to minimize the use of anesthetics and avoid the occurrence of postoperative adverse conditions when ensuring the anesthesia effect is a difficult problem to be solved in general anesthesia surgery for clinical elderly patients (9, 10). Acupuncture analgesia has recently been a hot topic of academic research. Compared with conventional acupuncture, EA is more effective and convenient, so EA is often used to assist anesthesia and analgesia in various surgical procedures. (10, 11). It has been reported that in a variety of local anesthesia surgerys, EA can significantly

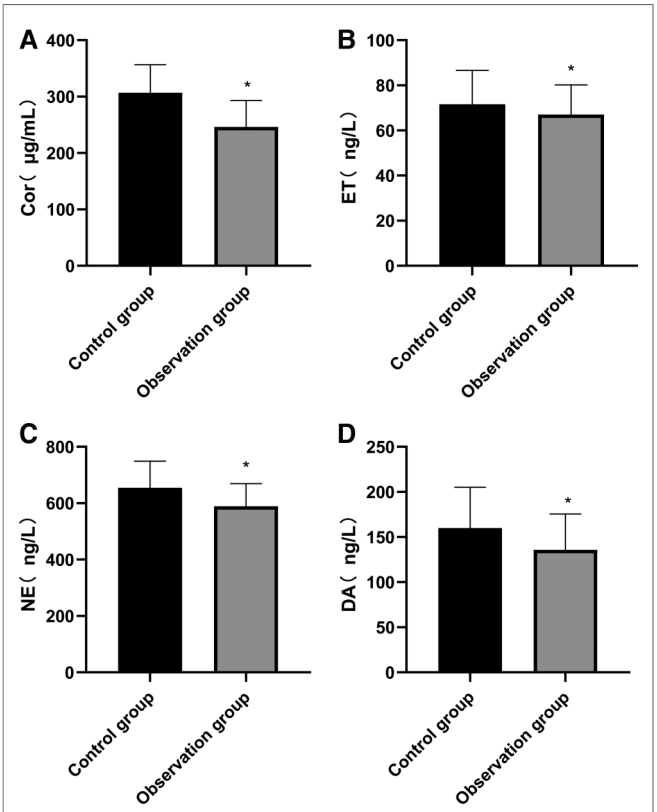

FIGURE 2 | Comparison of stress state index after surgery between two groups. Note: Compared with the control group, $^{*}p < 0.05$.

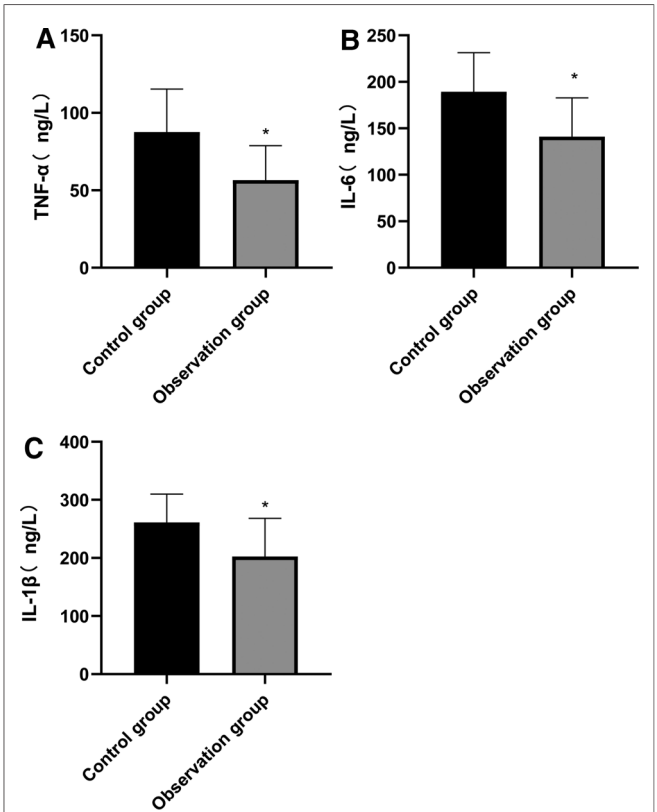

FIGURE 3 | Comparison of postoperative inflammatory factor level between two groups. Note: Compared with the control group, $^{*}p < 0.05$.

enhance the perioperative analgesic effect, improve hemodynamic abnormalities, and reduce the incidence of adverse reactions after anesthesia. Regarding the related mechanisms of acupuncture and moxibustion analgesia, it is currently mainly believed that electroacupuncture can regulate the expression and activity of ion channels, regulate the balance of peripheral pro-inflammatory and anti-inflammatory cytokines, inhibit the activation of spinal glial cells, inhibit pain-related signaling pathways at the spinal cord level, and regulate pain-related brain regions and cerebral circuits (12, 13). In our experiment, we selected the five acupoints of Baihui (GV20), Hegu (LI 4), Neiguan (PC 6), Shenmen (HT 7) and Zusanli (ST 36), which are commonly used anesthesia acupoints in acupuncture. At the same time, we have found in the previous clinical practice that the combination of these five acupoints has good analgesic and sedative effects in the treatment of other diseases (14, 15).

When patients undergo surgical trauma, the release of inflammatory mediators will lead to increased nervous system sensitivity, increased pain, significant stress response, and the appearance of agitation (16, 17). The results of this study showed that the patients in the observation group were better than those in the control group in pain severity, agitation and respiratory normalization time after surgery. It was analyzed that EA could stimulate the central nervous system to up-regulate the secretion of morphine-like neurotransmitters with endogenous analgesic effects, such as β -endorphin and at the same time, the signal from acupuncture points could inhibit the transmission of pain signals at nearby spinal stages to the central nervous system, thus increasing the pain threshold of the body (18, 19). In addition, stimulant actions such as tracheal intubation and extubation performed on patients during the surgery will lead to the aggravation of stress response of the body and trigger agitation reaction. However, acupuncture at Hegu (LI 4) exerts analgesic effect and remarkably reduces the sensitivity of the throat to exert a sedative effect (20, 21). Therefore, EA combined with general anesthesia is more effective than general anesthesia alone.

A variety of stimulating operations in tumor resection can lead to the over-activation of the hypothalamic-pituitary-adrenal axis (HPA) and abnormal excitation of the sympathetic center, which in turn causes related reactions of catecholamines, massive release of stress-related neurotransmitters such as serum Cor and ET, and inflammatory factors such as TNF-α and IL-6. However, under the action of long-term high concentration of stress neurotransmitters such as serum Cor and ET and inflammatory factors, patients are vulnerable to accelerated apoptosis of hippocampal neurons and cognitive impairment, which reduces the efficacy of the surgery and has a poor prognosis (22, 23). Stress state can

lead to the disorder of endocrine and neurotransmitters in patients, and Cor, ET, NE and DA are the representative indicators. These indicators are usually used to evaluate the stress of the body clinically. The results of this study also showed that the serum levels of Cor, ET, NE, DA, TNF-α, IL-6 and IL-1β in the observation group were lower than those in the control group, indicating that in response to the stress trauma caused by surgery in elderly patients, based on conventional anesthesia, acupuncture could effectively stabilize the internal environment in patients and inhibit the abnormal secretion of neurotransmitters and inflammatory factors, which might be related to the bidirectional regulation of acupuncture on the HPA axis. When the HPA axis was abnormally excited, acupuncture anesthesia could significantly reduce the sympathetic excitability and inhibit catecholamine (24, 25). In addition, stress, inflammatory reaction and tumor can cause the body to be in an immunosuppressed state. Acupuncture at Zusanli (ST 36) and other acupoints has an immunoregulatory effect, and can strengthen cellular and humoral immunity by regulating the number and function of leukocytes, lymphocytes and immunoglobulins (26). In this study, the T lymphocyte subsets in the two groups of patients were lower than those before surgery, while the levels of CD_3^+, CD_4^+, and CD_4^+/CD_8^+ at 24 h after surgery were higher than those in the control group, indicating that acupuncture enhanced the immune function of patients and their immunosuppression due to surgical stress and inflammatory reaction was weak.

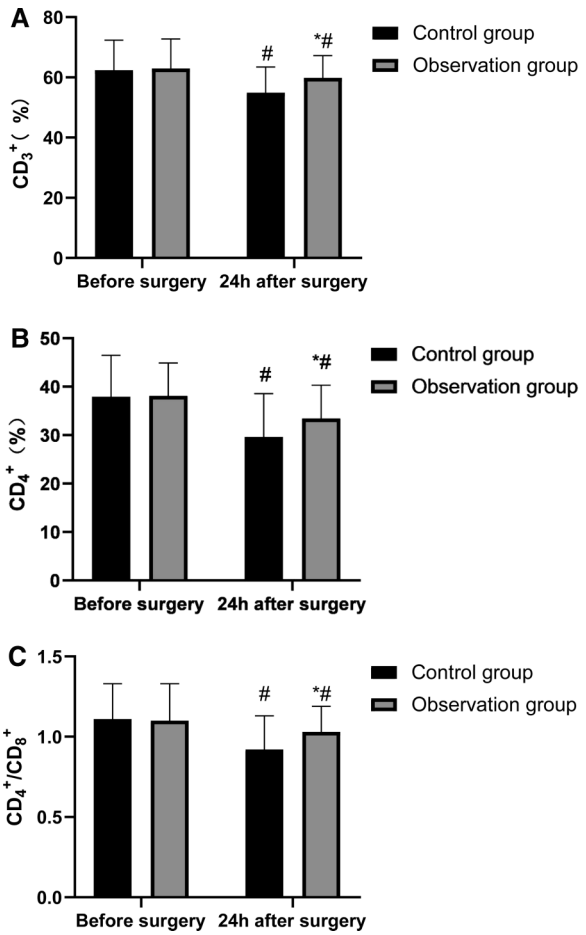

FIGURE 4 | Comparison of T lymphocyte subsets between two groups. Note: Compared with the control group, $^*p < 0.05$; Compared with the same group before surgery, $^*p < 0.05$.

Organ function of elderly patients deteriorates. After general anesthesia, central nervous system function is damaged and gastrointestinal motility is decreased due to excessive or intolerance of anesthetics, hemodynamic changes, surgical trauma and other factors, which in turn leads to postoperative cognitive impairment and intestinal adhesion (27). In this study, the adverse reactions of patients in the observation group were only manifested as nausea and vomiting, and no severe adverse reactions such as intestinal obstruction and cognitive impairment was observed. The total incidence of adverse reactions was significantly lower than that in the control group, which might be due to the efficacy of acupuncture in exciting the vgaus nerve, dilating blood vessels, and reducing myocardial oxygen consumption, in addition to inhibiting the excitement of the sympathetic nerve, thereby avoiding excessive disorder of body hemodynamics. In addition, acupuncture can also reduce the penetration of pro-inflammatory factors into the blood-brain barrier, reduce the occurrence of inflammatory reactions in the central nervous system, promote blood perfusion in brain regions, and enhance oxygen supply capacity in the brain, thereby alleviating the cascade reactions of inflammatory injury and protecting cognitive function (28). Therefore, acupuncture combined with general anesthesia is safer, and it is of great significance for the elderly patients who need major surgery.

TABLE 2 | Comparison of adverse drug reactions between the two groups during treatment (*n*,%).

Groups	Cognitive disorder	Nausea and vomiting	Intestinal obstruction	Intestinal adhesion	Total incidence of adverse reactions
Control group ($n = 59$)	5	5	1	1	12 (20.34)
Observation group ($n = 59$)	0	2	0	0	2 (3.40)
χ^2 value					8.104
p value					0.004

CONCLUSION

In summary, acupuncture anesthesia combined with general anesthesia has good anesthesia effect in elderly patients undergoing gastrointestinal tumor resection, which can stabilize the body environment of patients, alleviate postoperative stress response and inflammatory response, and regulate body immune function. Moreover, it is highly safe and can significantly reduce the occurrence of postoperative adverse reactions.

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 has been approved by the ethical Committee of Rizhao Central Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JX is the first author, he is the executor and writer of the paper. The second author is PL, he is responsible for searching data and data analysis. The third author is LZ, she is responsible for research design. QC is the corresponding author, he is ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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OPINION
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Opinion: Research Progress of Surgical Treatment of Osteoarthritis

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Keywords: surgical treatment, osteoarthritis, artificial joint replacement, arthroscopic debridement, minimally invasive surgery (MIS)

INTRODUCTION

Osteoarthritis (OA) is one of the most common joint diseases, mainly due to the degeneration of articular cartilage and the abnormal biosynthesis of proteoglycan in articular cartilage, which seriously affects the quality of life of patients. At present, the incidence of osteoarthritis is mainly concentrated in middle-aged and elderly people over 40 years old, with a prevalence rate of 17.0%. However, there are also studies showing that the incidence still exists in children and infants, but it is more related to genes and environment. In the next few decades, the prevalence of OA will gradually increase, which will seriously affect people's health and quality of life, and bring a huge burden to China's national economic and social development (1).

In addition to affecting physical health, OA can also affect mental health. Studies have shown that patients with OA have a higher probability of depressive symptoms than healthy groups (2). Another study found a strong relationship between OA and memory loss (3). At the same time, OA can increase the risk of cardiovascular disease (4–6).

The risk factors of OA are diverse, including heredity, aging, obesity and so on. In the early stage of OA, the cartilage surface is still intact. The lesions first manifest as molecular changes in the extracellular matrix (7), **Figure 1**: Rat osteoarthritis(Cartilage cell hypertrophy and differentiation); accompanied by chondrocyte hypertrophy and differentiation, marker expression, destruction of cartilage integrity, and subsequent apoptosis of articular chondrocytes (8). Relevant studies have found that cytokines are closely related to the pathogenesis of OA. In patients with OA, cartilage matrix homeostasis is destroyed by pro-inflammatory cytokines and chemokines (IL-1, IL-6, and IL-8), which stimulate macrophages and chondrocytes to co-produce proteases, nitric oxide (no) and eicosanoids, etc, which participate in the process of catabolism and induce apoptosis (9). which in turn induces synthesis of MMPs (MMP-1, MMP-3, and MMP-13) through amplification of pro-inflammatory cytokines (such as TNF-α, IL-6 and IL-8), increase the destruction of articular cartilage cells (10).

At present, according to the progress of the disease, its treatment methods are mainly divided into three categories. Firstly, basic treatment mainly focuses on acupuncture, moxibustion, massage and exercise in traditional Chinese medicine, mainly for patients with mild symptoms; Secondly, drug treatment, mainly non steroidal anti-inflammatory drugs, analgesics, intra-articular injection drugs, etc; Thirdly, surgical treatment is mainly for patients with advanced OA, such as articular cartilage repair, arthroscopic cleaning, artificial joint replacement and so on.

MAIN SURGICAL TREATMENT OF OSTEOARTHRITIS

Joint Debridement

Joint debridement is a basic surgical operation. The early treatment of joint diseases plays a decisive role in wound healing and the recovery of the function and shape of injured tissues,

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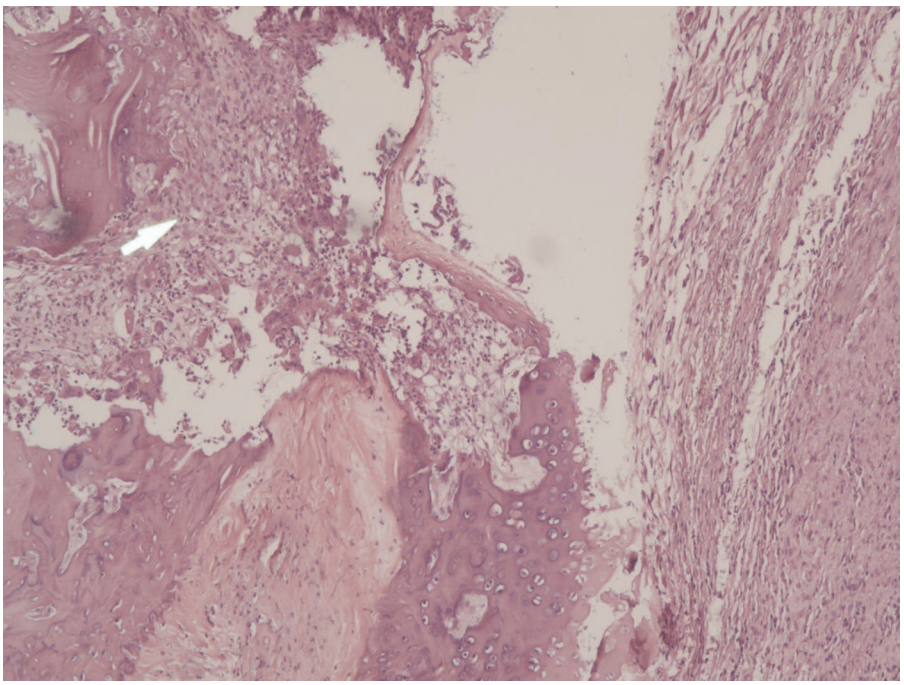

FIGURE 1 | Rat osteoarthritis(Cartilage cell hypertrophy and differentiation).

which should be paid attention to. In clinic, joint debridement is often combined with artificial prosthesis surgery. In order to prevent the formation of sinus tract in joint surgery, joint debridement is often used to keep the prosthesis, and the patient is debrided at the right operation time, so as to prevent the fever caused by infection from being difficult to cure and hinder the formation of the final sinus tract. In most cases, debridement can effectively remove the dead and inflammatory tissues around the joints of patients, and can significantly reduce the recurrence rate of patients with low-grade infection.

Arthroscopic Debridement

For mild to moderate arthritis, joint debridement is recommended, which can effectively remove intra-articular effusion and improve joint function. However, in view of the older age of OA patients and the fact that arthroscopic debridement can not completely repair bone joints and damaged cartilage tissue, some patients treated with arthroscopic debridement alone are not effective. And in the current surgery, the patient will be placed in the supine position, and the waist will be anesthetized, and the surgical site will be disinfected with a disinfectant spread towel. Most of the surgical methods are to take the anteromedial approach of the knee joint to operate on the patient, and then the operating instruments will be placed in turn, and the anteromedial approach will be used to place the light source.

The researchers found that ultrasonic conduction percutaneous local drug penetration has the advantages of high local drug concentration and avoidance of liver first-pass effect and is widely used in clinical practice. Therefore, after arthroscopic debridement, topical ultrasound percutaneous administration can achieve better results, can significantly relieve the patient's knee joint pain, swelling and other symptoms, and improve knee joint function. Its mechanism of action may be related to this combination therapy. The expression levels of BGP, OPG, and RANKL, which are biochemical indicators of benign regulation of bone metabolism, were significantly down-regulated in vivo. However, arthroscopy technology can not fully meet the needs of patients, mainly for patients with moderate osteoarthritis. Severe patients eventually need artificial joint replacement to solve the end-stage joint degeneration.

Artificial Joint Replacement

Artificial joint replacement is the most effective surgical method for the treatment of end-stage degenerative joint diseases and other joint diseases. It can improve the joint mobility and relieve patients' joint pain symptoms in the short term after surgery, so as to meet the requirements of high quality of life for patients. During the operation, the surgeon will adjust according to the patient's operation position, such as knee joint, hip joint, ankle joint, etc. will perform lower limb operation in supine position, while shoulder joint, elbow joint, etc. will perform upper limb operation in beach chair position (a supine position in which the upper body is higher than the operating table plane); After that, the doctor will cut the tissue of the patient's diseased position to expose the joints at the

surgical site; Remove the joint replacement part; Implant artificial prosthesis; Confirm whether the reduction and fixation are satisfactory; Rinse the incision, and finally sew and bandage.

As stated in the manuscript before, the biggest problem in artificial joint replacement is the aseptic loosening of the prosthetic joint, which is the main complication affecting the life of the prosthesis. Complications caused by prosthesis infection will greatly reduce the recovery rate of patients, and there is a higher possibility that patients can't bear the discomfort and pain caused by complications, and even take their lives. It seriously hinders the popularization and application of artificial joints and people's confidence in joint replacement surgery. Prosthetic joint revision surgery is much more difficult than primary joint replacement surgery. In the operation, there will be a bigger problem on the surgical surface, and there is a great risk of infection in debridement, and the postoperative recurrence rate is extremely high. And revision surgery is more traumatic, has a high risk of death during the operation, and has poor postoperative joint function recovery, which often brings huge physical and economic burdens to patients.

DISCUSSION

The development of materials science has become a key research field in bone and joint development. And the most important mechanism of prosthesis is the absorption and dissolution of bone around the prosthesis induced by wear particles. Therefore, the first step is to explore the mechanism of osteolysis from the biological point of view and find the key biological factors, so as to prevent the dissolution of bone tissue around the prosthesis; Secondly, focus on the prosthesis materials, to create more wear-resistance and more compatible with human tissue prosthesis materials. 3D printing technology can print more personalized joint materials, with better wedge fit, which is more conducive to the recovery of patients.

In recent years, minimally invasive surgery has gradually become the treatment trend of knee OA because of its advantages of small trauma and rapid recovery. Minimally invasive technology can reduce patients' pain, reduce the amount of bleeding and have better postoperative activity function, but it is difficult to ensure the accuracy of prosthesis position. Recently, with the application of computer navigation and robot technology in treatment, the defect of inaccurate positioning of minimally invasive technology has been made up. Computer navigation can accurately calculate the amount of osteotomy and guide the position and angle of prosthesis placement. Compared with the traditional method, it has the advantages of high precision of prosthesis implantation, good recovery of lower limb force line and good recovery of postoperative knee function (11). Moreover, the update of technology has made the age problem of patients gradually disappear. In the future, no matter how old or old the patients are, there will be a chance to be cured. And the development of interdisciplinary integration will inevitably bring more convenience and advantages to the surgical treatment of bone and joint patients.

AUTHOR CONTRIBUTIONS

PZ (First Author): Conceptualization, Methodology, Software, Investigation, Formal Analysis, Writing - Original Draft; ML: Data Curation, Writing - Original Draft; Software, Validation; KC: Visualization, Investigation; Writing - Review & Editing; YL: Resources, Supervision; Formal Analysis; YL (Corresponding Author): Conceptualization, Funding Acquisition, Resources, Supervision, Writing - Review & Editing. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Efficacy of Bevacizumab Combined with Pemetrexed in the Treatment of Recurrent and Metastatic Cervical Cancer

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Background: To investigate the efficacy and safety of bevacizumab combined with pemetrexed in the treatment of recurrent and metastatic cervical cancer.

Methods: Clinical data of 65 patients with recurrent and metastatic cervical cancer who were admitted to our hospital were collected for retrospective analysis. All patients were administered with bevacizumab combined with pemetrexed for 4–6 cycles (21 days as 1 cycle). The short-term clinical efficacy and adverse reactions were compared between the two groups. In addition, the survival status of patients was followed up and recorded.

Results: At least 4 cycles of chemotherapy were given to the 65 patients. There were 0 cases of complete response (CR), 14 cases of partial response (PR), 36 cases of stable disease (SD) and 15 cases of progressive disease (PD). The objective response rate (ORR) and the disease control rate (DCR) were 21.5% (14/65) and 76.9% (50/65), respectively. DCR was superior in patients with squamous cell carcinoma to that in those with adenocarcinoma ($p = 0.039$), but no statistically significant difference was found in ORR. Patients with extra-pelvic metastatic lesions had a better efficacy than those with intra-pelvic metastatic lesions, but the difference was not statistically significant ($p > 0.05$). The post-treatment adverse reactions mainly involved fatigue, nausea and vomiting, bleeding, leukopenia, anemia, thrombocytopenia, transaminase elevation, hypertension, proteinuria and neurotoxicity, most of which were grade I–II that ameliorated after symptomatic therapy. Grade III adverse reactions mainly included pain in 5 cases (7.7%), leukopenia in 17 cases (26.2%), anemia in 22 cases (33.8%), thrombocytopenia in 6 cases (9.2%), hypertension in 5 cases (7.7%) and neurotoxicity in 7 cases (10.8%). The follow-up results manifested that median overall survival (OS) and median progression-free survival (PFS) were 10.6 months and 6.6 months, respectively.

Conclusion: Bevacizumab combined with pemetrexed exhibits certain efficacy in the treatment of recurrent and metastatic cervical cancer, with tolerable adverse reactions. Therefore, this therapeutic option deserves clinical popularization and application.

Keywords: bevacizumab, pemetrexed, cervical cancer, efficacy, treatment

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INTRODUCTION

Patients with recurrent and metastatic cervical cancer are usually treated by means of chemotherapy, surgery and/or radiotherapy, but they have a poor prognosis. Generally, replacement of chemotherapy agents or optimal supportive therapy is available for those with failure of first-line chemotherapy. However, the therapeutic methods are reported to be limited (1). Bevacizumab can prolong the survival time of patients with advanced cervical cancer, as previously discussed, and has been approved by the European Union (EU) and U.S. Food and Drug Administration for the treatment of advanced cervical cancer (2, 3). According to National Comprehensive Cancer Network (NCCN) guidelines and expert consensus of the Chinese Society of Clinical Oncology (CSCO), pemetrexed, with favorable efficacy in the treatment of multiple tumors, is recommended for the second-line and above chemotherapy of cervical cancer (4, 5). This study aimed to investigate the efficacy and safety of bevacizumab combined with pemetrexed as a second-line chemotherapy regimen for patients with recurrent and metastatic cervical cancer.

MATERIALS AND METHODS

General Data

Clinical data of 65 patients with recurrent and metastatic cervical cancer who were admitted to our hospital were collected. The patients were aged 36.4–71.1 years old, averagely (60.4 ± 9.4) years old. The inclusion criteria were as follows: (a) patients histopathologically diagnosed with cervical cancer, (b) those with disease progression or relapse after first-line combination chemotherapy or concurrent chemotherapy and radiotherapy, (c) those with a measurable target lesion on CT, MRI or ultrasound images, (d) those with basically normal routine blood tests and no obvious hepatic and renal dysfunction, (e) those with an Eastern Cooperative Oncology Group (ECOG) score of 0–2 points, and (f) those with an expected survival time ≥3 months. The exclusion criteria involved: (a) patients with allergy to pemetrexed or bevacizumab, (b) those with severe cardiac, pulmonary, hepatic or renal impairment, (c) those with coagulation disorder within 2 weeks prior to treatment, (d) those with hepatitis B or HIV infection, (e) those with requirement of anticoagulant therapy for relevant diseases, (f) those with other malignancies, or g) those with mental disorders or unable to cooperate in treatment for other reasons. The general information and clinical baseline data of patients are displayed in **Table 1**. This study complied with the *Declaration of Helsinki*, and all patients signed written informed consent.

TABLE 1 | Baseline demographic and clinical characteristics of the studied patients.

Parameters	*n*, % (*n* = 65)
Age (years)	
<50	43 (66.2%)
≥50	22 (33.8%)
Histology	
Squamous cell carcinoma	49 (75.4%)
Adenocarcinoma	16 (24.6%)
Metastatic sites	
Pelvic	24 (36.9%)
Extrapelvic	41 (63.1%)
ECOG	
0	3 (4.6%)
1	45 (69.2%)
2	17 (26.2%)
Courses of chemotherapy	
4	13 (20.0%)
5	33 (50.8%)
6	19 (29.2%)

Notes: ECOG, Eastern Cooperative Oncology Group.

Therapeutic Methods

Bevacizumab (Shanghai Roche Pharmaceutical Co., Ltd., Shanghai, China) was administered by intravenous drip, 15 mg/kg, on the 1st day. The dosage would be adjusted in case of body mass change more or less than 10%. Pemetrexed (Shandong Qilu Pharmaceutical Co., Ltd) 500 mg/m^2 was given by intravenous drip (>10 min), on the 2nd day. The treatment lasted for 4–6 cycles (21 days as 1 cycle). One week prior to administration with pemetrexed, patients took orally 400 μg of folic acid daily, and were intramuscularly injected with 1,000 μg of vitamin B_{12}. Dexamethasone (4 mg) was given orally, twice daily, 1 day before, on the day of and 1 day after treatment with pemetrexed. Folic acid was discontinued 21 days after last administration with pemetrexed. Vitamin B_{12} was injected once every 3 cycles.

Observational Indicators

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was utilized to evaluate the clinical efficacy with following indicators: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Objective response rate (ORR) = (CR + PR)/(total cases) × 100%, and disease control rate (DCR) = (CR + PR + SD)/(total cases) × 100%.

During the follow-up period, adverse reactions were recorded and evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0.

Through follow-up visits, progression-free survival (PFS) and overall survival (OS) were recorded. The period from enrollment to disease progression or death was regarded as PFS, while that from enrollment to death for any reason was defined as OS. The follow-up period ended in May 2021.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 software (IBM, Armonk, NY, USA) was adopted for statistical analysis.

Measurement data were expressed by mean ± standard deviation ($\bar{\chi} \pm s$) and compared by two-sample *t*-test between two groups. Enumeration data were expressed by percentage (%), and compared by chi-square test between two groups. Kaplan-Meier method was employed to plot the survival curve. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of Short-Term Clinical Efficacy

At least 4 cycles of chemotherapy were given to the 65 patients. There were 0 cases of CR, 14 cases of PR, 36 cases of SD and 15 cases of PD. ORR and DCR were 21.5% (14/65) and 76.9% (50/65), respectively (**Table 2**).

There were 0 cases of CR, 12 cases of PR, 29 cases of SD and 8 cases of PD among 49 patients with squamous cell carcinoma. ORR and DCR were 24.5% (12/49) and 83.7% (41/49), respectively. Among 16 patients with adenocarcinoma, there were 0 cases of CR, 2 cases of PR, 7 cases of SD and 7 cases of PD. ORR and DCR were 12.5% (2/16) and 56.3% (9/16), respectively. Among 24 patients with intra-pelvic metastasis, there were 0 cases of CR, 4 cases of PR, 12 cases of SD and 8 cases of PD. ORR and DCR were 16.7% (4/24) and 66.7% (16/24), respectively. Among 41 patients with extra-pelvic metastasis, there were 0 cases of CR, 10 cases of PR, 24 cases of SD and 7 cases of PD. ORR and DCR were 24.4% (10/41) and 82.9% (34/41), respectively. After combination treatment with bevacizumab and pemetrexed, DCR was superior in patients with squamous cell carcinoma to that in those with adenocarcinoma ($p = 0.039$), but no statistically significant difference was found in ORR. Patients with extra-pelvic metastatic lesions had a better efficacy than those with intra-pelvic metastatic lesions, but the difference was not statistically significant ($p > 0.05$).

Incidence of Adverse Reactions

The post-treatment adverse reactions mainly involved fatigue, nausea and vomiting, bleeding, leukopenia, anemia, thrombocytopenia, transaminase elevation, hypertension, proteinuria and neurotoxicity, mostly in grade I–II, which were ameliorated after symptomatic therapy. No grade IV adverse reactions and no progressive diseases and deaths related to adverse reactions were observed in both groups. Grade III adverse reactions mainly included pain in 5 cases (7.7%), leukopenia in 17 cases (26.2%), anemia in 22 cases (33.8%), thrombocytopenia in 6 cases (9.2%), hypertension in 5 cases (7.7%) and neurotoxicity in 7 cases (10.8%). The adverse reactions regarding bevacizumab were mainly hypertension, proteinuria and bleeding (**Table 3**).

TABLE 2 | Tumor response of the studied patients.

Parameters	*n*, % (*n* = 65)
Complete response (CR)	0 (0%)
Partial response (PR)	14 (21.5%)
Stable disease (SD)	36 (55.4%)
Progressive disease (PD)	15 (23.1%)
ORR (CR + PR)	14 (21.5%)
DCR (CR + PR + SD)	50 (76.9%)

Notes: ORR, Objective response rate; DCR, Disease control rate.

Postoperative Follow-up Visits of Patients in the Two Groups

As of May 2021, all patients were followed up for 3–24 months. The median OS and median PFS were 10.6 months and 6.6 months, respectively. Kaplan-Meier method was employed to plot the survival curve (**Figure 1**).

TABLE 3 | Comparison of adverse reactions of the studied patients

	Grade I–IV (*n* = 65)	Grade III–IV (*n* = 65)
Pain	21 (32.3%)	5 (7.7%)
Fatigue	39 (60.0%)	0 (0%)
Nausea and vomiting	35 (53.8%)	0 (0%)
Diarrhea	9 (13.8%)	0 (0%)
Bleeding	20 (30.8%)	0 (0%)
Leukopenia	33 (50.8%)	17 (26.2%)
Anemia	36 (55.4%)	22 (33.8%)
Thrombocytopenia	15 (23.1%)	6 (9.2%)
Transaminase elevation	12 (18.5%)	0 (0%)
Hypertension	16 (24.6%)	5 (7.7%)
Proteinuria	8 (12.3%)	0 (0%)
Thromboembolism	1 (1.5%)	0 (0%)
Neurotoxicity	8 (13.3%)	7 (10.8%)
Skin diseases	14 (21.5%)	0 (0%)

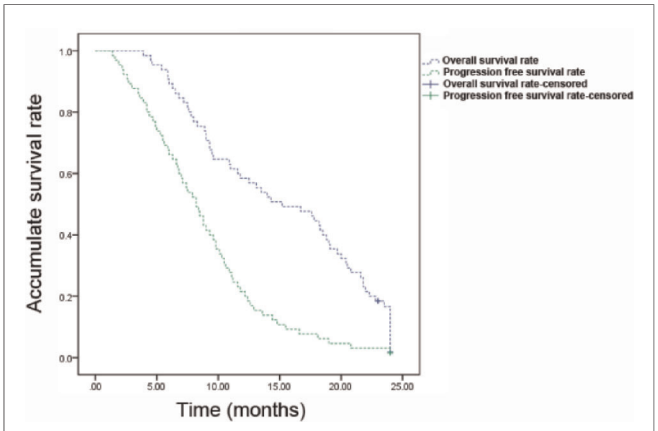

FIGURE 1 | Kaplan-Meier survival curves of patients with recurrent metastatic cervical cancer. The overall survival rate and progression free survival rate of patients were shown.

DISCUSSION

As a common malignant tumor affecting the female reproductive system, cervical cancer ranks second in the mortality rate among tumors in females (6). According to the statistics, about 130,000 cases are newly diagnosed with cervical cancer in China each year, and relapse and metastasis following treatment may occur in 15%–30% of patients. Limitations exist regarding therapeutic regimens for patients with refractory cervical cancer, especially those with continuous progression after multiple courses of radiotherapy and multi-line platinum-based combination chemotherapy. Then, platinum single-agent chemotherapy is usually administered again. However, the therapeutic efficacy is unsatisfactory, and the OS is short. Additionally, the 5-year survival rate is only 10%, and the quality of life is poor. For these reasons, numerous studies have been devoted to the targeted therapy which has become a trend of future development (7, 8).

Bevacizumab is a recombinant humanized monoclonal antibody that can selectively bind to human vascular endothelial growth factor (VEGF) and block its biological activity, and inhibit the binding of VEGF to its receptors Flt-1 and KDR on endothelial cells, thus reducing tumor angiogenesis and suppressing tumor growth (9). The extensive anti-tumor activity of bevacizumab has been reported among various cancers, such as colon cancer, non-small cell lung cancer, epithelial ovarian cancer and breast cancer (10–13). Moreover, bevacizumab is increasingly used in the treatment of cervical cancer. Wright et al. (14) reported that bevacizumab combined with 5-fluorouracil (5-FU) has a DCR reaching 67% and a median PFS of 4.3 months in the treatment of recurrent cervical cancer (14). The mid-term analysis of the U.S. GOG 240 manifested that after chemotherapy combined with bevacizumab, the survival period of patients who suffer from intractable, recurrent or metastatic cervical cancer has been prolonged by about 4 months, the median survival period is 17 months, the effective rate is 48%, and the mortality rate is reduced by 29% (3). Another multi-center study displayed a favorable progression-free survival after administration with bevacizumab, and exhibited survival period exceeding 6 months in 24% of patients, 7.3 months of median OS and a drug response rate of 10.9% (15). Therefore, bevacizumab has successively been approved by the EU and U.S. Food and drug administration for the treatment of advanced cervical cancer. Accordingly, cervical cancer has become the first gynecological tumor whose OS can be effectively prolonged by anti-angiogenesis agents (2). Furthermore, the latest version of NCCN guidelines has issued the application of bevacizumab combined with cisplatin and paclitaxel for recurrent or metastatic cervical cancer as the first-line therapeutic agents (16).

Pemetrexed is a synthetic multi-target antifolate and contains pyrrolidine grouping in structure, which can effectively inhibit dihydrofolate reductase, glycinamide ribonucleotide formyl transferase and thymidylate synthase and block thymidine and purine synthesis, thus affecting nucleic acid synthesis in tumor cells to exert anti-tumor effects (17). Previous studies have confirmed the effectiveness of single agent pemetrexed in the treatment of multiple tumors (18). The research on pemetrexed as a second-line treatment of cervical cancer manifested that 15% (4/27) and 59% (16/27) of patients achieve PR and SD, and PFS and OS are 3.1 months and 7.4 months, respectively (19). Pemetrexed was recommended for the second-line and above chemotherapy of cervical cancer by the NCCN guidelines in 2016.

In this study, ORR and DCR were 21.5% (14/65) and 76.9% (50/65), respectively, in patients with recurrent and metastatic cervical cancer receiving bevacizumab combined with pemetrexed as the second-line treatment. The follow-up results denoted that median OS and median PFS were 10.6 months and 6.6 months, respectively. DCR was superior in patients with squamous cell carcinoma to that in those with adenocarcinoma ($p = 0.039$), but no statistically significant difference was found in ORR. Patients with extra-pelvic metastatic lesions had a better efficacy than those with intra-pelvic metastatic lesions, but the difference was not statistically significant ($p > 0.05$). The findings demonstrated the certain efficacy of chemotherapy combined with targeted drugs. As reported, bevacizumab combined with chemotherapy exhibits better PR than pemetrexed or bevacizumab alone, greater SD than bevacizumab single agent but similar to pemetrexed, and more favorable PFS and OS than either of the two (15). Therefore, combination of bevacizumab and pemetrexed as a second-line treatment is superior to its single-agent therapy in terms of short-term clinical efficacy for patients with recurrent and metastatic cervical cancer. With respect to safety, this study revealed that the adverse reactions during treatment were mainly in grade I–II, and grade III–IV severe adverse reactions mainly included leukopenia, anemia, thrombocytopenia, hypertension and neurotoxicity, which could be basically tolerated. In addition, no death related to treatment was observed. These findings confirmed the safety of combined therapy.

The present study was a retrospective study with limited sample sizes and relatively short follow-up period, and the follow-up content was not comprehensive enough. Thus, in the future, multi-center, large-sample, prospective clinical trials should be carried out to validate the conclusions of this study.

CONCLUSION

Bevacizumab combined with pemetrexed exhibits certain efficacy in the treatment of recurrent and metastatic cervical cancer, with tolerable adverse reactions. Therefore, this therapeutic option deserves clinical popularization 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/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

YH and QX designed the study and performed the experiments, YH and JW collected the data, QX and SX analyzed the data, YH and QX prepared the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Statistical Analysis of IABP-Surgery Data with the Co-use of Anticoagulants, Pulse of Dorsalis Pedis Artery, D-Dimer Data, and Coagulation Function

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Data analysis was performed on IABP (intra-aortic balloon pump) patients for the use of anticoagulants, pulse of dorsalis pedis artery, D-dimer data, and coagulation function. According to the differential diagnosis of 52 patients admitted to hospital, data on the use of anticoagulants, dorsalis pedis artery pulsation, D-dimer data, and coagulation function were collected. These data were analyzed by using a nonparametric test, linear regression analysis, adjustment effect analysis, and chi-square test. Some findings of the analysis included: (1) There were differences in the dorsalis pedis artery pulsation of samples from different sexes, all of which were significant. (2) Coagulation function has a significant positive relationship with D-dimer. (3) When the D-dimer affects the prognosis, the regulatory variable (dorsalis pedis artery pulse) is at different levels, and the influence amplitude has significant differences. (4) Samples taken with different anticoagulants all showed significant differences in the dorsalis pedis artery pulsation.

Keywords: intra-aortic balloon pumping, nursing care, SPSS, analysis, retrospective study

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INTRODUCTION

Mathematical model–based scenario analysis and interventions are very useful in clinical studies (1). There are many tools that can be used for the analysis and interventions, including meta-analysis (2), AI-based methods (3), Matlab platforms (4), SAS, STATA and R programs (5), network analysis (6), molecular modeling (7), and so forth. Some of them have been designed with simple software for us to use, whereas others need programming and require typical levels

of computer knowledge. Therefore, it is very important to integrate medicine with mathematics and computer science (8).

Intra-aortic balloon pump (IABP) is a typical nursing tool in cardiovascular indications for over 50 years (9). In many of the IABP studies, mathematics and computer science have been widely used in statistical analysis for presenting novel findings and conclusions. Georgeson et al. (10) have constructed a decision model for IABP analysis. Moustafa et al. (11) performed a meta-analysis using data from the Pubmed, EMBASE, and Cochrane Central databases. Millet et al. (12) have conducted a cost analysis for a retrospective study by chart review in 2016–2019. Gu et al. (13) have used numerical analysis for heart failure, IABP, ECMO, and ECMO plus IABP.

The above mathematical tools are frequently used in clinical studies; however, they seem complicated for non-professional readers to understand. SPSS is a typical and easy tool in scientific analysis (14, 15). The results and conclusions are easily understood. In this work, SPSS analysis was performed with the data of the IABP patients for the use of anticoagulants, pulse of dorsalis pedis artery, D-dimer data, and coagulation function. According to the differential diagnosis of patients admitted to hospital, data on the use of anticoagulants, dorsalis pedis artery pulsation, D-dimer data, and coagulation function were collected. These data were analyzed by using a nonparametric test, linear regression analysis, adjustment effect analysis, and chi-square test. The results and findings can be used for future IABP studies in medicine and statistics.

OBJECTIVE AND METHODS

Table 1 shows the age distribution of different patients in the admission diagnosis, and the total number of samples is 52. A total of five diseases were recorded, and five samples were not recorded. There were 38 males and 14 females. The raw information is shown in **Supplementary material**. The results are analyzed using SPSS (Statistical Product and Service Solutions).

RESULTS AND DISCUSSION

As shown in **Table 2**, the non-parametric test was used to study the difference of gender in one item concerning the pulsation of the dorsalis pedis artery. As shown in the table, there were two groups (female and male) of gender, so the Mann–Whitney test statistic was used for analysis. For the dorsalis pedis artery pulsation, samples from different genders showed differences, and all of them showed significant differences ($p < 0.05$).

The specific analysis showed that gender had a significant effect at the 0.05 level on the dorsalis pedis artery pulsation ($p = 0.025 < 0.05$), and the specific comparison with the difference in the median showed that the medians were equal. p-values less than 0.05 showed a significant difference, but there was no difference in the median, indicating that the source of the difference was different types of data distribution.

As shown in **Table 3**, linear regression analysis was performed with the coagulation function as the independent variable and D-dimer as the dependent variable. As shown in the table, the model formula is: D-dimer = 12.706 + 0.542 × coagulation function, and the model R square value is 0.245, which means that the coagulation function can explain the 24.5% change of the D-dimer. When the model was subjected to an F-test, it was found that the model passed the F-test ($F = 16.257$, $p \leq 0.001$), which indicates that clotting function must affect the D-dimer.

The final analysis showed that the regression coefficient value of the coagulation function was 0.542 ($t = 4.032$, $p \leq 0.001$), indicating that the coagulation function had a significant positive effect on the D-dimer.

As shown in **Table 4**, the regulatory effects were divided into three models, with the independent variable (D-dimer) included in Model 1. In Model 2, regulatory variables (the pulse condition of dorsalis pedis artery) were added on the basis of Model 1, and in Model 3, interactive terms (the product term of the independent variable and the regulatory variable) were added on the basis of Model 2. For Model 1, its purpose is to study the effect of the independent variable (D-dimer) on the dependent variable (outcome) without considering the interference of the regulatory variable (dorsalis pedis artery pulse). As shown in **Table 4**, the independent variable (D-dimer) showed significant values ($t = -2.451$, $p = 0.018 < 0.05$), meaning that the D-dimer had a significant effect on outcomes. The adjustment effect can be viewed in two ways. The first way

TABLE 2 | Non-parametric test analysis results.

	Median sex M (P25, P75)		Mann–Whitney test statistic *U* value	Mann–Whitney test statistic *z* value	*p*
	Female (*n* = 14)	Male (*n* = 38)			
Dorsalis pedis artery pulsation	7.000 (4.0,7.0)	7.000 (7.0,7.0)	174.000	−2.240	0.025*

*$p < 0.05$.

TABLE 1 | Basic statistics of the survey.

	Admission diagnosis (mean standard deviation)						*F*	*p*
	Coronary atherosclerotic heart disease (*n* = 4)	Heart failure (*n* = 2)	Myocarditis (*n* = 1)	Heart disease (*n* = 23)	Acute myocardial infarction (*n* = 17)	No record (*n* = 5)		
Age	68.00 ± 5.29	82.50 ± 20.51	64.00	67.26 ± 14.23	67.41 ± 11.73	74.80 ± 2.28	0.854	0.519

TABLE 3 | Results of linear regression analysis ($n = 52$).

	Non-standardized coefficient		Normalization coefficient	*t*	*p*	VIF	R^2	Adjust *r*	*F*
	B	Standard error	*Beta*						
Constant	12.706	3.627	–	3.503	≤0.001*	–	0.245	0.230	$F(1,50) = 16.257$, $p \leq 0.001$
Coagulation function	0.542	0.134	0.495	4.032	≤0.001*	1.000			

Dependent variable: D-dimer.
D-W value: 2.053.
*$p < 0.01$.

TABLE 4 | Adjustment effect analysis results.

	Model 1	Model 2	Model 3
Constant	1.885** (22.033)	1.885** (21.822)	1.849** (21.622)
D-dimer	−0.016* (−2.451)	−0.016* (−2.413)	−0.016* (−2.453)
Dorsalis pedis artery pulsation		0.009 (0.209)	0 (0.005)
D-dimer × Dorsal artery pulsation			0.006* (2.044)
Sample size	52	52	52
R^2	0.107	0.108	0.179
Adjust *r*	0.089	0.072	0.128
Variance ratio	$F(1,50) = 6.008$, $p = 0.018$	$F(2,49) = 2.968$, $p = 0.061$	$F(3,48) = 3.500$, $p = 0.022$
ΔR^2	0.107	0.001	0.071
ΔF-value	$F(1,50) = 6.008$, $p = 0.018$	$F(1,49) = 0.044$, $p = 0.835$	$F(1,48) = 4.178$, $p = 0.046$

Dependent variable: outcome.
*$p < 0.05$.
**$p < 0.01$. *t-value in parentheses.*

is to view the significance of the *F*-value change from Model 2 to Model 3. The second way is to check the significance of the interaction items in Model 3. The regulation effect is analyzed in the second way this time. As shown in **Table 4**, the interaction term of the D-dimer and dorsalis pedis artery pulse was significant ($t = 2.044$, $p = 0.046 < 0.05$). This means that when the D-dimer affects the outcome, the regulating variable (dorsalis pedis artery pulse) has a significantly different influence amplitude at different levels, as shown in the variable relationship in **Figure 1**.

As shown in **Table 5**, chi-square test (cross-analysis) was used to study the difference relationship of the use of anticoagulants to a total of one item of dorsal artery pulse. From this table, it can be seen that the use samples of different anticoagulants showed a significant difference with respect to a total of one item of dorsal artery pulse ($p < 0.05$), which means that the use samples of different anticoagulants showed a difference with respect to a total of one item of dorsal artery pulse. In conclusion, samples taken with different anticoagulants showed significant differences for all the dorsalis pedis pulses.

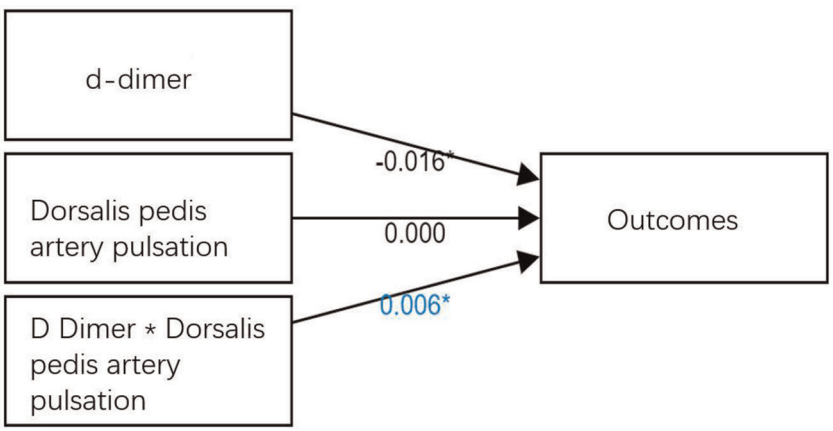

FIGURE 1 | Variable relationships.

TABLE 5 | Chi-square test analysis results.

Subject	Name	Use of anticoagulant (%)			Total	χ^2	*p*
		Low molecular heparin sodium injection	Anonymous	Naltrexate calcium for injection			
Dorsalis pedis artery pulsation	Good	0 (0.00)	0 (0.00)	1 (3.13)	1 (1.92)	36.837	0.012*
	The right side is weak, and the left side cannot be touched.	0 (0.00)	0 (0.00)	1 (3.13)	1 (1.92)		
	Left side not palpable, right side weak	0 (0.00)	0 (0.00)	1 (3.13)	1 (1.92)		
	Weak	3 (16.67)	0 (0.00)	0 (0.00)	3 (5.77)		
	Strong	0 (0.00)	0 (0.00)	1 (3.13)	1 (1.92)		
	Weak	0 (0.00)	0 (0.00)	1 (3.13)	1 (1.92)		
	Good	12 (66.67)	1 (50.00)	21 (65.63)	34 (65.38)		
	Good	0 (0.00)	1 (50.00)	0 (0.00)	1 (1.92)		
	Good–strong	0 (0.00)	0 (0.00)	1 (3.13)	1 (1.92)		
	Good–weak	1 (5.56)	0 (0.00)	0 (0.00)	1 (1.92)		
	Weaker	2 (11.11)	0 (0.00)	5 (15.63)	7 (13.46)		
Total		18	2	32	52		

*$p < 0.05$.

CONCLUSION

Data analysis was performed on 52 patients. According to the differential diagnosis of patients admitted to hospital, data on the use of anticoagulants, dorsalis pedis artery pulsation, D-dimer data, and coagulation function were collected. These data were analyzed by using a non-parametric test, linear regression analysis, adjustment effect analysis, and chi-square test. Some findings of the analysis included: (1) There were differences in the dorsalis pedis artery pulsation of samples from different sexes, all of which were significant. (2) Coagulation function has a significant positive relationship with D-dimer. (3) When the D-dimer affects the prognosis, the regulatory variable (dorsalis pedis artery pulse) is at different levels, and the influence amplitude has significant differences. (4) Samples taken with different anticoagulants all showed significant differences in the dorsalis pedis artery pulsation.

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 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

HC, ZS, and YZ contributed to the conception and design of the study and wrote the first draft of the manuscript. ZZ, LL, XT, JP, and XP contributed to the data collection and analysis. YZ and YZ contributed to manuscript revision, reading, and project management. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/article/10.3389/fsurg.2022.919009/full#supplementary-material.

Supplementary Data Sheet S1 | Raw data for the SPSS analysis.

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Correlation Among Self-Care Ability, Psychological Status, and Quality of Life in Discharged Patients with Hepatolithiasis Complicated with Diabetes Mellitus and T-Tube

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Objectives: This study aimed to investigate the correlation between self-care ability, psychological status, and quality of life in patients with hepatolithiasis complicated with diabetes mellitus with T-tube.

Methods: The purpose of this study was to select a total of 240 patients with hepatolithiasis complicated with diabetes with T-tube from June to September 2019 in a Third-class Grade A hospital in Changsha, Hunan Province. Self-designed general information questionnaire, self-care ability implementation scale (ESCA), self-rating anxiety scale (SAS), self-rating depression scale (SDS), and quality of life scale (SF-36) were used to conduct a questionnaire survey. The correlation among self-care ability, psychological status, and quality of life of patients with hepatolithiasis complicated with diabetes mellitus with T-tube was analyzed.

Results: The total score of self-care ability of 240 patients with hepatolithiasis combined with diabetes with T-tube was positively correlated with the total score of quality of life ($p < 0.05$). The standard scores of anxiety and depression were negatively correlated with the total score of quality of life ($p < 0.05$). The total score of self-care ability was negatively correlated with the standard score of anxiety and depression ($p < 0.05$).

Conclusion: Improving the self-care ability of patients with hepatolithiasis complicated with diabetes with T-tube and improving their anxiety and depression can improve their quality of life, which provides reference for further study.

Keywords: Hepatolithiasis complicated with diabetes mellitus, T-tube, self-care ability, psychological status, quality of life

INTRODUCTION

Hepatolithiasis, which is defined as the stones formed in each branch bile duct above the confluence of the left and right hepatic ducts, has a high prevalence in Asia (1–3). In western countries, hepatolithiasis has a much lower incidence (4, 5). However, the incidence of hepatolithiasis is increasing in Western countries due to the increase in immigration from high prevalent areas (5–7). Surgical management has long been a primary treatment of hepatolithiasis, and a T-tube is usually retained after operation (8). However, the T-tube placement time is usually 2–3 months, and it can be as long as 3–6 months for complicated cases. Improper nursing will easily lead to complications such as tract infection and T-tube shedding (8).

Diabetes mellitus refers to the presence of hyperglycemia, which is a kind of prevalent chronic lifelong metabolic disease all over the world (9, 10). Various complications caused by long-term metabolic problems and continuous hyperglycemia can gradually damage the patient's tissues and organs, which results in a high mortality rate (11–13). With the change in people's lifestyle and diet structure, the incidence of hepatolithiasis with diabetes is increasing, which seriously affects the quality of life of patients with hepatolithiasis and diabetes with T-tube. Therefore, it is necessary to conduct nursing interventions and take some measures to improve their quality of life.

Previous studies reported a relationship between anxiety and depression, quality of life, and self-care ability of patients with heart failure (14, 15), colorectal cancer (16), or other diseases (17, 18). However, few literature works mention the relationship of these three factors in patients with hepatolithiasis complicated with diabetes mellitus with T tube. The purpose of our study is to research the correlation between self-care ability, psychological status, and quality of life of patients with hepatolithiasis complicated with diabetes mellitus and T-tube to provide a reference for further research.

OBJECTIVES AND METHODS

Research Objects

A total of 240 patients with hepatolithiasis complicated with diabetes with T-tube from June to September 2019 in a Third-class Grade A hospital in Changsha, Hunan Province were selected as the research objects.

Inclusion and Exclusion Criteria

Inclusion criteria are as follows:

(1) age: ≥18 years and ≤65 years;
(2) medical diagnosis of hepatolithiasis and diabetes mellitus, recovered and discharged with T-tube after surgical treatment; and
(3) informed consent and voluntary participants.

Exclusion criteria are as follows:

(1) those with serious complications or critical illness who can not take care of themselves;
(2) people with a history of mental illness; and
(3) those who have language communication barriers and can not communicate normally.

Research methods

The main research tools that were used in this study are as follows: a general information questionnaire, self-care ability implementation scale (ESCA), self-rating anxiety scale (SAS), self-rating depression scale (SDS), and quality of life scale (SF-36).

Survey Tools

General Information Questionnaire

The general information questionnaire includes the age, gender, family income, education level, marital status, occupation, main caregivers, and disease-related information of the subjects.

Self-Care Ability Implementation Scale

This scale was compiled by American scholars Kearney and Fleischer (19), and Cronbach's α coefficient was 0.86–0.92 (20). There are 43 items that include four dimensions: self-concept, self-care responsibility, self-care skills, and health knowledge level. Each item of the scale scored from 0 to 4, with a total score of 172. The higher the score, the stronger the self-care ability. The level of self-care ability is evaluated by a scoring index. The scoring index >66% is in a high grade, 33%–66% is in a medium grade, and <33% is in a low grade.

Self-Rating Anxiety Scale

This scale was developed by Zung (21), and Cronbach's α coefficient was 0.807. There are 20 items in total, which are described by a standard score. Standard score = total rough score × 1.25. The score index <50 is normal, 50–59 is mild anxiety, 60–69 is moderate anxiety, and >69 is severe anxiety. The higher the standard score, the more severe the symptoms.

Self-Rating Depression Scale

SDS was compiled by Zung (22), and Cronbach's α coefficient was 0.854. There are 20 items in total, which are described by a standard score. The higher the standard score, the more severe the symptoms are. The cut-off value of the SDS standard score is 53, of which <53 is normal, 53–62 is mild depression, 63–72 is moderate depression, and >73 is severe depression.

Quality of Life Scale (SF-36)

The quality of life scale (SF-36) adopts the Chinese version of the reliability and validity scale tested by Li's team (23), and Cronbach's α coefficient is 0.763. SF-36 has 36 items in total that include eight health dimensions and a self-assessment of health changes. These health dimensions are role-physical (RP), mental health (MH), vitality (VT), bodily pain (BP), social functioning (SF), physiological functioning (PF), general health (GH), and role-emotional (RE). Eight dimensions are divided into the mental health field and the physical health field. The total score of quality of life is the sum of scores in

eight dimensions. The higher the score, the better the patient's quality of life.

Statistical Methods

Statistical analysis was performed on all experimental data using SPSS 20.0 software. The data on frequency, percentage, and Spearman rank correlation were analyzed.

TABLE 1 | General information of research objects ($n = 240$, %).

Variable	Category	Frequency	Percentage
Gender	Man	87	36.25
	Woman	153	63.75
Age	18–30 years	29	12.08
	31–45 years	181	75.42
	>45 years	30	12.50
Marital status	Unmarried	55	22.92
	Married	185	77.08
Educational level	Junior high school or below	135	56.25
	High school	74	30.83
	Junior college degree or above	31	12.92
Occupation	Farmer	103	42.92
	Enterprise and public institution	63	26.25
	Others	74	30.83
Monthly household income	≤2,000 RMB	146	60.83
	2,001–5,000 RMB	74	30.83
	≥5,000 RMB	20	8.33
First operation	Yes	133	55.42
	No	107	44.58
Days after operation	≤14 days	144	60.00
	15–30 days	62	25.83
	>30 days	34	14.17
Sequence of diagnosis of hepatolithiasis and diabetes mellitus	Hepatolithiasis first	203	84.58
	Diabetes mellitus first	18	7.50
	Both at the same time	19	7.92
Diagnosis time of diabetes mellitus	<6 months	89	37.08
	6 months–3 years	104	43.33
	>3 years	47	19.58
First discharge with T-tube	Yes	219	91.25
	No	21	8.75
T-tube clamped	Yes	198	82.50
	No	42	17.50
Recovery status of wound	Well	216	90.00
	Worse	24	10.00
Main caregiver	By other people	180	75.00
	By myself	60	25.00
Nursing ways of T-tube	By medical institution	69	28.75
	Nurse's home care	116	48.33
	Self-care	55	22.92
Control of blood sugar	Good	65	27.08
	Bad	93	38.75
	Not monitored	82	34.17

RESULTS AND DISCUSSION

In this study, a total of 248 questionnaires were sent out, of which 240 were valid. The effective recovery rate was 96.7%. There are 87 males and 153 females (**Table 1**).

As shown in **Table 2**, the total score of self-care ability was negatively correlated with the standard score of anxiety and depression ($r = -0.424$, -0.400, $p < 0.05$). Additionally, the score of each dimension has negative significance with psychological status. Therefore, the stronger the self-care ability of patients with hepatolithiasis and diabetes with T tube, the better their psychological status, and vice versa. This is consistent with the research results of scholars such as Patrick (24). The reason may be that patients with good self-care ability know the importance of self-care, which can stimulate their self-responsibility to actively learn relevant health knowledge and nursing skills from passive acceptance to active participation. Patients know more about diseases and nursing knowledge so that they can treat diseases correctly and maintain a good psychological state to enhance patients' confidence in overcoming diseases.

The results of **Table 3** showed that the total score of the SF-36 scale was positively correlated with the total score of self-concept, self-care responsibility, self-care skills, and health knowledge level ($r = 0.263$, $p < 0.05$). It is consistent with the results of Patrick (24) and Kessing (25). From the table, we found that the higher quality of life of patients with hepatolithiasis complicated with diabetes mellitus and T-tube was closely related to their stronger self-care ability. The main reasons are that patients having strong self-concept and awareness of self-recognition can cooperate with the medical treatment positively so as to improve their body function and their quality of life. Therefore, nursing staff should improve patients' weaknesses in personalize training and health education in continuing home care to improve their quality of life.

As shown in **Table 4**, the total score of the SF-36 scale was negatively correlated with the standard score of anxiety and depression ($r = -0.285$, -0.266, $p < 0.05$). Therefore, the better

TABLE 2 | Correlation between self-care ability and psychological status of discharged patients with hepatolithiasis and diabetes mellitus with T-tube ($n = 240$).

Variable	Statistics	Standard score of anxiety	Standard score of depression
Total score of self-care ability	*r*	−0.424**	−0.400**
	p	<0.001	<0.001
Self-concept	*r*	−0.508**	−0.353**
	p	<0.001	<0.001
Self-care responsibility	*r*	−0.320**	−0.234**
	p	<0.001	<0.001
Self-care skills	*r*	−0.144*	−0.192**
	p	0.026	0.003
Health knowledge level	*r*	−0.201**	−0.296**
	p	0.002	<0.001

*$p < 0.05$; **$p < 0.01$.

TABLE 3 | Correlation between self-care ability and quality of life in discharged patients with hepatolithiasis and diabetes mellitus with T-tube ($n = 240$).

Variable	Statistics	Total score of self-care ability	Self-concept	Self-care responsibility	Self-care skills	Health knowledge level
Total score of SF-36	*r*	0.263**	0.242**	0.231**	0.239**	0.108
	p	<0.001	<0.001	<0.001	<0.001	0.094
Physiological functioning (PF)	*r*	0.235**	0.184**	0.234**	0.230**	0.123
	p	<0.001	0.004	<0.001	<0.001	0.058
Role-physical (RP)	*r*	0.136*	0.101	0.166**	0.103	0.035
	p	0.036	0.120	0.010	0.112	0.594
Bodily pain (BP)	*r*	0.037	0.164*	0.111	0.051	−0.109
	p	0.572	0.011	0.086	0.434	0.091
General health (GH)	*r*	−0.089	−0.004	−0.071	−0.155*	−0.034
	p	0.170	0.952	0.271	0.016	0.603
Vitality (VT)	*r*	0.069	0.068	0.078	−0.015	0.079
	p	0.287	0.295	0.231	0.812	0.224
Social functioning (SF)	*r*	0.189**	0.143*	0.127*	0.175**	0.132*
	p	0.003	0.026	0.049	0.007	0.041
Role-emotional (RE)	*r*	0.204**	0.169**	0.154*	0.272**	0.043
	p	0.001	0.009	0.017	<0.001	0.509
Mental health (MH)	*r*	0.047	0.194**	−0.007	−0.015	0.011
	p	0.473	0.003	0.908	0.818	0.863

*$p < 0.05$; **$p < 0.01$.

TABLE 4 | Correlation between psychological status and quality of life in discharged patients with hepatolithiasis and diabetes mellitus with T-tube ($n = 240$).

Variable	Statistics	Standard score of anxiety	Standard score of depression
Total score of SF-36	*r*	−0.285**	−0.266**
	p	<0.001	<0.001
Physiological functioning (PF)	*r*	−0.362**	−0.371**
	p	<0.001	<0.001
Role-physical (RP)	*r*	−0.051	−0.114
	p	0.428	0.078
Bodily pain (BP)	*r*	−0.011	0.062
	p	0.868	0.337
General health (GH)	*r*	0.086	0.079
	p	0.185	0.224
Vitality (VT)	*r*	−0.170**	−0.087
	p	0.008	0.177
Social functioning (SF)	*r*	−0.346**	−0.326**
	p	<0.001	<0.001
Role-emotional (RE)	*r*	−0.079	−0.077
	p	0.224	0.237
Mental health (MH)	*r*	−0.356**	−0.244**
	p	<0.001	<0.001

*$p < 0.05$; **$p < 0.01$.

the psychological status of discharged patients with hepatolithiasis and diabetes mellitus with T-tube, the higher the patients' quality of life, and vice versa. The results were consistent with the research results of Patrick (24) and Park (26). Although hepatolithiasis is a benign disease, it has a high recurrence rate with some complications (27). Diabetes mellitus is a typical physical and mental disease with a long course and many complications (28). Patients with hepatolithiasis complicated with diabetes mellitus and T-tube are prone to psychological problems and stress due to their awareness of the difficulty in curing their diseases completely and the inconvenience of these diseases to their daily life and social work, which will lead to abnormal emotional control and result in a significant negative impact on their quality of life. Therefore, in the management and treatment of patients with hepatolithiasis complicated with diabetes, we should not only pay attention to the improvement of patients' physiological functions but also intervene in the factors that affect their psychology and life behavior.

CONCLUSION

Our study focused on exploring the correlation between self-care ability, psychological status, and quality of life in discharged patients with hepatolithiasis complicated with diabetes mellitus and T-tube. Data showed that (1) patients' self-care ability was negatively associated with their psychological status ($p < 0.05$), (2) self-care ability of 240 patients with hepatolithiasis combined with diabetes and T-tube was positively correlated with their quality of life ($p < 0.05$), and (3) psychological status has a negative difference with the quality of life ($p < 0.05$). From the results, it can be seen that stronger self-care ability and lower anxiety and depression level were closely related to the higher quality of life.

In this work, we demonstrated that promoting the self-care ability of patients with hepatolithiasis complicated with

diabetes and T-tube and improving their psychological status can improve their quality of life. Our findings highlight the necessity of psychological interventions and guidance of self-recognition of patients, which provide a reference for further study on the improvement of quality of life for this population.

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 Ethical Review Committee of 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

CH and YW contributed to the conception and design of the study and wrote the first draft of the manuscript. YC contributed to manuscript revision, reading, and project management. ZS, HZ, ZT, HC, and BZ contribute to data collection and analysis. All authors contributed to the article and approved the submitted version.

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Effect of Orem's Self-Care Theory Combined with Active Pain Assessment on Pain, Stress and Psychological State of Children with Nephroblastoma Surgery

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Background: With the development of medical technology and the innovation of various surgical options, the survival time of children with nephroblastoma is significantly prolonged. However, postoperative pain and stress response have been plagued by children with nephroblastoma during the postoperative treatment. At present, there is still a lack of effective care programs.

Methods: We accessed our institutional database to retrospectively screen clinical data from all children with nephroblastoma who were surgically treated in our hospital between July 2020 and July 2021. Some children received routine care, while others received Orem-based self-care theory and active pain assessment.

Results: According to the inclusion and exclusion criteria, 150 children with nephroblastoma who underwent surgical treatment were included in this study. On the third day after surgery, the scores of pain control effect and satisfaction degree of pain education in the study group were higher than those in the control group, and the physical and daily life influence, emotion influence, and pain experienced in the study group were lower than those in the control group. The differences were statistically significant ($p < 0.001$). There was no significant difference in C-SUPPH and ESCA scores between the two groups before nursing ($p > 0.05$). After nursing, the C-SUPPH and ESCA scores of the two groups were higher than those before nursing, and the C-SUPPH and ESCA scores of the study group were higher than those of the control group ($p < 0.05$). Before nursing, the levels of ACTH, Cor, and ANP between the two groups were not statistically significant ($p > 0.05$). The levels of ACTH, Cor, and ANP in the two groups were lower than those before nursing and 3 d and 7 d after nursing, and the index levels after 7 d of nursing were lower than those after 3 d of nursing. After nursing, the levels of ACTH, Cor, and ANP in the study group at each time point were lower than those in the control group ($p < 0.05$). There was no significant difference in SAS and SDS scores between the two groups before nursing ($p > 0.05$). After nursing, the SAS and SDS scores of both groups were lower than those before nursing,

and the SAS and SDS scores of the study group were lower than those of the control group ($p < 0.05$). There was no significant difference in PSQI scores between the two groups before nursing ($p > 0.05$). After nursing, the PSQI scores of the two groups were lower than those before nursing, and the PSQI scores of the study were lower than those of the control group ($p < 0.05$). The average daily crying time, the average hospitalization time, and postoperative off-bed time in the study group were shorter than those in the control group ($p < 0.05$).

Conclusion: Orem's self-care theory combined with active pain assessment can reduce pain in children undergoing nephroblastoma surgery, improve their stress response and psychological state, and improve their sleep quality, which is conducive to postoperative recovery and worthy of promotion.

Keywords: nephroblastoma surgery, Orem's self-care theory, active pain assessment, psychological state, stress response

INTRODUCTION

Nephroblastoma is an embryonal malignancy tumor with the highest incidence of abdominal tumors in children. The exact cause of the disease remains unclear (1). From the perspective of embryology, nephroblastoma develops from an abnormal proliferation of persistent postrenal blastocysts (2). Tumor tissue can break through the renal dorsal membrane and destroy the kidney skin, renal pelvis, kidney, etc., resulting in abnormal renal function. Besides, some tumor cells can invade the blood vessels of the renal hilus or even the surrounding tissues, endangering life (3). Therefore, timely surgical treatment is essential to save the lives of children. Pain is a protective mechanism of the body, which is used to restrict the postoperative activities of children undergoing surgery and avoid adverse consequences. However, the pain will not only cause a huge psychological burden but also limit other immune functions, cause different degrees of stress response, and increase the rate of postoperative lesion metastasis (4). Therefore, postoperative pain in children with nephroblastoma is the key link in postoperative nursing.

Orem's self-care theory is a new type of nursing model. The self-care theory emphasizes self-care as the center, with the ultimate goal of enabling individuals to take up the responsibility of self-care (5). Nursing intervention based on Orem's theory focuses on being people-oriented, which can help patients improve their self-nursing ability and maintain a good psychological state on the basis of comprehensive nursing. In addition, pain assessment is the basis of pain management. The study indicates that targeted measures based on the results of active pain assessment can effectively relieve postoperative pain in children (6). This study analyzed the influence of pain, stress, and psychological state of children with nephroblastoma surgery after surgery based on Orem's self-care theory and active pain assessment.

MATERIALS AND METHODS

Research Object

This study has been approved by the Ethics Committee of our hospital, and all patients have been informed and consented. All the data have been confirmed.

We accessed our institutional database to retrospectively screen clinical data from all children with nephroblastoma who were surgically treated in our hospital between July 2020 and July 2021. The inclusion criteria are as follows: (1) All children who underwent nephroblastoma surgery; (2) children aged 6–10 years;and (3) children with good communication skills and able to objectively answer questions. The exclusion criteria are as follows: (1) all patients with other malignant tumors and distant metastasis; (2) severe impairment of organ function; (3) children with cognitive impairment; (4) intraoperative and postoperative blood transfusion; and (5) children with a history of epilepsy. Clinical data deficiencies were excluded, and the cooperation with the investigator was refused in the midway. According to the different nursing methods, the participants were divided into a study group and a control group.

Care Methods

All the children received routine pain intervention, living nursing, vital sign monitoring, condition monitoring, and incision prevention of infection after operation. Children were urged to undergo rehabilitation training as soon as possible. Medication guidance was given to children, and parents were given education on the related knowledge of active pain after surgery, explaining the causes of pain and the use of analgesic drugs. Psychological nursing was carried out to eliminate anxiety and fear of children and their families.

In the study group, Orem's self-care theory was added to routine nursing. (1) Complete compensation system: Children lack self-nursing knowledge at the initial stage of admission. Nurses should do all kinds of nursing work to meet the normal requirements of children as much as possible. According to the actual situation, cognitive behavioral therapy, music therapy, therapeutic communication, exercise therapy, art therapy, reading therapy, virtual reality therapy, and other methods were selected to conduct psychological counseling for children. (2) Partial compensation system: At this stage, children are required to participate in activities together, and they can be required to independently take nursing of themselves, such as dressing, bathing, eating, and defecating.

Encourage children to adjust their emotions in the treatment and nursing process and maintain a good psychological state. (3) Support and education system: During hospitalization, nurses should teach children self-nursing skills to improve their self-nursing ability as much as possible. Emotional and information support should be given, and medical staff should try their best to praise the children with soothing, encouraging, hinting, and praising language to improve their health awareness and treatment compliance. Children and their families should be taught self-nursing methods and precautions after discharge, emphasizing the importance of self-nursing to patients and improving the ability and enthusiasm of self-nursing.

Meanwhile, the active pain state of children was evaluated. The pain should be tracked once every 4 h. When the FAS score of the child dropped to Grade I or II and the NRS score <4, it was changed to be evaluated once every 8 h. Pain assessment should be stopped when the child's pain disappears. The assessment tools were the Digital Pain Rating Scale (NRS) and the Chinese Version of the Four-Level Functional Activity Score (FAS) (7, 8). The NRS scale was mainly used for children to assess their own pain subjectively. The scale was composed of 0–10 numbers, with 0–3 points indicating that the pain was within the tolerance range and did not affect normal life and sleep, 4–6 points meaning that the pain is more obvious and the basic living and sleep have interfered, and 7–10 points meaning severe pain that the children cannot tolerate basically. The FAS scale is mainly used for the assessment of postoperative active pain, and it is assessed according to the degree of pain endured by children. Grade I indicates that pain could not limit the children from completing a functional activity normally. Grade II indicates that the children with mild pain restriction completed a functional activity. Grade III indicates that the pain moderately restricted the children to complete a functional activity. Grade IV indicates severe pain that limits the child's ability to complete a functional activity, and activity is not recommended for this grade. No drug intervention was given when the FAS score was Grade I. Psychological intervention was given to divert patients' attention to pain when the FAS score was Grade II or NRS score >4. When the FAS score was Grade III or IV or the NRS score was greater than 7, an intramuscular injection of analgesic drugs was administered.

Both groups were intervened for 3 weeks.

Observation Index

(1) On the third postoperative day, the Houston Pain Inventory (HPOI) (9) was used to assess the pain control effects of two groups, including pain control effect, physical and daily life influence, emotional influence, pain experience, and satisfaction degree of pain education with 33 items in five dimensions. Among them, the higher the scores of pain control effect and satisfaction degree of pain education were, the more satisfied the pain control effect was. The lower the scores of body and daily life influence, emotion influence, and pain experience were, the more satisfied the pain control effect was.

(2) Before and after nursing, the self-management efficacy scale (C-SUPPH) (10) and self-nursing ability scale (ESCA) (11) were used to evaluate the level of self-efficacy and self-nursing ability of the two groups, respectively. The C-SUPPH scale consisted of 28 items in three dimensions: self-decompression, self-decision-making, and positive attitude, with each item scoring 1–5 points and a total score of 28–140 points. The higher the total score is, the higher the self-efficacy is. The ESCA scale consisted of 43 items in four dimensions: self-concept, self-nursing responsibility, self-nursing skills, and health knowledge level. Each item was scored with 0–4 points, and the total score was 0–172 points. The higher the score is, the higher the self-nursing ability is.

(3) Before nursing, after nursing for 3 days, and after nursing for 7 days, 5 mL of fasting elbow venous blood was collected, and the upper serum was centrifuged to detect the serum adrenocorticotropic hormone (ACTH), cortisol (Cor), and atrial natriuretic peptide (ANP) levels in the children. Serum ACTH and Cor were detected by a chemiluminescence method. The detection instrument was a 180SE automatic chemiluminescence instrument manufactured by Bayer. The kit was purchased from Roche Diagnostic Products (Shanghai) Co., Ltd., and the procedures strictly followed the instructions. Serum ANP was detected by a double-antibody sandwich method. The kit was purchased from BioTek Co., Ltd. The detection instrument was a BioTek800TS multifunctional microplate reader. The inspection step was carried out strictly in accordance with the instructions. The absorbance OD value of each well was measured at a wavelength of 450 nm by the microplate reader.

(4) The self-rating anxiety scale (SAS) (12) and the self-rating depression scale (SDS) (13) were used to assess the psychological state before and after nursing, which included 20 items, with a total score of 80 points. The higher the total score is, the worse the psychological state of the children is.

(5) The Pittsburgh Sleep Index Scale (PSQI) (14) was used to evaluate the sleep quality of children in the two groups before and after nursing. The PSQI included seven items of sleep quality, sleep latency, sleep time, sleep efficiency, sleep disorders, hypnotic drugs, and daytime dysfunction, with a total score of 21 points. The higher the score is, the worse the sleep quality is. All scales were evaluated by specialist nurses.

(6) The average daily crying time, average hospitalization time, and postoperative off-bed time were compared between the two groups.

Statistical Methods

SPSS22.0 software was used for processing. The continuous variable data of experimental data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and adopted a *t*-test. The classified variable data and descriptive analysis were expressed as % and adopted a χ^2 test. $p < 0.05$ indicated a significant difference.

RESULTS

Finally, based on inclusion and exclusion criteria, 150 children with nephroblastoma who underwent surgical treatment were included in this study.

As shown in **Figure 1**, on the third day after surgery, the scores of pain control effect and satisfaction degree of pain education in the study group were higher than those in the control group, and the physical and daily life influence, emotion influence, and pain experienced in the study group were lower than those in the control group. The differences were statistically significant (t values were 6.662, 14.570, 21.582, 14.302, and 11.786, $p < 0.001$).

As shown in **Table 1**, there was no significant difference in C-SUPPH and ESCA scores between the two groups before nursing ($p > 0.05$). After nursing, the C-SUPPH and ESCA scores of the two groups were higher than those before nursing, and the C-SUPPH and ESCA scores of the study group were higher than those of the control group ($p < 0.05$).

As shown in **Table 2**, before nursing, the levels of ACTH, Cor, and ANP between the two groups were not statistically significant ($p > 0.05$). The levels of ACTH, Cor, and ANP in

TABLE 1 | Comparison of C-SUPPH and ESCA scores between two groups of children before and after nursing ($\bar{x} \pm$ s, score).

Group	*n*	C-SUPPH		ESCA	
		Before nursing	After nursing	Before nursing	After nursing
Study group	75	73.96 ± 12.59	94.51 ± 6.20*	91.98 ± 15.27	107.98 ± 10.63*
Control group	75	74.17 ± 12.47	89.59 ± 7.34*	92.66 ± 15.14	104.21 ± 10.35*
t	–	0.103	4.435	0.274	2.201
p	–	0.918	<0.001	0.785	<0.001

*Note: compared with the same group before care, *p < 0.05.*

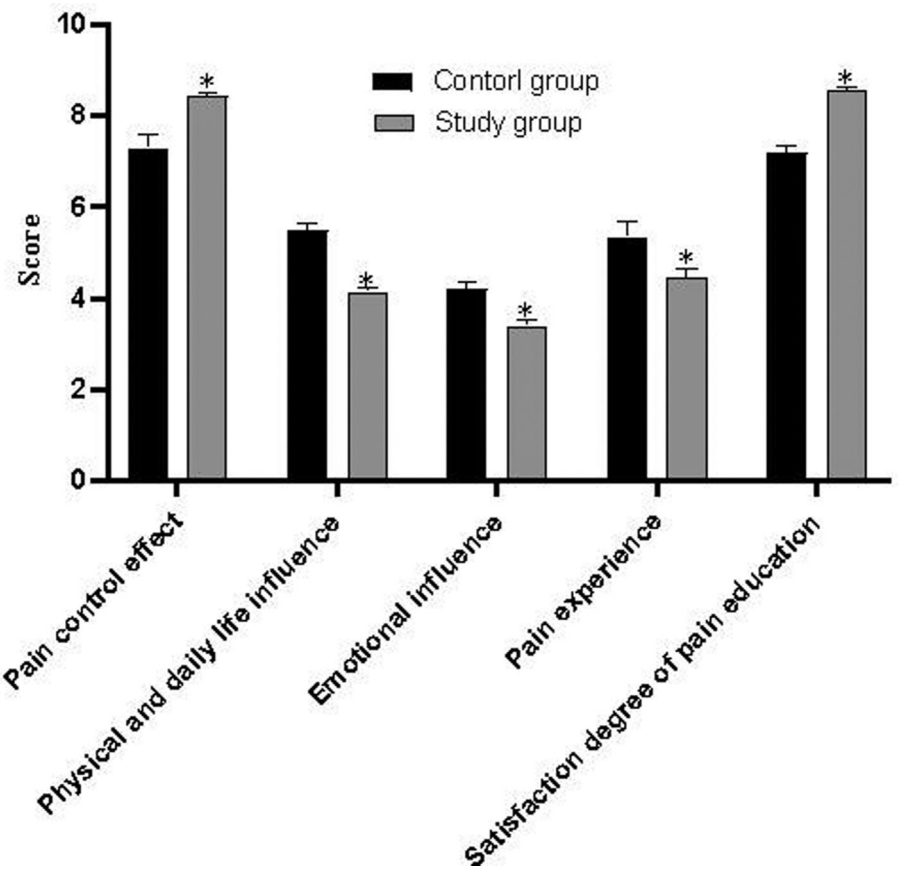

FIGURE 1 | Comparison of HPOI scores between the two groups.

TABLE 2 | Comparison of ACTH, Cor, and ANP levels between two groups of children before and after nursing ($\bar{x} \pm s$).

Group	*n*	ACTH(pmol/L)			Cor (nmol/L)			ANP(nmol/L)		
		Before nursing	After nursing for 3 days	After nursing for 7 days	Before nursing	After nursing for 3 days	After nursing for 7 days	Before nursing	After nursing for 3 days	After nursing for 7 days
Study group	75	30.16 ± 5.01	20.94 ± 4.86*	13.20 ± 2.51*,**	549.38 ± 24.18	430.28 ± 31.59*	408.29 ± 25.64*,**	0.75 ± 0.21	0.56 ± 0.19*	0.38 ± 0.11*,**
Control group	75	30.74 ± 5.46	26.25 ± 4.97*	16.39 ± 3.17*,**	538.63 ± 24.78	459.69 ± 30.74*	426.98 ± 27.36*,**	0.76 ± 0.23	0.64 ± 0.21*	0.44 ± 0.18*,**
t	–	0.678	6.616	6.832	2.689	5.778	4.317	0.278	2.446	2.463
p	–	0.499	<0.001	<0.001	0.008	<0.001	<0.001	0.781	0.016	0.015

*Note: compared with the same group before care, *p < 0.05. Compared with the same group after nursing for 3 days, **p < 0.05.*

TABLE 3 | Comparison of SAS and SDS scores between two groups of children before and after nursing ($\bar{x} \pm s$, score).

Group	*n*	SAS		SDS	
		Before nursing	After nursing	Before nursing	After nursing
Study group	75	56.39 ± 8.12	40.20 ± 6.24*	51.96 ± 7.33	39.37 ± 3.67*
Control group	75	57.84 ± 8.33	46.33 ± 7.25*	50.85 ± 7.49	43.23 ± 4.02*
t	–	1.080	5.550	0.917	6.141
p	–	0.282	<0.001	0.361	<0.001

*Note: compared with the same group before care, *p < 0.05.*

TABLE 4 | Comparison of PSQI scores between two groups of children before and after nursing ($\bar{x} \pm s$, score).

Group	*n*	Before nursing	After nursing
Study group	75	15.29 ± 2.16	10.93 ± 1.38*
Control group	75	15.87 ± 2.37	12.45 ± 2.15*
t	–	1.566	5.153
P	–	0.119	<0.001

*Note: compared with the same group before care, *p < 0.05.*

TABLE 5 | Comparison of average daily crying time, average hospitalization time, and postoperative off-bed time between two groups of children ($\bar{x} \pm s$).

Group	*n*	Average daily crying time (min/d)	Average hospitalization time (d)	Postoperative off-bed time (d)
Study group	75	35.95 ± 6.07	11.39 ± 2.52	3.01 ± 1.06
Control group	75	40.21 ± 5.82	13.48 ± 2.14	3.49 ± 1.25
t	–	4.387	5.475	2.536
p	–	<0.001	<0.001	0.012

the two groups were lower than those before nursing and 3 d and 7 d after nursing, and the index levels after 7 d of nursing were lower than those after 3 d of nursing. After nursing, the levels of ACTH, Cor, and ANP in the study group at each time point were lower than those in the control group ($p < 0.05$).

As shown in **Table 3**, there was no significant difference in SAS and SDS scores between the two groups before nursing ($p > 0.05$). After nursing, the SAS and SDS scores of both groups were lower than those before nursing, and the SAS and SDS scores of the study group were lower than those of the control group ($p < 0.05$).

As shown in **Table 4**, there was no significant difference in PSQI scores between the two groups before nursing ($p > 0.05$). After nursing, the PSQI scores of the two groups were lower than those before nursing, and the PSQI scores of the study were lower than those of the control group ($p < 0.05$).

As shown in **Table 5**, the average daily crying time, the average hospitalization time, and postoperative off-bed time in the study group were shorter than those in the control group ($p < 0.05$).

DISCUSSION

Nephroblastoma is currently the most important malignant solid tumor threatening the life safety of children, and surgery is the most important treatment in clinical practice. Pain is one of the most important complications in these types of patients after surgery. Moreover, children have poor self-control ability and are weak, and their tolerance to pain is much lower than that of adults (15). However, studies have shown that effective pain care for children undergoing nephroblastoma surgery is very important to promote postoperative rehabilitation; so, seeking an effective nursing plan has become the focus of clinical attention.

Severe pain will aggravate adverse psychological stress and promote adverse neuroendocrine and metabolic reactions in the body. Also, malignant stress is often not conducive to the recovery of children's condition (16). Some studies have pointed out that self-care ability can improve the clinical outcome and psychological state of patients undergoing surgery to a certain extent and maintain and promote health status.

In this study, the results showed that after nursing, the C-SUPPH and ESCA scores of the study group were higher than those of the control group, while the stress response index level, psychological state score, and PSQI score were lower than those of the control group ($p < 0.05$). This indicates that the implementation of the nursing plan based on Orem's self-care theory can not only physiologically alleviate the pain of children and alleviate the stress of surgery but also effectively alleviate the anxiety and depression of children after surgery and improve their sleep quality. Self-care theory is a comprehensive nursing model proposed by Dorothea E. Orem, a famous contemporary American nursing theorist (17). The main purpose of self-care theory is to help patients improve their consciousness and ability of self-care on the basis of all-round and comprehensive nursing and also play a role in improving their psychological status (18). In our study, during the period of nursing care, through constantly stimulating the subjective initiative of children, their psychological status was changed so that they could actively participate in the treatment and gradually take up the responsibility of care for themselves. Unlike control group patients who received the traditional care model, under the support of personalized care plan, patients in the research group were strictly observed for their self-care consciousness, psychological state, and self-care ability, so the nursing effect was obviously superior to that in the control group.

Assessment of postoperative active pain in children is also an effective means to relieve pain in children (19). At present, most hospitals in many countries around the world have established assessment programs for postoperative active pain, but little attention has been paid to the effect of postoperative pain on functional activities in China (20). Some scholars pointed out that the application of active pain assessment in clinical practice can be used as the basis for the evaluation of analgesic efficacy and treatment of active pain, which can effectively control the pain in patients and improve the quality of postoperative pain management.

It has been pointed out that subjective evaluation tools can directly reflect the subjective pain feelings of patients and provide a certain reference for formulating appropriate intervention measures. NRS is a commonly used assessment tool for clinical evaluation of patients' subjective pain in the past (21). However, the defect of this scale lies in that it can only reflect patients' subjective pain perception, cannot objectively reflect patients' ability to complete a functional activity, and cannot assess patients' actual activities, thus affecting the treatment of active pain in patients after surgery. FAS is an objective application evaluation tool with medical staff as the main body. Medical staff observe the completion of functional activities of patients and make the corresponding evaluation of activity level, which can make up for the deficiencies of NRS to a certain extent (22).

The results of this study show that the control group only used the NRS score to understand the functional activities of the patients, while the study group used the NRS score for the subjective feelings of the patients and the four-level FAS score objectively evaluated by medical staff to evaluate the pain severity of the patients, which provided a valuable reference index for the treatment of active pain and thus promoted the improvement of the quality of postoperative pain management. The evaluation results based on the HPOI scale showed that the scores of pain control effect and pain education satisfaction in the study group were higher than those in the control group, and the scores of body and daily life influence, emotion influence, and pain experienced in the study group were lower than those in the control group with statistically significant differences ($p < 0.05$), which confirmed the application value of NRS combined with FAS scale activity evaluation in pain care for children with nephroblastoma after operation. In addition, the daily crying time, average hospital stay, and the first time to get out of bed in the study group were shorter than those in the control group ($p < 0.05$). It also indicates that postoperative self-care for children with nephroblastoma and effective pain assessment with appropriate assessment tools have significant advantages in promoting postoperative recovery and shortening treatment time.

CONCLUSION

In summary, Orem's self-care theory combined with active pain assessment can reduce pain in children undergoing nephroblastoma surgery, improve their stress response and psychological state, and improve their sleep quality, which is conducive to postoperative recovery and 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

This study was approved by the ethics committee of our hospital. All subjects gave informed consent and signed the informed consent form. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YT is the first author, and she is the executor and writer of the paper. The second author is YC, and she is responsible for data search and data analysis. The third author is YL, and she is responsible for research design. YT is the corresponding author, and she ensures that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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Correlation of NO and ET-1 Levels with Blood Pressure Changes in Hemodialysis Patients after Arteriovenous Fistula Surgery

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Hemodialysis (HD) is the most common renal replacement therapy for patients with end-stage renal disease (ESRD) and can significantly reduce mortality and improve the quality of life of patients. The occurrence of intradialytic hypotension and intradialytic hypertension are important risk factors for death and disability during dialysis in patients with ESRD, yet their etiology remains unclear, and some studies suggest that nitric oxide (NO) and endothelin-1 (ET-1) may play an important role in these hemodynamic alterations. For this purpose we examined the changes in NO and ET-1 levels during hemodialysis in 30 patients on maintenance hemodialysis (MHD) after arteriovenous fistula surgery. Thirty dialysis patients were divided into group I (stable blood pressure during dialysis), group II (Intradialytic hypotension) and group III (Intradialytic hypertension) according to the change of blood pressure (BP) during hemodialysis, with 10 cases in each group. BP of MHD patients were measured Pre-dialysis (Pre-D), at 1 h of dialysis (1h-D), at 2 h of dialysis (Mid-D, 2h-D), at 3 h of dialysis (3h-D), and at the end of dialysis (Post-D); and blood samples were taken from the arterial end at Pre-D, Mid-D, and Post-D to measure NO and ET-1 levels. The results of the analysis showed that as dialysis proceeded and ended, the NO levels in the three groups gradually decreased, with significant differences compared with those before dialysis ($p < 0.05$); the ET-1 levels in group III gradually increased, with significant differences compared with those before dialysis ($p < 0.05$), while the increasing trend of ET-1 levels in group I and group II was not significant. The increasing trend of MAP in group I was not significant ($p > 0.05$); MAP in group II showed a gradual decrease and MAP in group III showed an increasing trend, and the difference between MAP after dialysis and before dialysis was significant ($p < 0.05$). Correlation analysis showed a significant positive correlation between ET-1 levels and MAP in Group III at Mid-D ($r = 0.847$, $p = 0.002$). This shows that serum ET-1 and NO levels are significantly higher than normal in MHD patients after arteriovenous endovascular fistula surgery, and both ET-1 and NO levels are changing during dialysis, and there may be a link between their changes and blood pressure changes.

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It is suggested that the blood pressure fluctuations that occur during dialysis in MHD patients may be related to endothelial cell dysfunction.

Keywords: arteriovenous fistula surgery, hemodialysis, blood pressure changes, NO, ET-1

INTRODUCTION

Hemodialysis (HD) was clinically applied in the 1960s and is currently the most commonly used blood purification therapy for the treatment of end-stage renal disease (ESRD) (1, 2). In recent years, the composition ratio of dialysis complications has changed with the advancement of HD technology, including the improvement of dialysis machines, the improvement of dialysis water quality, the application of dialyzers with good membrane biocompatibility, etc. (3, 4). However, acute hemodynamic changes during dialysis are still common, mainly in the form of intradialytic hypotension and intradialytic hypertension (5, 6). Poor BP (BP) control is a common complication in patients with ESRD-HD and an independent risk factor for patient prognosis. Unlike the control of BP in general patients, HD patients need to control BP not only during HD but also during the fluctuation of BP during HD. However, some studies (6, 7) have shown that intra-dialysis hypotension and intra-dialysis hypertension caused by fluctuations in BP during dialysis can increase the incidence of cardiovascular time and mortality in HD patients. Therefore, the pathogenesis of hypotension and hypertension during HD, if fully understood and effectively controlled, may have a significant impact on the long-term survival and quality of life of HD patients.

Studies (8, 9) have found that endothelin (ET-1) and nitric oxide (NO) may be involved in the onset and progression of BP changes during dialysis in HD patients. ET-1 is the most potent vasoconstrictor substance identified, and it is widely distributed in cardiovascular and neural tissues, and the increased peripheral vascular resistance in essential hypertension may be related to its excessive production (10). NO is a gaseous biological messenger molecule that is widely involved in a variety of physiological and pathological processes in the body, and is considered to be a regulatory mediator in the regulation of vascular tone and maintenance of BP stability (11, 12). The aim of this study was to investigate the relationship between the expression of serum ET-1 and NO levels and BP changes in patients with different degrees of BP in ESRD treated with HD after action endovenous fistula surgery and their correlation.

MATERIALS AND METHODS

Study Subjects

30 patients who underwent regular hemodialysis after arteriovenous endovascular fistula in our hemodialysis center from January 2020 to December 2021 were selected. Medical history, physical examination, X-ray examination, electrocardiogram, echocardiogram, and relevant laboratory tests were taken at the time of enrollment. A mercury column sphygmomanometer was used to measure BP in the right upper arm of patients, and 30 patients with ESRD were divided into three groups according to the changes in BP during HD, with 10 patients in each group: patients with stable BP during HD were group I; patients with hypotension during HD were group II, mainly manifested by a sudden drop in systolic blood pressure (SBP) with symptoms, SBP <90 mmHg or SBP drop ≥20 mmHg, or at least 50% of the dialysis treatment process showed systolic blood pressure <90 mmHg or SBP decrease ≥20 mmHg; hypertension during HD was the Group III, which mainly showed normal blood pressure or hypertension before dialysis, but the mean arterial pressure (MAP) increased more than 15 mmHg during dialysis compared with that before dialysis.

Inclusion Criteria

Patients with ESRD aged >18 years, dialysis age >3 months, 2–3 dialysis sessions per week, 3.5–4 h per session. Combined with sleep apnea syndrome, insulin resistance syndrome and other diseases that more significantly affect ET-1 and NO levels.

Exclusion Criteria

Patients with tumors; patients with failed kidney transplants; patients with abnormal mental behavior; patients with 2 interruptions or transfers from dialysis treatment; patients with acute complications such as infections and bleeding.

Research Methodology

Treatment

All MHD patients were dialyzed 2 to 3 times a week for 4 h each time with Baxter CTl90 dialyzer, Fresenius 4008B or 4008S dialysis machine with blood flow rate of 250 mL/min and dialysate flow rate of 500 mL/min, normal heparin anticoagulation and bicarbonate dialysis.

Clinical Data were Collected

Including age, sex, primary disease, BP, dialysis time, previous cardiovascular disease, and biochemical indexes [included white blood cells (WBC), hemoglobin (Hb), platelets (PLT), serum albumin (SAB), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and parathyroid hormone (PTH)]. In ESRD patients, the age of dialysis (months), type of dialyzer used, ultrafiltration volume, BP Pre-dialysis (Pre-D), BP at l, 2, and 3 h of dialysis, and BP at the end of dialysis (Post-D) were recorded, and the brachial BP on the non-endovascular side was measured. Each measurement was taken 3 times and the mean value was taken.

Blood Specimen Collection

The blood specimens were collected at Pre-D, 2 h of dialysis (Mid-D, 2h-D) and at Post-D, respectively, by lowering the blood flow rate to 50 ml/min and taking blood specimens at the arterial end of the dialysis line after stopping ultrafiltration and ineffective dialysis for 1 to 2 min.

Blood Pressure Measured and Recorded

Patients in both groups were measured by dedicated medical staff with an electronic sphygmomanometer in a lying position with the measuring arm at the same level as the heart and the sphygmomanometer. 3 groups of dialysis patients rested for 10 min before dialysis, and the blood pressure was measured Pre-D, at 1 h of dialysis (1 h-D), at 2 h-D, at 3 h of dialysis (3h-D) and at Post-D on the upper arm without fistula. MAP = (SBP - diastolic blood pressure)/3 + diastolic blood pressure.

Laboratory Tests

blood samples were drawn from the arterial end of HD patients at Pre-D, at Mid-D and at Post-D. The detection of NO was performed by chemiluminescence method, and the kit was purchased from Nanjing Jiancheng Institute of Biological Engineering; the detection of ET-l was performed by enzyme-linked immunoassay, and the kit was purchased from ADL, USA. The reference range of normal value of NO: (39.00 ± 11.00) μmol/L; the reference range of normal value of ET-1: (50.8 ± 7.58) pg/mL.

Statistical Methods

SPSS 22.0 statistical software was used to analyze the data, Prism 7.0 was used to create the statistical graphs. Count data were expressed as rates (%) with a chi-square test. The measurement data were described as mean ± standard deviation (Mean, SD) using t or F test. correlation between ET-1 and MAP was analyzed using pearson correlation analysis. $\alpha = 0.05$ was the test level.

RESULTS

Comparison of General Data Between HD Different BP Patient Groups

No statistically significant differences ($p > 0.05$) were found between group I, group II and group III in terms of general information such as gender, age, dialysis age, dry weight, water loss and primary disease (**Table 1**).

Comparison of Clinical and Biochemical Indexes Among Group I, Group II and Group III

Baseline values of serological markers such as WBC, Hb, PLT, SAB, TG, TC, HDL, LDL, and PTH were collected for comparison in the three groups. The results showed that none of the differences in clinical biochemical indices among group I, group II and group III were statistically significant ($p > 0.05$) (**Figure 1**).

Comparison of Serum NO and ET-1 Levels at Pre-D, Mid-D and Post-D in Group I, Group II and Group III

Serum ET-1 and NO levels at Pre-D were significantly higher than normal in all three groups. Univariate analysis of ET-1 and NO levels Pre-D in the three groups showed that the differences were not statistically significant ($p > 0.05$). As dialysis progressed and ended, the NO levels in the three groups gradually decreased and were significantly different from those Pre-D ($p < 0.05$); the ET-1 levels in group III gradually increased and were significantly different from those Pre-D ($p < 0.05$), while the increasing trend of ET-1 levels in group I and group II was not significant ($p > 0.05$) (**Table 2** and **Figure 2**).

Comparison of MAP During HD in Group I, Group II and Group III

The difference of MAP at Pre-D in the three groups was not statistically significant ($p > 0.05$). As dialysis proceeded, the increasing trend of MAP in group I was not significant ($p > 0.05$); MAP in group II showed a gradually decreasing trend, and the MAP Post-D was significantly lower than that Pre-D ($p < 0.05$); MAP in group III showed an increasing trend, and the MAP Post-D was significantly higher than that Pre-D ($p < 0.05$) (**Table 3** and **Figure 3**).

Correlation Analysis of ET-1 Levels and MAP at 2h-D (Mid-D) in Group III

By compared and analyzed **Figures 2**, **3** we founded that both ET-1 levels and MAP levels showed an increasing trend during dialysis in group III. Therefore, we further analyzed the correlation between ET-1 and MAP in group III, and the showed that the level of ET-1 at Mid-D in group III was significantly positively correlated with MAP ($r = 0.847$, $p = 0.002$) (**Figure 4**).

TABLE 1 | Comparison of general data between HD different BP patient groups.

Information		Group I ($n = 10$)	Group II ($n = 10$)	Group III ($n = 10$)	p value
Male (%)		5 (50.00)	4 (40.00)	6 (60.00)	0.670
Age (years; Mean, SD)		65.49 ± 10.21	66.00 ± 8.51	66.33 ± 7.24	0.977
Dialysis age (months; Mean, SD)		60.46 ± 26.34	51.23 ± 25.20	46.35 ± 20.16	0.665
Dry weight (kg; Mean, SD)		62.81 ± 9.80	59.76 ± 7.62	58.77 ± 10.20	0.603
Water loss (kg)		2.56 ± 1.01	2.62 ± 0.33	2.45 ± 0.87	0.889
Primary disease	Diabetes mellitus (%)	0 (0.00)	1 (10.00)	4 (40.00)	0.185
	Chronic nephritis (%)	6 (60.00)	7 (70.00)	2 (20.00)	
	Hypertensive nephropathy (%)	2 (20.00)	1 (10.00)	2 (20.00)	
	Other (%)	2 (20.00)	1 (10.00)	2 (20.00)	

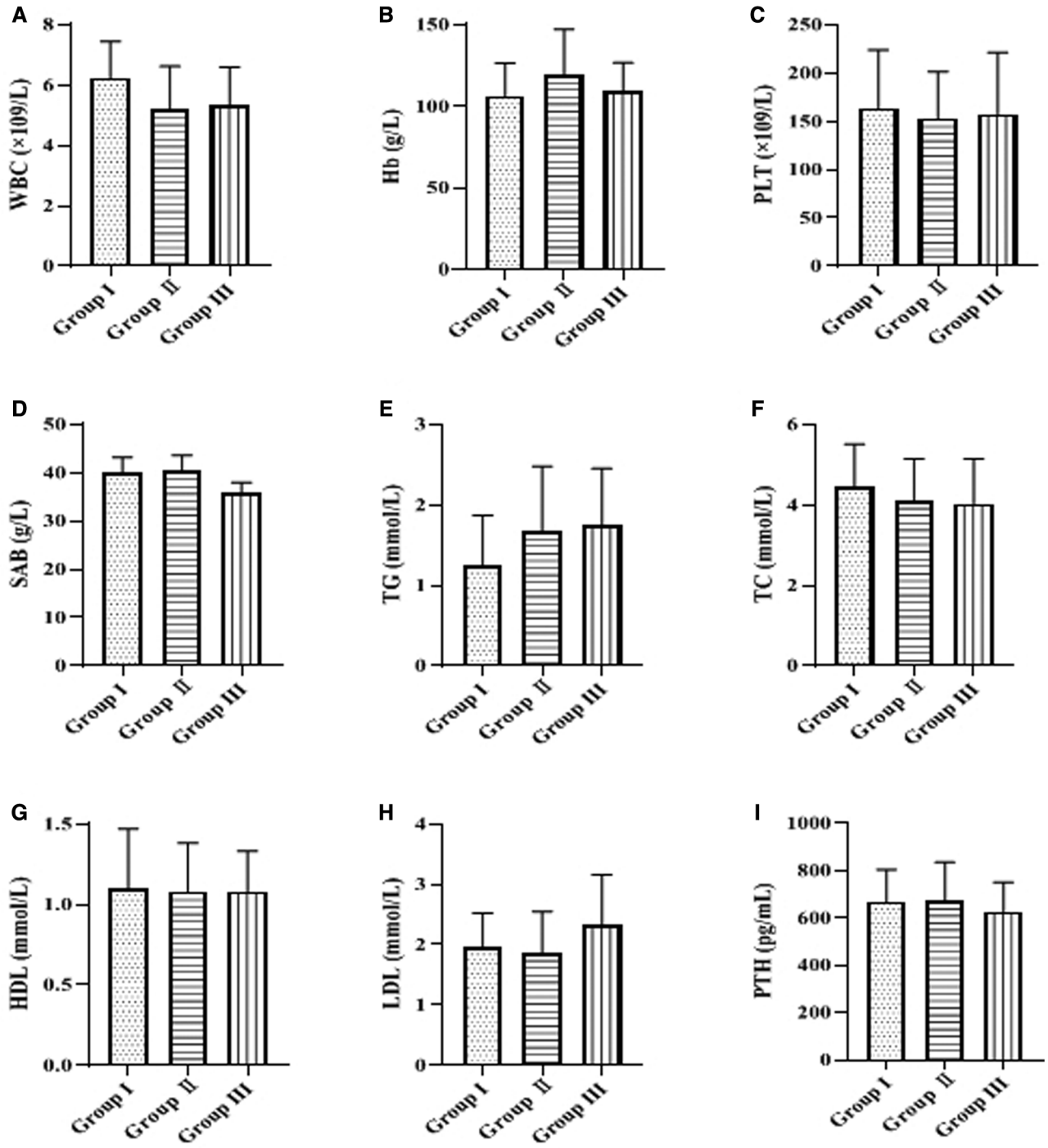

FIGURE 1 | Comparison of clinical and biochemical indexes. The levels of white blood cells (WBC), hemoglobin (Hb), platelets (PLT), serum albumin (SAB), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and parathyroid hormone (PTH) are indicated in descending order from **A** to **I**.

DISCUSSION

With the improvement of socio-economic level and people's living conditions in China, more and more ESRD patients can choose continuous hemodialysis (MHD) as an alternative therapy. However, intradialytic hypotension and intradialytic hypertension due to fluctuations in BP during dialysis in patients with MHD are important risk factors for

cardiovascular and cerebrovascular complications, morbidity and mortality, and all-cause mortality in dialysis patients (14, 15). Recent studies (16, 17) have shown that intradialytic hypotension is associated with patient prognosis and is an independent risk factor for high hospitalization rates in MHD patients, as well as reduced survival; intradialytic hypertension is an independent risk factor for increased mortality in MHD patients. There are numerous studies on the mechanisms of combined hypertension on dialysis, while the main mechanism for the occurrence of blood pressure fluctuations during dialysis is not clear (18). Meanwhile, the smooth control of blood pressure during dialysis in MHD patients has great significance for improving the prognosis of dialysis patients and improving the quality of survival of dialysis patients.

TABLE 2 | Comparison of serum NO and ET-1 levels at Pre-D, Mid-D and Post-D in group I, group II and group III (Mean, SD).

Indicators/groups	ET-1(pg/mL)	NO (μmol/L)
Group I ($n = 10$)		
Pre-D	142.26 ± 38.34	136.50 ± 40.81
Mid-D	124.37 ± 36.54	69.16 ± 20.28*
Post-D	140.30 ± 41.57	54.23 ± 8.04*,**
Group II ($n = 10$)		
Pre-D	153.86 ± 32.26	160.18 ± 43.65
Mid-D	147.60 ± 17.53	81.20 ± 25.48*
Post-D	140.34 ± 40.25	62.19 ± 17.20*
Group III ($n = 10$)		
Pre-D	120.23 ± 42.18	155.34 ± 46.71
Mid-D	170.62 ± 20.87*	82.06 ± 20.83*
Post-D	165.42 ± 44.58*	57.26 ± 10.2*,**

*Note: Compared with the same group at Pre-D, *$p < 0.05$; compared with the same group at Mid-D, **$p < 0.05$.*

It is now believed that vascular endothelial injury is an important pathophysiological basis for cardiovascular disease, and in chronic kidney disease, endothelial dysfunction is often seen in the early stages of disease development, with patients commonly having abnormal endothelial function (19). Studies (20–22) have shown that vascular endothelial function is closely related to the dynamic levels of NO and ET-1, where ET-1 acts on ETA receptors in smooth muscle cells to promote calcium ion release and enhance extracellular calcium ion inward flow, resulting in strong vasoconstriction, which leads to an increase in SVR. NO is an important vasodilator with the opposite effect of ET-1, which is widely distributed in the body and can modulate vascular tone, inhibit platelet

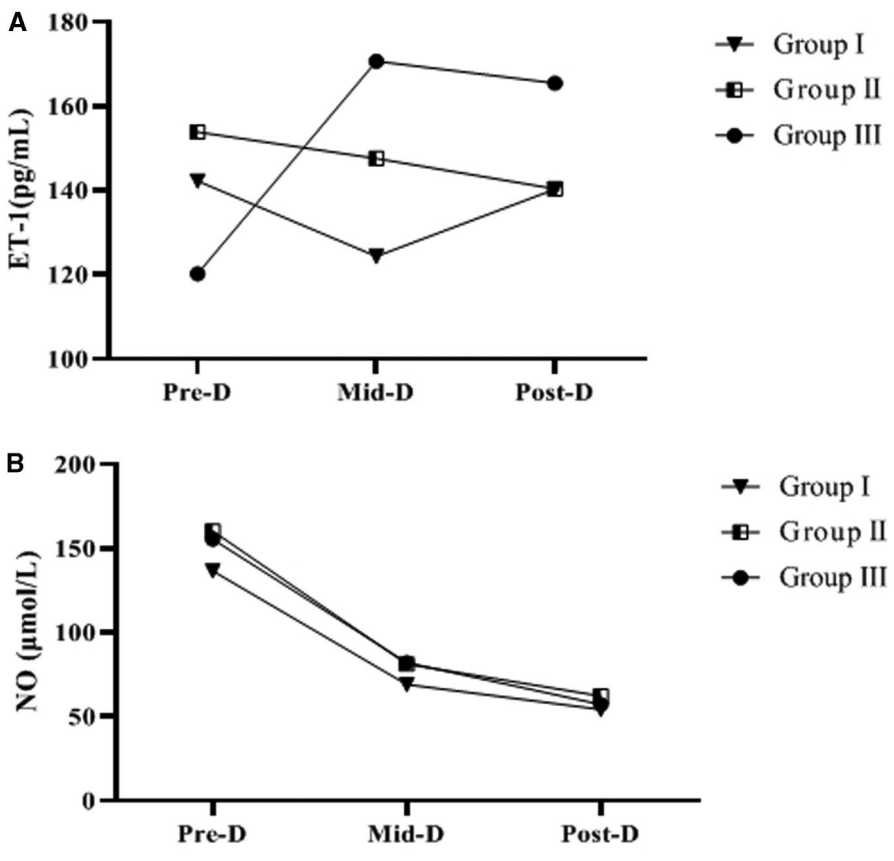

FIGURE 2 | Trends of ET-1, NO levels in the three groups. **A** indicates the trend in ET-1 levels. **B** is the change trend of NO level.

TABLE 3 | Comparison of MAP during HD in group I, group II and group III (Mean, SD).

Time/group	Pre-D	1 h-D	2 h-D	3 h-D	Post-D
Group I ($n = 10$)	95.23 ± 12.28	100.06 ± 13.25	102.36 ± 11.58	98.27 ± 12.14	99.87 ± 10.56
Group II ($n = 10$)	108.30 ± 14.50	101.25 ± 12.77	93.23 ± 10.18	91.56 ± 10.26	90.24 ± 11.31*
Group III ($n = 10$)	98.70 ± 13.68	103.24 ± 15.16	109.58 ± 14.73	116.50 ± 13.29	122.06 ± 15.14*,**,***

*Note: Compared with the same group at Pre-D, *$p < 0.05$; compared with group I at Post-D, **$p < 0.05$; compared with group II at Post-D, ***$p < 0.05$.*

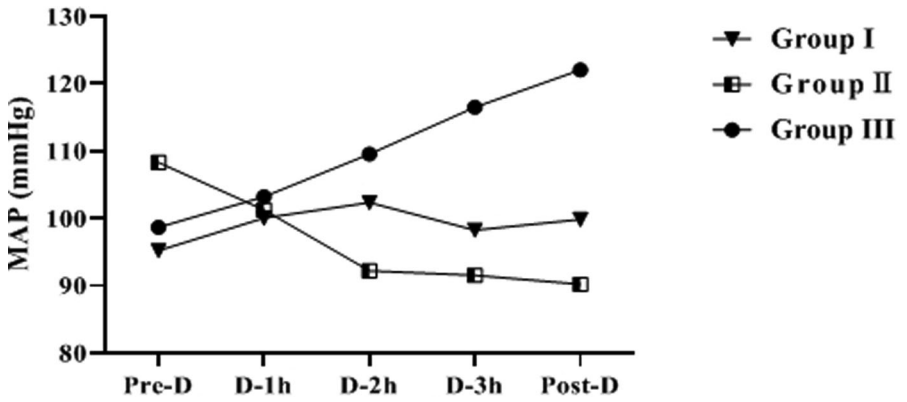

FIGURE 3 | Trend of MAP changes during dialysis in 3 groups.

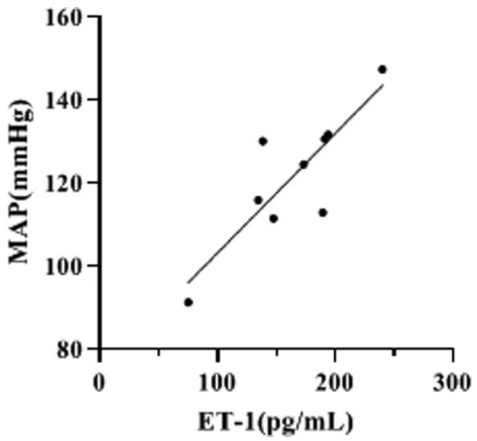

FIGURE 4 | Correlation analysis of ET-1 levels and MAP at 2 h-D (Mid-D) in group III.

monthly endothelial adhesion and thrombosis to prevent vascular endothelial disorders and atherosclerosis (23, 24).

In this study, serum NO and ET-1 levels were found to be significantly higher than normal in patients with MHD, which is consistent with many literature reports (25–27). Meanwhile, this study found that serum NO levels in all three groups showed a gradual decrease during dialysis, and there were statistical differences between the three groups before and after dialysis when comparing serum NO levels themselves. The consideration may be related to the smaller molecular weight and stronger dispersion properties of NO, which is gradually removed by dialysis during the dialysis process and the amount removed increases with time, etc. However, we also found no statistical difference in NO levels in group II dialysis compared with the post-dialysis group, while the other two groups were statistically different, suggesting that the occurrence of hypotension in dialysis may still be related to NO levels. The effect of NO is not only to achieve peripheral vasodilation, but also to inhibit sympathetic nerve endings, to inhibit the release of catecholamines, and to inhibit their biological activity, which can inhibit autonomic function and can act synergistically with prostaglandins to cause a drop in blood pressure in patients on dialysis (28, 29). However, this study did not find any significant correlation between changes in NO levels before and after dialysis and changes in MAP, considering that the reason is mainly that NO, as a small molecule, can be removed by hemodialysis. In addition, this study also found that the changes in serum ET-1 levels at Pre-D and Post-D in group I and group II were not significant, but the ET-1 levels in group III were significantly higher at Mid-D than Pre-D and were still higher than the Pre-D levels at Post-D ($p < 0.05$), showing the same change trend as their MAP changes. The correlation analysis of MAP and ET-1 in dialysis showed a significant correlation ($p < 0.05$), which suggests that serum ET-1 levels may be associated with the development of hypertension in dialysis.

In conclusion, serum ET-1 and NO levels were significantly higher than normal in MHD patients after arteriovenous fistula surgery, and both ET-1 and NO levels were changing during dialysis, and there may be a link between their changes and blood pressure changes. suggesting that the blood

pressure fluctuations that occur during dialysis in MHD patients may be related to endothelial cell dysfunction. As this study was a retrospective analysis, the conclusions obtained need to be supported by prospective studies with larger 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 author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by our medical ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YL and HL are the mainly responsible for the writing. YL is mainly responsible for data analysis. HL and YS are responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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Application of e-PTFE Frontalis Suspension in the Treatment of Congenital Ptosis in Children

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Purpose: Analysis of the value of expanded polytetrafluoroethylene (e-PTFE) frontalis suspension applied to children with congenital ptosis.

Methods: Eighty clinical cases of children with congenital ptosis from October 2019 to October 2021 were randomly selected from our hospital. All children were divided into the observation group ($n = 44$) treated with e-PTFE frontalis suspension and the control group ($n = 36$) treated with frontalis flap suspension according to the treatment procedure. Comparison of eyelid condition [palpebral fissure height, margin reflex distance (MRD), eyelid closure time], ocular surface status [corneal fluorescein staining (CFS) score, tear film breakup time (TBUT), surgical eye lacrimal river height (LRH), sehirmer test I (STI)], frontal muscle strength of affected side, cosmetic results and complications in both groups at 1, 6 and 12 months postoperative follow-up.

Results: At 1, 6 and 12 months after surgery, there was no significant difference in terms of palpebral fissure height and MRD between both groups ($p > 0.05$); After surgery, the eyelid closure time was shorter in the observation group than in the control group ($p < 0.05$). At 1, 6 and 12 months after surgery, the CFS scores were lower in the observation group than in the control group ($p < 0.05$); At 6 and 12 months after surgery, the TBUT was longer and the surgical eye LRH was higher in the observation group than in the control group ($p < 0.05$); At 1, 6, and 12 months after surgery, there was no significant difference in STI between both groups ($p < 0.05$). At 1, 6 and 12 months after surgery, the frontal muscle strength of affected side was higher in the observation group than in the control group ($p < 0.05$). At 1, 6, and 12 months after surgery, there was no significant difference in cosmetic results between both groups ($p > 0.05$). The overall complication rate in the observation group (6.82%) was lower than that in the control group (25.00%) ($p < 0.05$).

Conclusion: The surgical and cosmetic results of e-PTFE frontalis suspension and frontalis flap suspension applied to congenital ptosis are comparable, but the former has the advantage of faster postoperative recovery, better ocular surface status, less frontali muscle strength damage and fewer complications.

Keywords: congenital ptosis, e-PTFE, frontalis suspension, frontalis flap suspension, children

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INTRODUCTION

With the exclusion of the effects of the frontalis muscle, ptosis can be diagnosed when the upper eyelid margin covers the upper edge of the cornea by more than 2 mm when the eyes are open and level-viewing, which is a common eyelid deformity caused by weak or defective upper eyelid muscle development or oculomotor and cervical sympathetic insufficiency (1, 2). The child has partial or complete loss of levator muscle function, and partial or complete ptosis of the upper eyelid obscuring the pupil. In mild cases, it affects the appearance and has a negative impact on psychological and personality development during the growth of the affected child; in severe cases, the pupil is obscured, affecting visual development and leading to form deprivation amblyopia (prevalence up to 20%–30%) with or without refractive error, which can also lead to abnormal development of the neck muscles and cervical spine (3, 4). Especially in patients with monocular disease, the degree of amblyopia is deeper and the correction is more difficult, and active surgical treatment, refractive correction, and amblyopia treatment are required during the critical period of visual development (3–6 years old) of children (5).

Among the current domestic and international corrective procedures, frontalis suspension is the generally accepted type of surgery. It moves the pedicled frontalis tissue flap directly down the eyelid to fix and lift the upper lid. Compared with the clinically common levator muscle shortening, the frontalis muscle flap has better elasticity and greater muscle strength, which is conducive to the adjustment of the tarsal radian in clinical operations, and the postoperative aesthetic effect of patients is more durable, but the application effect of different materials during the operation is still controversial (6). Expanded polytetrafluoroethylene (e-PTFE) is a new type of medical polymer material with good biocompatibility, convenient material extraction, good flexibility, high strength, good operating feel and minimally invasive effect (7, 8). Its unique microporous structure allows human tissue cells and blood vessels to grow in and form tissue connections without causing tissue reactions. It is now widely used in pediatric surgery to adapt to the growth of children's tissues (9). This study compares the near and long-term efficacy and safety of e-PTFE frontalis suspension with frontalis flap suspension in children with congenital ptosis, with the aim of providing a relevant reference for the use of e-PTFE frontalis suspension in children with congenital ptosis.

MATERIALS AND METHODS

Research Object

Eighty clinical cases of children with congenital ptosis from October 2019 to October 2021 were randomly selected from our hospital. All children were divided into the observation group ($n = 44$) treated with e-PTFE frontalis suspension and the control group ($n = 36$) treated with frontalis flap suspension according to the treatment procedure. Inclusion criteria: age 1–6 years old; Meet the 2017 "Expert Consensus on Diagnosis and Treatment of Ptosis" (10) for the diagnosis and classification criteria of moderate and severe ptosis: When children open their eyes and look straight ahead, those with ptosis covering more than 4–6 mm above the cornea and the amount of ptosis >2–≤4 mm are considered moderate; those with ptosis that cover the upper part of the cornea by >6 mm and the amount of ptosis >4 mm are considered severe; congenital ptosis; unilateral disease; those who had completed routine ophthalmic examination before surgery; preoperative Bell's sign positive; those who presented with symptoms such as visual impairment and pupil narrowing; those with poor upper eyelid levator function or whose upper eyelid levator structure had been damaged; the family members of the children all signed and agreed to obey the treatment. Exclusion criteria: bilateral disease; ptosis caused by acquired factors, such as surgery, trauma, tumor invasion, levator aponeurosis hole or rupture, oculomotor nerve or oculomotor nerve branch paralysis, myasthenia gravis, myotonia syndrome, progressive muscular dystrophy; persons with other ophthalmic diseases such as corneal disease, glaucoma, ocular trauma, extensive extraocular muscle fibrosis syndrome, etc.; persons with systemic diseases; persons with abnormal intellectual development, mental disorders, etc. that prevented them from cooperating with the study. Comparing the general conditions of age, gender, enrolled affected eyes, and degree of ptosis in both groups, $p > 0.05$, which available for comparative study, as shown in **Table 1**.

Surgery Methods

Both groups of children underwent routine ophthalmological examination after hospitalization. Including fundus, anterior segment and refractive status, frontalis muscle strength, eyelid closure, levator muscle strength, margin reflex distance (MRD), Bell's sign, etc. on the basis of it.

In the observation group, e-PTFE frontalis suspension was applied to treat: The child was placed supine, and after successful general anesthesia with sevoflurane inhalation, a double eyelid incision was made at 2–3 mm of skin from the upper eyelid margin, and a 0.5 cm skin incision was made on the inner and outer 1/3 of the brow arch and 2 cm above the brow arch. The subcutaneous tissue and the orbicularis oculi muscle were separated from the incision to expose the tarsal plate. The e-PTFE material was secured to the tarsus 3 mm from the upper lid margin using 6-0 polypropylene synthetic sutures. A 0-gauge curved needle was used to tract the e-PTFE material through a subcutaneous tunnel to reach the deeper tissue under the arch of the eyebrow. The height of the eyelid was adjusted, the suspension material was ligated and buried under the frontalis muscle, and Frost protective suture was made on the lower eyelid margin.

In the control group, the frontalis flap suspension was applied to treat: The child was placed supine, and after successful general anesthesia with sevoflurane inhalation, a double eyelid line was drawn at a distance of 2–3 mm from the eyelid margin. The skin at the double eyelid line was incised, separated from the front and upward of the orbital septum under the orbicularis oculi muscle, the frontalis muscle flap was pulled down, and 3-needle mattress sutures were placed with tarsus by 4-0 mousse thread. The height of the eyelid margin was adjusted and the suture was ligated, and the Frost suture was placed on the lower eyelid.

In both groups, pressure bandages were applied to the operated eye and forehead to prevent bleeding and hematoma,

TABLE 1 | Comparison of general conditions of two groups.

Itmes	Observation group ($n = 44$)	Control group ($n = 36$)	t/χ^2 value	p value
Age ($\bar{x} \pm s$, years old)	3.64 ± 1.01	3.61 ± 0.96	0.135	0.893
Gender (n, %)			0.013	0.910
Male	25 (56.82)	20 (55.56)		
Female	19 (43.18)	16 (44.44)		
Enrolled affected eyes (n, %)			0.037	0.848
Left eye	35 (79.55)	28 (77.78)		
Right eye	9 (20.45)	8 (22.22)		
Degree of ptosis (n, %)			0.080	0.777
Moderate	28 (63.64)	24 (66.67)		
Severe	16 (36.36)	12 (33.33)		

and antibiotic eye ointment was applied to the conjunctiva. The corneal and postoperative swelling were observed after 24 h, and any problems discovered were treated promptly and the pressure bandage was removed after 48 h. Eye drops were used continuously during the day, and chlortetracycline eye ointment was applied at night. The sutures were removed 7 d after surgery, and the frontalis muscle exercise was performed.

Observation Index

(1) Comparison of eyelid status, including palpebral fissure height, MRD, and eyelid closure time, between the two groups of children at 1, 6, and 12 months postoperative follow-up.

(2) Comparison of the ocular surface status of children in the two groups at 1, 6 and 12 months postoperative follow-up. Including corneal fluorescein staining (CFS) score (the cornea was divided into 4 quadrants, each quadrant was assigned a score of 0–3 according to the no, light, moderate and severe degree of staining, with a total score of 0–12), tear film breakup time (TBUT) (after fluorescein staining of the tear film, the subject looked forward flatly and kept the eyes open after blinking several times, under the cobalt blue light of the slit lamp microscope, the time interval for the appearance of the first dry spot on the tear film surface was observed with a wide slit lamp strip, that is, the tear film breakup time, the normal value is 10–45 s), surgical eye lacrimal river height (LRH) (after fluorescein staining, the tear level at the junction of the light band projected on the surface of the cornea and conjunctiva and the light band of the lower eyelid margin under the slit lamp microscope, the normal tear river section is convex, with a height of 0.3–0.5 mm), sehirmer test I (STI) (5 min wet length and the time to 10 mm wet length were recorded using Whatmann No. 41 filter paper provided by BauschLomb Inc., USA).

(3) Comparison of the frontal muscle strength of the affected side in the two groups of children at 1, 6 and 12 months postoperative follow-up. Assessment by manual muscle testing (MMT), verbal instructions and actions, such as frowning, were demonstrated to the child, the completion of the expression muscle was observed and compared with the normal side. The MMT muscle strength grading criteria are shown in **Table 2**.

TABLE 2 | MMT muscle strength grading criteria.

Grade	Criteria
Grade 0	No signs of muscle contraction
Grade 1	Slight signs of muscle contraction
Grade 2	The range of motion is 1/4 of the normal side
Grade 3	The range of motion is 1/2 of the normal side
Grade 4	Muscle contraction is basically close to normal but slightly asymmetrical to the normal side
Grade 5	Normal muscle contraction and symmetry with normal side

TABLE 3 | Cosmetic results evaluation form.

Cosmetic results	Grade	Score	Criteria
Double eyelid incision	Very satisfied	3	Symmetrical, no elimination
	Satisfied	2	Partial disappearance of double eyelid to form asymmetry, but acceptable
	Poor	1	Complete disappearance of double eyelid or unacceptable asymmetry
Eyelid shape	Very satisfied	3	Natural symmetry, the radian is satisfied without peaks
	Satisfied	2	Moderately spiky or flat eyelid, satisfactory to both parent and doctor
	Poor	1	Eyelid appearance needs to be reworked
Double eyelid height symmetry	Very satisfied	3	Bilateral eyelid height difference ≤1 mm
	Satisfied	2	1 mm <Bilateral eyelid height difference ≤2 mm
	Poor	1	Bilateral eyelid height difference >2 mm

(4) Comparison of the cosmetic results of the two groups of children at 1, 6 and 12 months postoperative follow-up. Including three test items: double eyelid incision, eyelid shape, and double eyelid height symmetry, the specific grading standards and scores of each item are shown in **Table 3**.

(5) Comparison of postoperative complications in the two groups of children, including exclusion reactions (nodules, infections, granulomas), upper eyelid inversion trichiasis, exposure keratitis, and incomplete eyelid closure.

Statistical Methods

SPSS 22.0 software was applied, and the measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$) 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 Eyelid Status Between Two Groups in Each Month After Surgery

As shown in **Figure 1**, at 1, 6 and 12 months after surgery, there was no significant difference in terms of palpebral fissure height and MRD between both groups ($p > 0.05$); After surgery, the eyelid closure time was shorter in the observation group than in the control group ($p < 0.05$).

Comparison of Ocular Surface Status Between Two Groups in Each Month After Surgery

As shown in **Figure 2**, at 1, 6 and 12 months after surgery, the CFS scores were lower in the observation group than in the control group ($p < 0.05$); at 6 and 12 months after surgery, the TBUT was longer and the surgical eye LRH was higher in the observation group than in the control group ($p < 0.05$); at 1, 6, and 12 months after surgery, there was no significant difference in STI between both groups ($p < 0.05$).

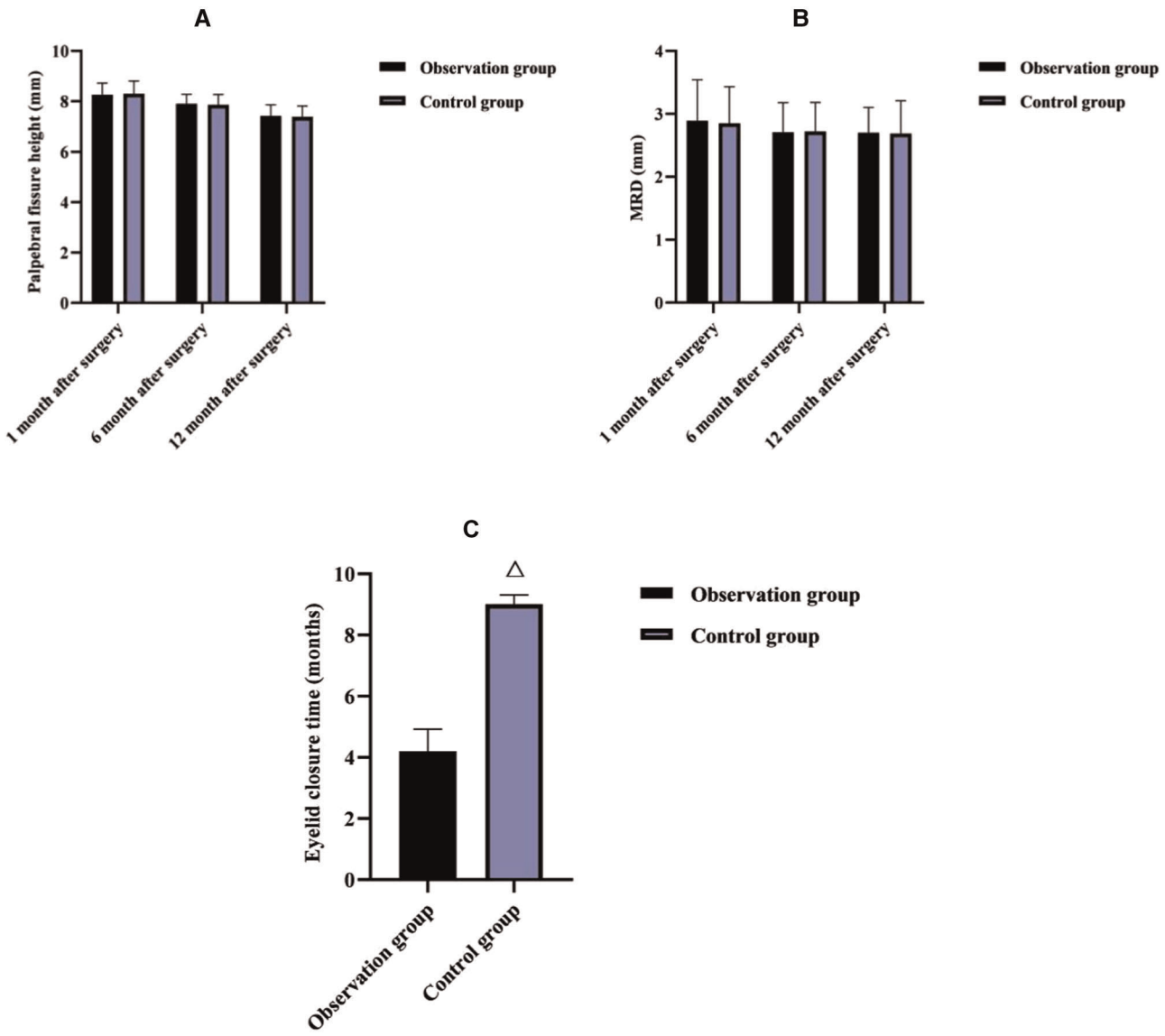

Figure 1 | Comparison of eyelid status between two groups in each month after surgery ($\bar{x} \pm s$). Note: (**A**) Palpebral fissure height (mm). (**B**) MRD (mm). (**C**) Eyelid closure time (months). Note: Compared with the observation group, $^{\triangle}p < 0.05$.

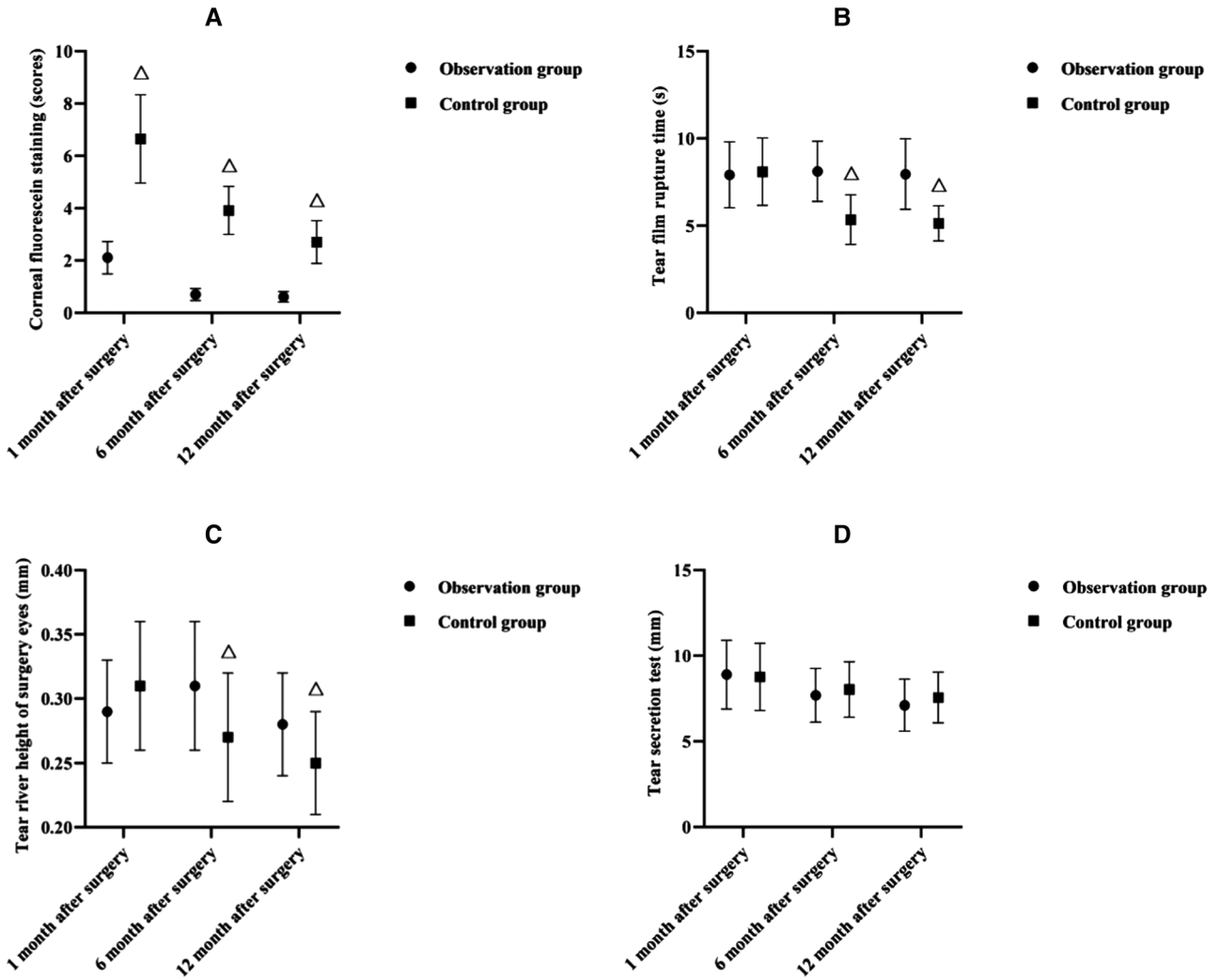

FIGURE 2 | Comparison of ocular surface status between two groups in each month after surgery ($\bar{x} \pm s$). Note: (**A**) Corneal fluorescein staining (scores). (**B**) Tear film rupture time (s). (**C**) Tear river height of surgery eyes (mm). (**D**) Tear secretion test (mm). Note: Compared with the observation group at the same time, $^{\triangle}p < 0.05$.

Comparison of Frontal Muscle Strength of Affected Side Between Two Groups in Each Month After Surgery

As shown in **Figure 3**, at 1, 6 and 12 months after surgery, the frontal muscle strength of affected side was higher in the observation group than in the control group ($p < 0.05$).

Comparison of Cosmetic Effect Between Two Groups in Each Month After Surgery

As shown in **Figure 4**, at 1, 6, and 12 months after surgery, there was no significant difference in cosmetic results between both groups ($p > 0.05$).

Comparison of Postoperative Complication Rates Between Two Groups

As shown in **Figure 5**, after surgery, in the observation group, one case (2.27%) of upper eyelid inversion trichiasis, one case (2.27%) of exposure keratitis, and one case (2.27%) of incomplete eyelid closure occurred; in the control group, two cases (5.56%) of exclusion reaction, three cases (8.33%) of upper eyelid inversion trichiasis, two cases (5.56%) of exposure keratitis, and two cases (5.56%) of incomplete eyelid closure occurred. The overall complication rate in the observation group (6.82%) was lower than that in the control group (25.00%) ($p < 0.05$).

DISCUSSION

Congenital ptosis, especially moderate and severe ptosis, affects children's visual function and aesthetics, and also interferes with their normal quality of life (11, 12). Hypoplasia of the levator palpebral is the main pathogenesis in congenital cases, and may also be associated with dysgenesis or insufficiency of the central and peripheral nerves which innervate the levator palpebral (13). Early surgical correction to restore the visual

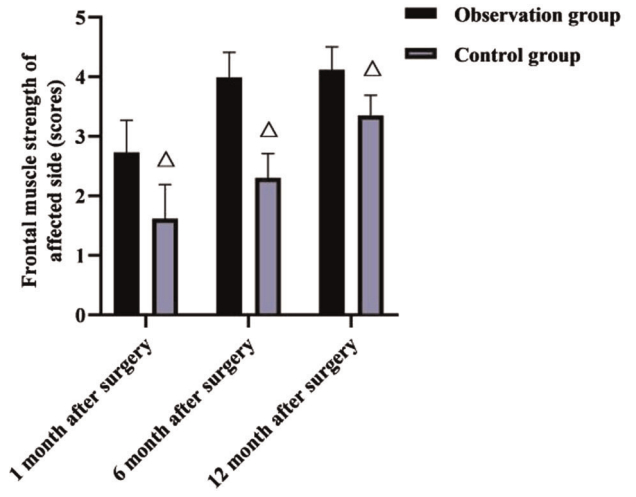

FIGURE 3 | Comparison of frontal muscle strength of affected side between two groups in each month after surgery ($\bar{x} \pm s$, score). Note: Compared with the observation group at the same time, $^{\triangle}p < 0.05$.

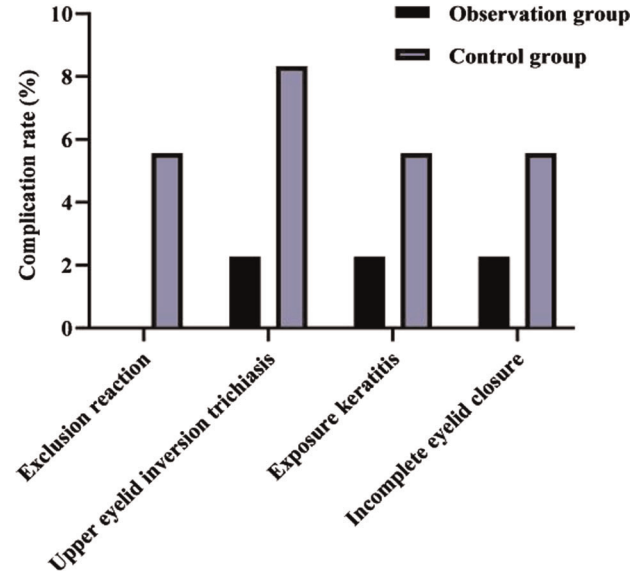

FIGURE 5 | Comparison of postoperative complication rates between two groups (n, %).

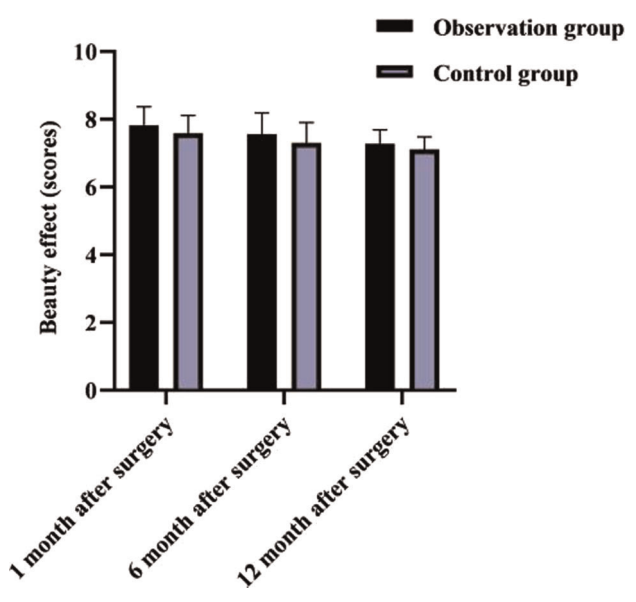

FIGURE 4 | Comparison of cosmetic effect between two groups in each month after surgery ($\bar{x} \pm s$, score).

function of children and improve the quality of life of children is the main treatment strategy at present, and the surgical method used has become a hot topic of clinical research. According to consensus (10), for moderate ptosis, because the pupil can be partially or completely exposed, form deprivation amblyopia is less likely to occur and can be surgically corrected with local anesthesia when the child is older, but considering psychosocial factors, surgery is recommended at preschool age, i.e., 3 to 5 years; for severe ptosis in one eye, where the pupil is completely obscured and the child looks with the head up, surgical correction is recommended around 1 year of age to prevent form-deprivation amblyopia and spinal developmental problems. In this study, 80 clinical cases of moderate to severe unilateral congenital ptosis between the ages of 1 and 6 years were selected for comparative analysis; all children had ptosis with poor muscle strength of the levator palpebral and were therefore treated with suspension surgery using the strength of the frontalis muscle.

The present results showed that at 1, 6, and 12 months postoperatively, there was no significant difference in the comparison of palpebral fissure height and MRD between the two groups, but postoperatively, the eyelid closure time was shorter in the observation group than in the control group. It is suggested that e-PTFE frontalis suspension is more effective than frontalis flap suspension in improving eyelid closure and accelerating upper lid function recovery in children with moderate to severe congenital ptosis. It is considered that the e-PTFE material is inherently elastic and allows for moderate contraction and extension of the eyelid, thus reducing the time required for eyelid closure (14). CFS is a direct measure of the state of the ocular surface epithelium (15); TBUT is a measure of tear film stability and is related to tear secretion, tear composition, and ocular surface status (16); LRH is an important indicator to assess the function of tear secretion and should not be less than 0.3 mm normally (17); STI is commonly used for the assessment of tear secretion function and is a test that is closely related to the tear film (18). In this result, at 1, 6 and 12 months after surgery, the CFS scores were lower in the observation group than in the control group; at 6 and 12 months after surgery, the TBUT was longer and the surgical eye LRH was higher in the observation group than in the control group; at 1, 6, and 12 months after

surgery, there was no significant difference in STI between both groups. The above indicates that e-PTFE frontalis suspension contributes to a reduction in the degree of postoperative local swelling, and interferes less with the ocular surface status of children with congenital ptosis, but there is no difference in the effect of the two surgical methods on the secretion of tears in children. Considering the reason, the eyelid is easy to swell after frontalis flap suspension in children with congenital ptosis, which leads to difficulty in closing the eyelid, disturbance of blink movement, and dryness and discomfort due to lack of protection of the cornea for a long time; in contrast, after e-PTFE frontalis suspension, the fibroblasts of the child can gradually infiltrate into and around the microporous structure of the e-PTFE patch within 14–28 days after implantation, and their secreted collagen fibrous capsules cover the gaps in the patch, which can avoid swelling of the eyelid to improve the ocular surface status (19).

The frontalis muscle, an important muscle tissue for raising the upper lid, works with the levator muscle to lift the upper lid, and plays an important role in cases of poor levator muscle strength. The frontal muscle flap belongs to the autologous tissue, which is not only rich in blood supply, but also has innervation and strong muscle strength, and because it is interwoven with the surrounding tissues, it is less prone to flap relaxation, which facilitates the ideal effect of frontal muscle flap repair, but can cause some damage to the patient's frontal muscle strength after surgery (20, 21). The present results showed that the frontal muscle strength of the affected side was higher in the observation group than in the control group at 1, 6 and 12 months after surgery.

The reason for this is considered to be that e-PTFE is relatively lighter in mass, which has less impact on the vascular circulation of the frontalis muscle during the operation, and it is not necessary to remove the suspension material again after the operation, so the damage to the frontalis muscle strength is smaller and the postoperative recovery is better. This result also showed that there was no significant difference between the two groups in comparing the cosmetic results at 1, 6 and 12 months after surgery. This may be due to the fact that the clinical use of the frontalis muscle flap for suspension has good elasticity, high muscle strength, and the operator can adjust the lid curvature according to the actual situation of the child, As a result, the double eyelid curvature after surgery is well formed, the appearance is natural, and the effect is lasting (22–24); Instead, the e-PTFE frontalis suspension surgery uses individualized double eyelid surgery, the surgeon tried to bury the e-PTFE material under the muscle as much as possible during the operation, and the broken end of the material is directly sewn with sutures firmly to increase the flatness, in addition, e-PTFE has excellent biocompatibility and extensibility, stable chemical properties, slow degradation rate, and long retention time, which is conducive to maximizing the postoperative aesthetic effect and long-term maintenance of children.

Traditional frontalis suspension is mostly sutured with mousse thread, which may cause self-rejection as a foreign body, and cause swelling of the eyelid, exposure keratitis, and incomplete closure of the eyelid, which affects the postoperative effect (25). In the present results, the incidences of exclusion reaction, upper eyelid inversion trichiasis, exposure keratitis and incomplete eyelid closure in the control group were higher than those in the observation group, which may be related to the above reasons. It is also suggested that e-PTFE, as a chemical material with high affinity and biocompatibility, has significant advantages in reducing the complications of frontalis suspension and improving the prognosis of children.

CONCLUSION

The surgical and cosmetic results of e-PTFE frontalis suspension and frontalis flap suspension applied to congenital ptosis are comparable, but the former has the advantage of faster postoperative recovery, better ocular surface status, less frontali muscle strength damage 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

This study was approved by the ethics committee of our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LM and LZ are the mainly responsible for the writing of the article. ZL is mainly responsible for research design. DW is mainly responsible for data analysis. YL and CZ are responsible for the guidance of the entire research. LM and ZL are co-first authors. All authors contributed to the article and approved the submitted version.

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Efficacy and Safety of Prostatic Artery Embolization in the Treatment of High Risk Benign Prostatic Hyperplasia and its Influence on Postoperative Life Quality of Patients

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Objective: To evaluate the efficacy, safety and postoperative quality of life of high risk benign prostatic hyperplasia (BPH) patients treated with prostatic artery embolization.

Methods: 34 patients with high-risk BPH were selectedfrom January 2020 to June 2021 in our hospital. All patients were treated with prostatic artery embolization. The changes of international prostate symptom score (IPSS), prostate volume (PV), remaining urine (RU), maximum urine flow rate (Qmax), quality of life scale -74(GQOLI-74), time to sleep without disturbance (HUS) judgment, self-rating anxiety scale (SAS) score and self-rating depression scale (SDS) were compared before operation, 1 month and 6 months after operation.

Results: Prostatic artery embolization was successful in all 34 patients, including unilateral embolization in 15 patients and bilateral embolization in 19 patients. No severe complications occurred in the postoperative patients. The IPSS, PV and RU levels of the patient one month and six months after surgery were lower than those before surgery, while the Qmax level was higher than that before surgery. Besides, the IPSS, PV and RU levels six months after surgery were significantly lower than those one month after surgery, and the Qmax level was significantly higher than that one month after surgery ($p < 0.05$). The GQOLI-74 score six months after surgery was significantly higher than that before surgery ($p < 0.05$). The HUS of the patient six months after surgery was significantly increased, and the SAS and SDS scores were significantly decreased as compared with those before surgery ($p < 0.05$).

Conclusion: For high-risk patients with BPH, prostate embolization is an effective and safe method, which can significantly improve the quality of life of patients after surgery and has good application prospects.

Keywords: benign prostatic hyperplasia, prostatic artery embolization, high risk, prostatic artery, quality of life

INTRODUCTION

With the accelerated aging of the population, the incidence of benign prostatic hyperplasia (BPH) is increasing among elderly men in China (1). Histologically, BPH is mainly characterized by hyperplasia of prostatic interstitial and glandular components, anatomically, enlarged prostate, which often leads to lower urinary tract symptoms, such as dysuria, frequent urination, urinary incontinence, etc (2, 3). Long-term development of the disease will cause serious damage to the bladder and kidney function, and have many adverse effects on patients' quality of life. In clinic, internal medicine treatment effect of some patients with benign prostatic hyperplasia is unsatisfactory, and they can not receive surgery (4, 5). In recent years, the development of surgical equipment, such as plasma and laser, has greatly improved the safety of prostate surgery, but there are still clinical complications. Especially some elderly and high-risk patients with high surgical risk can only accept indwelling catheter or cyctostomy for a long time. On the one hand, the quality of life can not be guaranteed, and on the other hand, the risk of infection is increased (6–8).

Therefore, finding a surgical approach with higher safety and ideal therapeutic effect is still the research focus in the treatment of BPH. Prostate artery embolization is a kind of interventional therapy that has appeared in recent years. The procedure includes selective intubation of bilateral prostatic arteries and injection of microspheres into both sides to realize prostatic artery embolization. It has the advantages of less bleeding, low incidence of complications during and after operative and outstanding therapeutic effect (9, 10). In this study, we treated high-risk BPH patients with prostatic artery embolization, aiming to explore the efficacy of this surgical method in the treatment of patients and the impact of related laboratory indicators, so as to provide a theoretical basis for the selection of surgical methods for BPH.

DATA AND METHODS

General Information

34 patients diagnosed as high-risk BPH in our hospital from January 2020 to June 2021, aged 74–85 years old, with the average age of (80.46 ± 2.27) years old were selected. The patients had hypertension, old myocardial infarction, esophageal cancer, cerebral infarction, chronic obstructive pulmonary disease, coronary heart disease and other diseases, and eight cases had more than two diseases. Inclusion criteria: Patients who were at least 70 years old and diagnosed as BPH; by B-scan ultrasonography or MRI; The clinical symptoms include different degrees of dysuria, nocturia, and fine urine rheology in lower urinary tract syndrome. Combined with cardiopulmonary dysfunction, unable to tolerate routine surgery; Poor effect of medical treatment. All preoperative patients have informed consent and signed the operation consent form. Exclusion criteria: patients with prostate cancer or other malignant tumors of the urinary system; Patients with severe urethral stricture; Acute urinary infection or acute prostatitis infection; Allergic to iodine contrast agent; Severe coagulation dysfunction; Severe renal insufficiency.

Research Methods

All patients were examined by PSA, MRI, color ultrasound of urinary system, aerodynamic test and digital rectal examination before operation. The malignant tumor of prostate, pathological urethral stricture and bladder neck outlet obstruction were excluded. Besides, IPSS, PV, Qmax, RU, GQOLI-74, HUS, SAS and SDS were performed. The preoperative database was established.

All patients were operated under local anesthesia. Routine preoperative indwelling catheter. The bladder of catheter was used to mark the position of the prostate. Take the supine position of the patient. Routine disinfection, towel laying and local anesthesia were carried out. After the right femoral artery was successfully punctured by Seldnger method, the catheter sheath was inserted into the 4f catheter. Cobra catheter which introduced 4F through the sheath was superselected to bilateral internal iliac arteries for rotational angiography to understand the source of the prostate artery. After the angle at which the prostatic artery could be clearly displayed was selected, Pro great micro-catheter was used for super-selection of the prostatic artery, and rotational angiography was performed to identify the prostatic artery, followed by embolization treatment. A suspension of polyvinyl alcohol particles (150–350 μm) was selected as the embolic agent, mixed with the contrast agent evenly and then slowly injected under digital subtraction angiography. In this process, it must be confirmed that there is no reflux to prevent ectopic embolism until blood flow to the prostate aorta stops. Internal iliac artery angiography was performed again, and after the complete embolism was confirmed, the contralateral prostate artery was concretized in the same way. After the opration, the puncture sheath was pulled out and the puncture site was locally compressed and bandaged. The local compression was carried out for 2 h, and the patient were bedridden for 6–24 h. After the operation, levofloxacin (0.5 g, 1 time /d) was orally taken for 2–3 days to prevent infection (shandong Lu Kang pharmaceutical group saite co., ltd., H20067724), and ibuprofen sustained-release capsule (0.3 mg, 2 times/d) was orally taken to relieve pain (Changchun Overseas Pharmaceutical Group Co., Ltd., H2066622) and assist with symptomatic treatments such as hydration. Patients without uroschesis before operation were all kept with urethral catheterization for 1 week, while those who had difficulty urinating and uroschesis before operation and kept urethral catheterization continuously continued to use indwelling urinary catheter for 2 weeks.

To observe the success rate of prostatic artery embolization. All patients were followed-up in the outpatient department for 6 months after operation. IPSS, PV, Qmax, RU were reexamined to assess the improvement of symptoms and curative effect of the patients, and GQOLI-74, HUS and SAS and SDS scores were applied to evaluate the quality of life of the patients and to compare the changes and complications of the patients before and after operation.

Statistical Methods

SPSS22.0 software was used for processing. The experimental data are normally distributed, measurement data were expressed as mean standard deviation ($\bar{x} \pm s$), and the enumeration data were expressed as (%). t test analysis was used for pairwise comparison of measurement data among groups, and analysis of variance was used for multi-group comparison. The count data were tested by χ^2 test. The test level was $\alpha = 0.05$, and $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

The patient's Success Rate of Surgery and Perioperative Situation

Angiography of internal iliac arteries in 34 patients showed a total of 53 prostatic arteries, including 20 from the inferior vesical artery, 14 from the internal iliac artery, 13 from the internal pudendal artery, and 6 from the obturator artery. 52 prostatic arteries were successfully superselected and embolized, including 15 patients with unilateral embolism and 19 patients with bilateral embolism. One patient had a unilateral prostatic artery with severe tortuosity and no super-selective access to the microcatheter, and only unilateral prostatic artery embolization was performed. Bilateral embolization was successfully performed in the remaining 18 patients.

The urinary catheter was pulled out in 23 patients one week after operation, and all of them could urinate on their own. After retaining the urethral catheter for 2 weeks, the urinary catheter was removed from 11 patients, and 9 patients could urinate independently. However, the symptoms of the other 2 patients did not improve significantly. The indwelling urinary catheter was continued, and all patients could urinate independently after removing the urinary catheter one month after surgery.

Patients with Postoperative Complications

Four of the 34 patients had skin color changes in the buttocks after surgery that were considered to be caused by a small amount of embolic reflux without special treatment and returned to normal 5–7 days later. 6 patients developed perineal distension pain, and the symptoms gradually relieved within 4–7 days after local hot compress physiotherapy. 2 patients had postoperative urinary tract infection with mild fever, which improved after anti-inflammatory and symptomatic treatment. 4 patients presented with low grade fever, which improved after physical cooling. No serious complications such as hematuria, bladder spasm, urinary incontinence, large-scale skin color change of pudendal and medial femoral region, and skin necrosis were found in the remaining patients.

Comparison of Prostate Related Indicators Before and after Surgery in Patients

The IPSS, PV, and RU levels of the patient at 1 and 6 months after surgery were lower than those before surgery and significantly lower at 6 months after surgery than at 1 month after surgery ($p < 0.05$). Qmax levels at 1 and 6 months after surgery were higher than before surgery and significantly higher at 6 months after surgery than at 1 month after surgery ($p < 0.05$). See **Figures 1–4**.

Comparison of Patients' Quality of Life Before and after Surgery

Six months after surgery, the scores of psychological function, social function, material life and physical function of GQOLI-74 were significantly higher than those before surgery ($p < 0.05$). See **Figures 5–8**.

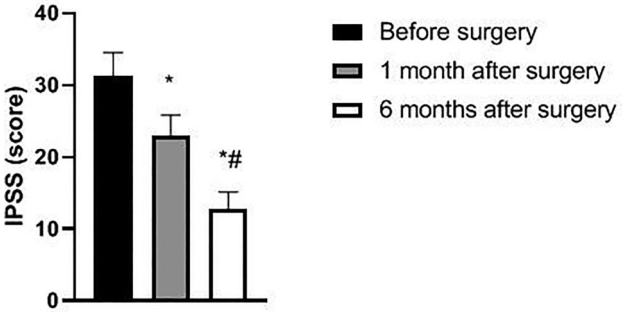

FIGURE 1 | Changes in IPSS of patients before and after surgery.

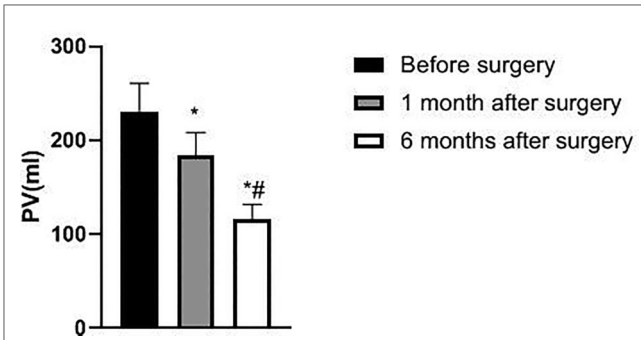

FIGURE 2 | Changes in PV of patients before and after surgery.

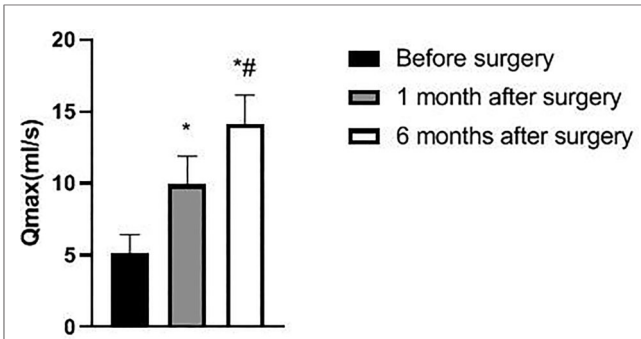

FIGURE 3 | Changes in Qmax of patients before and after surgery.

Comparison of HUS, SAS and SDS Scores of Patients Before and after Operation

The HUS of the patient six months after surgery was significantly increased, and the SAS and SDS scores were significantly decreased as compared with those before surgery ($p < 0.05$). See **Figures 9**, **10**.

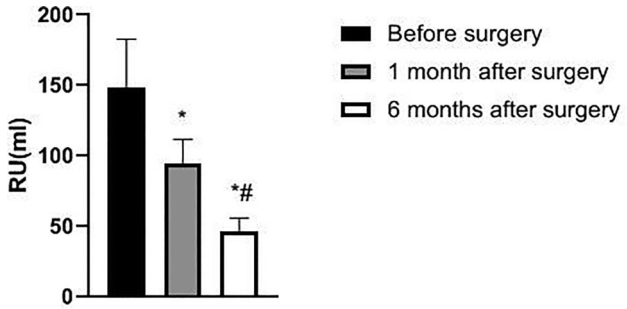

FIGURE 4 | Changes in RU of patients before and after surgery.

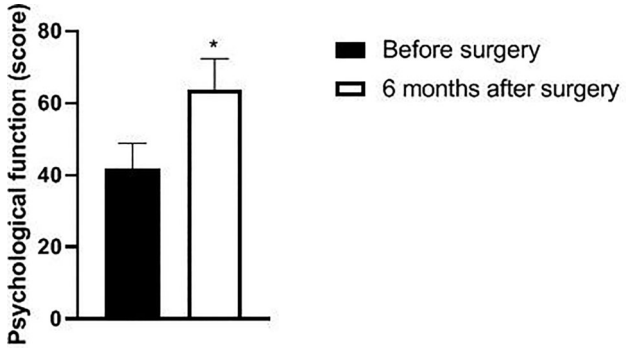

FIGURE 5 | Changes in psychological function scores of patients before and after surgery.

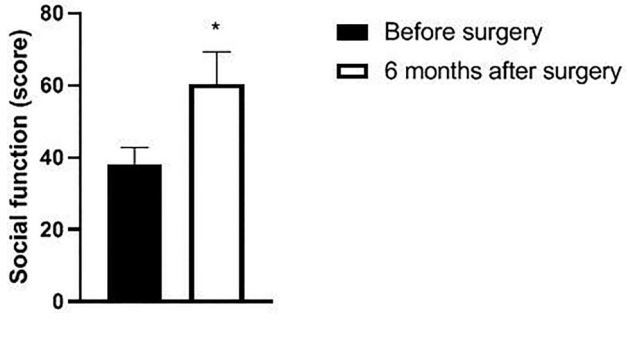

FIGURE 6 | Changes in social function scores of patients before and after surgery.

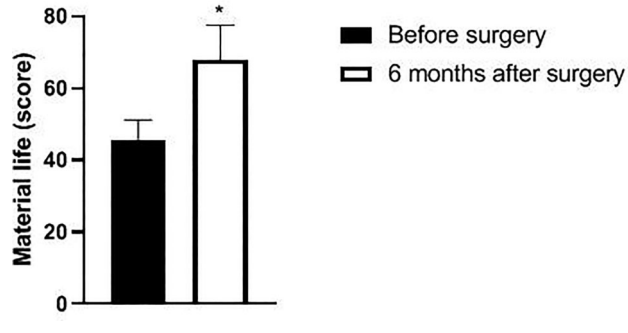

FIGURE 7 | Changes in material life scores of patients before and after surgery.

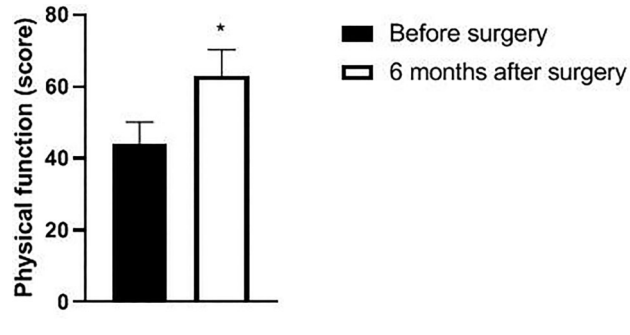

FIGURE 8 | Changes in body function scores of patients before and after surgery. Note: compared with before surgery, $*p < 0.05$. Note: compared with before operation, $*p < 0.05$; compared with one month after surgery, $\#p < 0.05$.

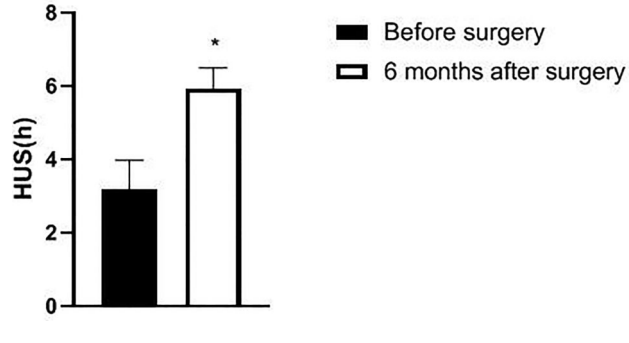

FIGURE 9 | Changes of HUS in patients before and after surgery.

DISCUSSION

BPH is the most common disease in elderly men. When the disease progresses to a certain stage, patients often suffer from

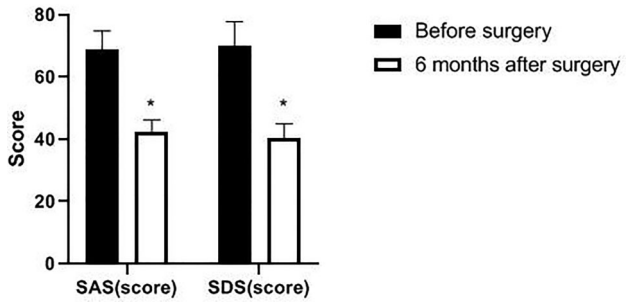

FIGURE 10 | Changes of SAS and SDS scores in patients before and after surgery. Note: compared with before surgery, $^{*}p < 0.05$.

chronic urinary retention due to obstruction of lower urinary tract, causing lower abdominal pain, repeated urinary tract infection, hematuria, which easily lead to serious coplications such as bladder dysfunction, renal insufficiency, electrolyte disturbance, etc., and poses a serious threat to the health of elderly men (11–13). Although BPH high-risk patients have obvious symptoms of lower urinary tract obstruction and their quality of life declines, their tolerance to anesthesia and surgical intervention is poor due to physical factors. Therefore, it is the common desire of patients and doctors to find a new treatment to improve the quality of lifeof patients.

Prostate embolization, as a new treatment, can be performed under local anesthesia, with little trauma. Its principle is to use the interventional method to symbolize the prostate artery and block the blood supply to the prostate, thus leading to ischemia, hypoxia, necrosis and atrophy of some prostate tissues, alleviating the obstruction of lower urinary tract and improving the symptoms (14–16). In this study, 34 patients with high-risk BPH were operated, and all operations were successful. There were 15 patients of unilateral embolism and 19 patients of bilateral embolism, and a total of 53 prostatic arteries were embolized. Only one patient received unilateral prostatic artery embolization, because one prostatic artery was too curved and microcatheter could not selectively enter. The key of prostate embolism is the superselective prostatic artery, while high-risk patients are generally older, with arteriosclerosis and tortuosity, which increases the difficulty of catheter insertion (17). In this respect, our experience was that the use of a coaxial microcatheter during the operation to indicate the angle of good starting point of prostate artery could lead to crooked blood vessel and improved the success rate of the operation.

Prostatic arterial embolization can be completed under local anesthesia, reducing the damage to the central nervous system. In addition, it can contract the prostate by blocking the blood supply to the prostate artery, which can improve the clinical symptoms and cause less trauma to the surrounding tissues, thus contributing to postoperative rehabilitation (18–20). The results showed that all 34 patients received good curative effects, and no severe complications occurred after the operation. Some studies believe that the use of prostatic embolism in the treatment of elderly patients with BPH can alleviate the patient's dysuria and improve the patient's urination function. The main reason is that prostatic artery embolization under fluoroscopic guidance can improve urethral obstruction, reduce the pressure of the middle lobe of the prostate on the urethra and cause little damage to the urethral tissue, thus improving urination function and reducing the incidence of urethral infection and other complications (21–24).

This study also showed that the prostate function-related indicators of the patient at one month and six months after surgery were significantly better than those before surgery, and PV was also significantly decreased. Prostatic arterial embolization can block the blood supply of the enlarged prostate by embolizing bilateral prostatic arteries, which can induce ischemic necrosis and apoptosis of prostate tissue and block the internal circulation of androgen to the prostate tissue, thus improving the therapeutic effect through androgen-related apoptosis (25, 26). At the same time, prostatic artery embolization can effectively destroy some prostatic nerves, thus eliminating the increase in smooth muscle tension in BPH patients, thus reducing urethral resistance and increasing urinary flow (27, 28). Considering the improvement in patients' quality of life scores and HUS, prostatic artery embolization is a recommended minimally invasive method to treat high-risk BPH patients (29).

In summary, prostate embolization is an effective and safe method with good application prospect for high-risk patients with BPH. However, due to the small sample size in this study, its long-term efficacy and safety require further observation and study.

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 This trial was approved by the local ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KW and MC are the mainly responsible for the writing. YL is mainly responsible for data analysis. WX, XL and YQ are responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Evaluation of Serum AMH, INHB Combined with Basic FSH on Ovarian Reserve Function after Laparoscopic Ovarian Endometriosis Cystectomy

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Objective: The value of serum AMH, INHB, and bFSH levels in assessing postoperative ovarian reserve function was analyzed by measuring serum anti-Mullerian hormone (AMH), inhibin B (INHB), and basal follicle-stimulating hormone (bFSH) levels in patients after laparoscopic cystectomy for endometrioma.

Methods: From June 2019 to December 2021, 124 patients underwent laparoscopic cystectomy for endometrioma in our hospital were selected, and the serum AMH, INHB, bFSH level, antral follicle count (AFC) of all patients before and after operation were detected and compared. According to the results of postoperative testing, all the patients were divided into normal group ($n = 86$), diminished ovarian reserve (DOR) group ($n = 27$), and premature ovarian failure (POF) group ($n = 11$). Pearson correlation model and subject operating characteristic curve (ROC) were used to analyze the correlation and diagnostic value of serum AMH, INHB and bFSH levels with postoperative ovarian reserve function, respectively.

Results: After operation, the levels of serum AMH, INHB and AFC in the DOR group and POF group decreased compared with those before the operation, and the serum bFSH levels increased ($p < 0.05$). After operation, the levels of serum AMH, INHB and AFC in DOR group and POF group were lower than those in normal group,and the serum bFSH levels were higher than the normal group; the levels of serum AMH, INHB and AFC in POF group were lower than those in DOR group, and the serum bFSH levels were higher than the DOR group ($p < 0.05$). Pearson analysis showed that serum AMH and INHB levels were negatively correlated with bFSH, and positively correlated with the number of AFC, the serum bFSH level was negatively correlated with the number of AFC ($p < 0.05$). The diagnostic values of serum AMH, bFSH, INHB and the combination of the three tests for postoperative abnormal ovarian reserve function were 0.866 (95% CI, 0.801–0.923), 0.810 (95% CI, 0.730–0.890), 0.774 (95% CI, 0.687–0.860) and 0.940 (95% CI, 0.900–0.981), respectively.

Conclusion: Serum AMH and INHB levels decreased and bFSH levels increased in patients after laparoscopic cystectomy for endometrioma, both of which were closely

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related to postoperative ovarian reserve function, and both could evaluate ovarian reserve function after ovarian cyst debulking, and the combined test could significantly improve the detection rate.

Keywords: ovarian endometriotic cyst, anti-mullerian hormone, inhibin B, follicle stimulating hormone, basic FSH

INTRODUCTION

Ovarian endometriotic cysts (OEMC), or chocolate cysts, are the most predominant pathological type of endometriosis, and OEMC mainly presents with dysmenorrhea, non-menstrual chronic pelvic pain, and in severe cases, infertility, which seriously affects the physical and mental health of patients (1). Laparoscopic debridement of cysts is currently the best method for the treatment of ovarian endometrial cysts, with the advantages of superior results, low postoperative recurrence rate and minimal trauma. Although surgery can remove lesions and relieve symptoms, postoperative risk events such as formation of venous thrombosis, intraoperative bleeding, postoperative infection, adhesion formation, and postoperative reduction of ovarian reserve function and recurrence of postoperative endometriosis can occur (2, 3). Reduced ovarian reserve function is a key factor in infertility in patients with endometriosis; therefore, it is important to fully grasp the postoperative ovarian reserve function of patients and to provide targeted treatment.

Anti-mullerian hormone (AMH) is considered to be an ideal indicator to evaluate ovarian reserve function and is positively correlated with the number of small antral follicles, which can reflect the number of early follicles in the ovary and the survival of primordial follicles (4, 5). Inhibin B (INHB) is produced by small antral follicles, in addition to assessing ovarian reserve, it can also stabilize T cell function and inhibit the overactivation of immune factors from causing damage to ovarian epithelial tissue (6, 7). Basic follicle stimulating hormone (bFSH) promotes follicle maturation, regulates growth and development, and is likewise used to assess ovarian reserve function (8). In this study, we investigated the value of serum AMH, INHB, and bFSH levels in assessing the postoperative ovarian reserve function of patients after laparoscopic ovarian endometriosis cyst debulking by measuring their serum AMH, INHB, and bFSH levels. The specific research is shown as follows.

MATERIALS AND METHODS

General Information

124 patients who underwent laparoscopic ovarian endometrioma cystectomy in our hospital from June 2017 to December 2019 were selected, aged 21–39 years, with an average age of (28.17 ± 5.71) years. Inclusion criteria: a diagnosis of OEMC or other benign ovarian lesions based on the patient's clinical presentation and imaging.; unilateral cystic lesions; normal menstruation; no history of taking sex hormone drugs within 3 months; no history of uterine-related surgery. Exclusion criteria: combined with endocrine diseases; combined with ovarian malignant tumors and other malignant tumors; patients with abnormal ovarian function such as polycystic ovaries; history of hormonal drug use within 6 months and history of pregnancy and lactation.

Research Methods

Cyst removal: All patients underwent laparoscopic cyst removal by the same group of physicians, i.e., the patient was put under general anesthesia, a pneumoperitoneum was established, a laparoscope was placed, the ovarian cortex was opened with an electric needle after exploration. The ovarian cortex was cut, the cyst wall was removed, the wound was electrocoagulated to stop bleeding, and the cyst was removed.

Serum AMH, INHB, bFSH levels and small antral follicle count (AFC) detection: 5 mL of cubital venous blood was drawn from the patient on the 2nd or 3rd day of preoperative menstruation and on the 2nd or 3rd day of postoperative menstrual period, and then centrifuged for 20 min at 3,000 r/min after 2 h resting. Serum AMH and INHB levels were measured by ELISA (kits purchased from Shanghai Kanglang Biotechnology Co., Ltd.), serum bFSH levels were measured by radioimmunoassay (kits purchased from Shanghai mlbio Co., Ltd.), and AFC was examined by ultrasound. According to the postoperative detection results, they were divided into normal group (86 cases), diminished ovarian reserve (DOR) group (27 cases), and premature ovarian failure (POF) group (11 cases). According to our standard determination, the normal levels of AMH were 2.00–10.00 ng/mL, INHB were 20–175 pg/mL, bFSH were 4–12 U/L, and AFC were ≥4. Normal group: all indexes and menstruation were normal. dOR group: serum bFSH was 12–40 U/L, AFC <4, regular menstrual cycle; POF group: serum bFSH >40 U/L, amenorrhea >6 months.

Statistical Methods

SPSS 22.0 software was used for processing data. The measurement data were expressed as, and the comparison was performed by one-way ANOVA, and the pairwise comparison was performed by the SNK-q method. Enumeration data were expressed as frequency and percentage [n(%)], and the χ^2 test was used. Correlation analysis was performed by using Pearson correlation analysis. The receiver operating characteristic curve (ROC) was drawn, and the area under the ROC curve (AUC) was used to evaluate the diagnostic value of serum AMH, INHB, and bFSH levels on ovarian reserve, and AUC > 0.7 was considered diagnostic significance. $p < 0.05$ means the difference was statistically significant.

RESULTS

Comparison of Postoperative Serum AMH, INHB, bFSH, and AFC in Three Groups of Patients

Preoperatively, there were no significant differences in serum AMH, INHB, bFSH levels and AFC counts among the three groups ($p > 0.05$). Postoperative serum AMH, INHB levels and number of AFC in the DOR and POF groups decreased compared with those before surgery and were lower than those in the normal group in the same period, while serum bFSH levels increased and were higher than those in the normal group in the same period, and the differences were statistically significant ($p < 0.05$). The postoperative serum AMH, INHB levels and number of AFC in the POF group were lower than those in the DOR group, and the serum bFSH levels were higher than those in the DOR group, and the differences were statistically significant ($p < 0.05$). See **Figure 1**.

Correlation Analysis Between Serum AMH, INHB, bFSH Levels and Postoperative Ovarian Reserve

Pearson analysis showed that serum AMH and INHB levels were negatively correlated with bFSH, and positively correlated with the number of AFCs; serum bFSH level was negatively correlated with the number of AFCs, as shown in **Table 1**.

The Diagnostic Value of Serum AMH, INHB Combined With bFSH on Postoperative Ovarian Reserve

The AUC of the predictive value of serum AMH for postoperative abnormal ovarian reserve function was 0.866 (95% CI, 0.801–0.923), with a sensitivity of 88.10% and specificity of 88.30% when the best cut-off value was 0.621; the AUC of the predictive value of serum INHB for postoperative abnormal ovarian reserve function was 0.810 (95% CI, 0.730–0.890), with

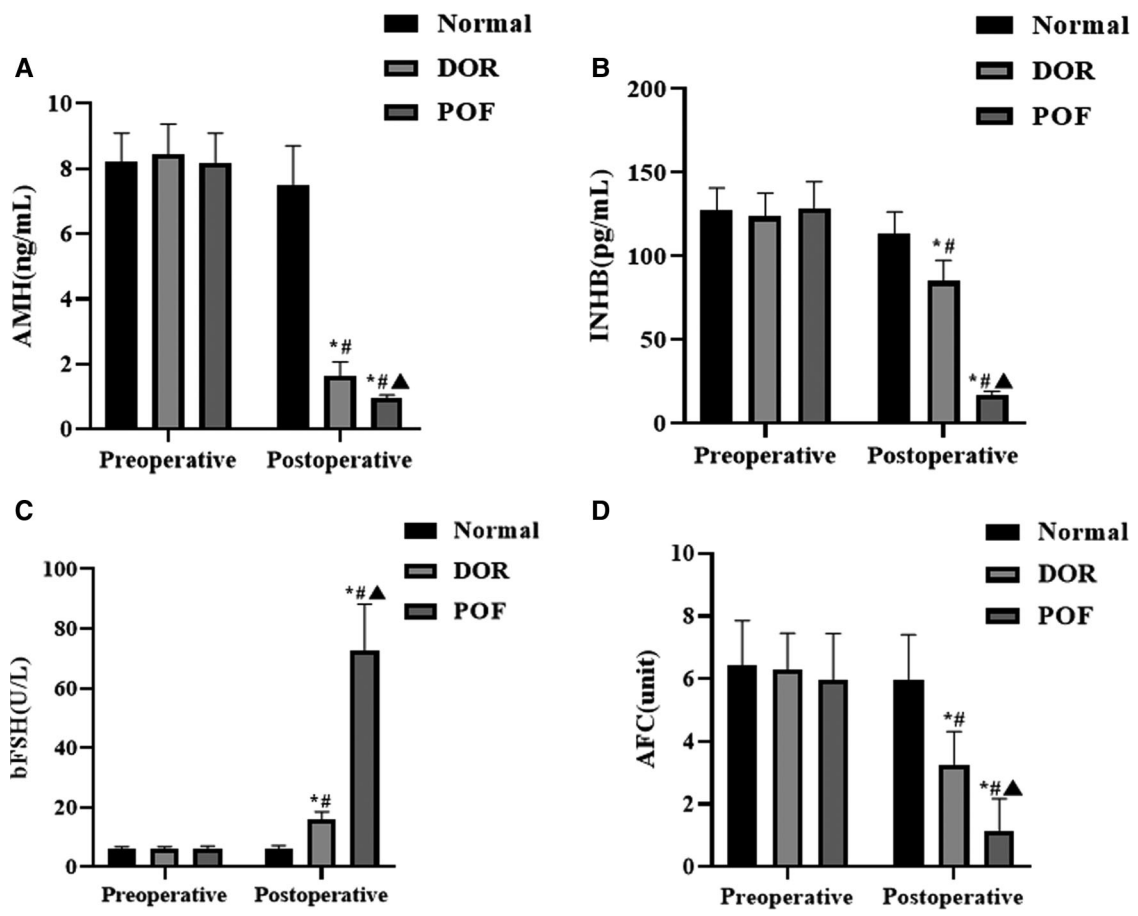

FIGURE 1 | Comparison of postoperative serum AMH, INHB, bFSH and AFC in patients (n, $\bar{x} \pm s$). Note: (**A**) is AMH, (**B**) is INHB, (**C**) is bFSH, and (**D**) is AFC. Compared with the same group preoperatively $^{*}p < 0.05$; compared with normal group after operation, $\#p < 0.05$; compared with DOR group after operation, $^{\blacktriangle}p < 0.05$.

TABLE 1 | Correlation analysis between serum AMH, INHB, bFSH levels and postoperative ovarian reserve.

Indicator	AMH		INHB		bFSH	
	r	*p*	*r*	*p*	*r*	*p*
bFSH	−0.615	0.011	−0.742	0.002	1	<0.001
AFC	0.659	0.007	0.718	0.003	−0.597	0.018

TABLE 2 | Diagnostic value of serum AMH, INHB combined with bFSH for postoperative ovarian reserve.

Indicator	AUC	Asymptotic 95% confidence interval		Best cutoff	Sensitivity (%)	Specificity (%)
		Lower limit	Upper limit			
AMH	0.866	0.801	0.932	0.621	88.10	88.30
INHB	0.810	0.730	0.890	0.528	65.00	87.80
bFSH	0.774	0.687	0.860	0.459	68.30	77.60
Serum AMH, INHB combined with bFSH	0.940	0.900	0.981	0.638	90.10	89.20

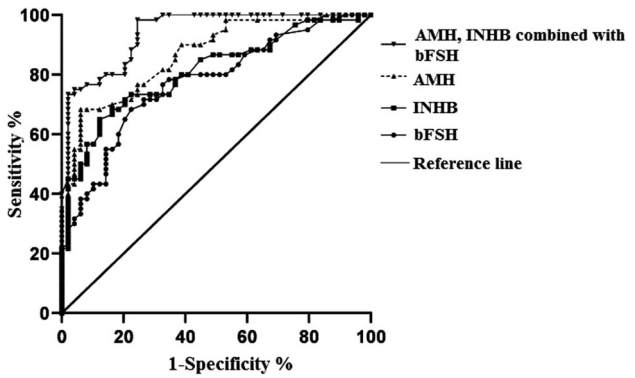

FIGURE 2 | The diagnostic value of serum AMH, INHB combined with bFSH on postoperative ovarian reserve.

a sensitivity of 65.00% and specificity of 87.80% when the best cut-off value was 0.528; the AUC of the predictive value of serum bFSH for abnormal postoperative ovarian reserve function was 0.774 (95% CI, 0.687–0.860), with a sensitivity of 68.30% and specificity of 77.60%. The AUC of the predictive value of serum AMH and INHB combined with bFSH for abnormal postoperative ovarian reserve function was 0.940 (95% CI, 0.900–0.981), and when the best cut-off value was 0.638, the sensitivity was 90.10% and the specificity was 89.20%. See **Table 2** and **Figure 2**.

DISCUSSION

Laparoscopic treatment has a high clearance rate for OEMC, but because of the tight connection between the cyst and normal ovarian tissue, intraoperative operations such as cyst wall stripping and hemostasis can easily cause follicle loss, resulting in compromised ovarian reserve function in patients (9, 10). Therefore, strengthening the screening of ovarian reserve after cyst dissection is of great significance for early intervention and improvement of patients' prognosis.

AMH is secreted by granulosa cells and its levels are relatively stable during the menstrual cycle. Its level reflects the number of primary follicles and regulates follicle maturation and development, thus it can be used as a serological marker to assess ovarian reserve function and ovarian responsiveness during ovulation (11, 12). INHB is also secreted by granulosa cells and its abnormal level is closely related to the abnormal function of ovarian granulosa cells, which can feedback inhibit the production of bFSH, while bFSH can promote the production of INHB by granulosa cells. In addition, INHB can also regulate the secretion of estradiol (E2), which can be used to evaluate ovarian reserve function (13, 14). AFC is a proven reliable index to assess ovarian reserve function, negatively correlated with patient age and closely related to ovarian responsiveness during the ovulatory cycle, which can truly reflect the patient's ovarian functional reserve (15). The results of this study showed that postoperative serum AMH, INHB levels and number of AFC in the DOR and POF groups decreased compared with those before surgery and were lower than those in the normal group in the same period, while serum bFSH levels increased and were higher than those in the normal group in the same period. The postoperative serum AMH, INHB levels and number of AFC in the POF group were lower than those in the DOR group, and the serum bFSH levels were higher than those in the DOR group Pearson analysis showed that serum AMH and INHB levels were negatively correlated with bFSH, positively correlated with AFC count, and serum bFSH level was negatively correlated with AFC count. All of these results indicate that serum AMH, INHB, and bFSH are all associated with ovarian function after laparoscopic ovarian endometriosis cyst debulking and that their serological levels change with changes in postoperative ovarian reserve function. It has been suggested that reduced serum AMH and INHB levels are associated with abnormal function of follicular granulosa cells, while reduced serum INHB levels make them less inhibitory to serum bFSH, which in turn causes abnormal ovarian reserve function in patients (16, 17).

Serum bFSH can be used as one of the important indicators for evaluating ovarian reserve function, but some studies (18) found that the serum bFSH level of some patients did not increase after cystectomy. Analysis of the reasons for this may be related to the fact that the patient had only one ovary removed and the other ovary could replace the function of the affected ovary. Therefore, the evaluation of ovarian reserve function after ovarian cyst debulking using

serum bFSH alone has the problem of poor specificity and sensitivity. Both Serum AMH and INHB belong to the transforming growth factor-β superfamily, and both serum levels are positively correlated with ovarian responsiveness and follicle number, both of which can be used to assess ovarian reserve function (19, 20). The results of this study found that the AUC of serum AMH, INHB, bFSH and the combination of the three for abnormal ovarian reserve after ovarian cystectomy were 0.866, 0.810, 0.774, and 0.940, respectively, which indicated that compared with serum bFSH, INHB and AMH alone for predicting ovarian reserve function after ovarian cyst debulking, the combined test significantly improve the detection rate of abnormal postoperative ovarian reserve function.

In conclusion, serum AMH and INHB levels decreased and bFSH levels increased in patients after laparoscopic cystectomy for endometrioma, which were closely related to postoperative ovarian reserve function and could be evaluated for ovarian reserve function after ovarian cystectomy, and the combined test can significantly improve the detection rate and facilitate the targeted treatment 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 medical ethics committee of our institution has given its consent to this study (2018004). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The first author is YT, she is responsible for the writing,research design,data analysis of the article. YL is responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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A Comparative Study of Hip Arthroplasty and Closed Reduction Proximal Femur Nail in the Treatment of Elderly Patients with Hip Fractures

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Objective: To compare the clinical effect of hip arthroplasty and closed reduction intramedullary nailing of proximal femur in the treatment of elderly hip fracture patients.
Methods: There are 90 elderly hip fracture patients being recruited in the present study. Fifty patients in Group A received closed reduction intramedullary nailing of proximal femur, and 40 patients in Group B received hip arthroplasty. All patients were followed up for 12 months after surgery, clinical outcomes included surgical indicators, visual analog scale (VAS) score, Harris score, quality of life, mental status, and complications.
Results: The surgery time, bleeding volume, infusion volume of patients in Group A are all significantly lower than those in Group B ($p < 0.05$), while the weight-bearing activity time and first workout time of Group A are all significantly higher than those in Group B ($p < 0.05$). The VAS score in patients of Group A at 1 week postoperative is significantly lower than that in patients of Group B ($p < 0.05$). The Harris score in patients of Group A at 3, 6, and 12 months postoperative are all significantly higher than those in patients of Group B ($p < 0.05$), and the excellent and good rate of hip function recovery at 12 months postoperative in patient of Group A is significantly lower than that in patients of Group B (80% vs. 95%, $p < 0.05$). Furthermore, The score of SF-36 standardized physical component, SF-36 standardized mental component and Barthel in patients of Group A at 6 months postoperative are significantly lower than those in patients of Group B ($p < 0.05$), and the score of mini-mental state examination is significantly higher ($p < 0.05$), while there are not significantly different at 12 months postoperative ($p > 0.05$). The incidence of postoperative complications in Group A was significantly lower than that in Group B (10% vs. 27.5%, $p < 0.05$).
Conclusion: Elderly hip fracture patients treated with closed reduction intramedullary nailing of proximal femur has less surgical trauma and lower complication rates, but slower postoperative recovery compared with hip arthroplasty.

Keywords: hip fracture, hip arthroplasty, closed reduction, intramedullary nailing, proximal femur nail

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INTRODUCTION

Hip fractures are the most common type of fractures in orthopedics, including intertrochanteric fractures, femoral–tibial fractures, and subtrochanteric fractures, with the highest incidence in elderly patients which is due to osteopenia or osteoporosis (1, 2) Hip fractures not only increase mortality and reduce the quality of life in older patients, but also cause patients to be unable to return to their pre-injury living environment, require higher levels of care, and so on (3, 4). Treatment protocols for hip fractures include both non-surgical and operative treatments, but non-surgical treatments have significant disadvantages including fracture malunion, nonunion, and complications from prolonged bed rest (5–7). Therefore, surgery is recommended for all elderly patients with hip fractures who tolerate surgery. Protocols for surgical treatment of hip fractures include dynamic hip screw, dynamic condylar screw, proximal femoral nail, proximal femoral nail antirotation, hip arthroplasty, etc (8).

Currently, proximal femur nail and hip arthroplasty are widely used in the treatment of hip fractures due to their suitability for various types of hip fractures, simple surgery, low blood loss, and low trauma (9, 10). However, many clinical studies have compared the efficacy of proximal femur nail and hip arthroplasty in the treatment of hip fractures, but the results have been inconsistent or even opposite (11, 12). In the present study, we designed to study the clinical effect of hip arthroplasty and closed reduction intramedullary nailing of proximal femur in the treatment of elderly hip fracture patients.

PATIENTS AND METHODS

Patients and Ethics Statement

There were 90 elderly hip fracture patients from January to December 2020 being recruited in the present study. Diagnostic reference for hip fractures "Guideline for the management of hip fractures 2020: Guideline by the Association of Anaesthetists" (13). According to the different surgical treatment methods, they were divided into Group A and Group B. Fifty patients in Group A received closed reduction intramedullary nailing of proximal femur, and 40 patients in Group B received hip arthroplasty. All patients recruited in this study were informed about the details of this study and signed informed consent. In addition, all patients enrolled in this study must meet the following criteria: Inclusion criteria: (1) over 60 years old; (2) hip fracture diagnosed by imaging; (3) surgery performed within 1 week of fracture; and (4) compliance with surgical criteria and signed informed consent. Exclusion criteria: (1) multiple fractures, or surgery performed over 1 week of fracture; (2) deep vein thrombosis, infection, cardiovascular and cerebrovascular disease, malignant tumor; (3) mental disability, intellectual disability, or communication difficulties; (4) Refracture after surgery; (5) failure to complete 12-month follow-up after surgery; (6) failure to cooperate with training; and (7) abnormal functions of organs such as liver and kidney.

Data Collection

We collected the demographic of patients including age, gender, height, and weight, and recorded the surgery information including American Society of Anesthesiologists (ASA) grade, the surgery time, bleeding volume, infusion volume, and we also recorded hospital stay time, weight-bearing activity time, and first workout time. Moreover, we used visual analog scale (VAS) score to evaluate the pain of patients at 1 h, 24 h, 48 h, and 1 week postoperative.

Follow-Up

All patients completed a 12-month follow-up after surgery, and the follow-up protocol was as follows: All patients returned to the hospital for imaging examinations and hip function assessments at 3, 6, and 12 months after surgery. And we used the Harris score to evaluate the hip function of patients before treatment and at 3, 6, and 12 months postoperative. According to the Harris score, the hip function recovery of elderly hip fractures patients was rated as excellent (Harris score ≥90), good (80≤ Harris score <90), medium (70≤ Harris score <80), and poor (Harris score <70) (14, 15). At 6 and 12 months postoperative, we used the health survey summary (MOS) item short form health survey (SF-36) and Barthel index to evaluate the life quality of patients, and used mini-mental state examination (MMSE) evaluate the mental state of patients.

Statistical Analysis

Data in this study were analyzed by SPSS20.0 (National Institute of Health in the USA). We used Student's *t*-test to compare the differences in measurement data between the two groups, and used the χ^2 test to compare differences in count data. $p < 0.05$ indicated significant difference.

RESULTS

Demographic and Perioperative Data

As shown in **Table 1**, the demographic of patients in Group A including age, gender, height, and weight are all no significantly different with patients in Group B ($p > 0.05$). At the same time, there is also no significant difference in ASA grade and the time of hospital stay between Group A and Group B ($p > 0.05$). However, the surgery time, bleeding volume, and infusion volume of patients in Group A are all significantly lower than those in Group B ($p < 0.05$), while the weight-bearing activity time and first workout time of patients in Group A are all significantly higher than those in Group B ($p < 0.05$) (**Table 1**).

Postoperative Pain

There is no significant difference in VAS score at 1, 24, and 48 h postoperative between Group A and Group B ($p > 0.05$), while the VAS score in patients of Group A at 1-week postoperative is significantly lower than that in patients of Group B ($p < 0.05$) (**Table 2**).

TABLE 1 | Comparison of demographic and perioperative data between the two groups.

Variables	Group A ($n = 50$)	Group B ($n = 40$)	χ^2/t	p-value
Age (years)	68.8 ± 2.3	69.0 ± 2.1	0.186	0.860
Gender (male/female, *n*)	23/27	18/22	0.009	0.925
Height (cm)	165.2 ± 10.2	164.8 ± 10.9	0.358	0.445
Weight (kg)	63.5 ± 7.8	63.9 ± 7.2	0.863	0.235
ASA (I + II/III, *n*)	42/8	31/9	0.613	0.434
Surgery time (min)	72.8 ± 10.1	89.5 ± 13.8	6.382	<0.001
Bleeding volume (ml)	234.8 ± 43.5	297.8 ± 56.7	7.013	<0.001
Infusion volume (ml)	115.8 ± 23.9	142.3 ± 35.9	6.265	<0.001
Hospital stay time (day)	15.8 ± 3.5	14.7 ± 3.8	0.627	0.279
Weight-bearing activity time (day)	4.3 ± 0.8	3.2 ± 0.6	8.126	<0.001
First workout time (day)	18.9 ± 3.8	12.3 ± 2.5	20.358	<0.001

TABLE 2 | Comparison of VAS scores at different time after operation between two groups of patients (score, $\bar{x} \pm S$).

Group	*n*	1 h	24 h	48 h	1 week
Group A	50	0.9 ± 0.2	4.2 ± 0.6	4.6 ± 0.8	1.2 ± 0.2
Group B	40	0.9 ± 0.3	4.3 ± 0.7	4.8 ± 0.9	2.5 ± 0.4
t		0.023	0.493	0.981	2.568
p		0.838	0.463	0.129	0.039

TABLE 3 | Comparison of Harris score between two groups of patients at different time after operation (score, $\bar{x} \pm S$).

Group	*n*	Preoperative	Postoperative (months)		
			3	6	12
Group A	50	46.2 ± 5.9	68.2 ± 7.2	79.6 ± 11.2	92.5 ± 10.8
Group B	40	46.9 ± 6.3	60.9 ± 10.2	68.5 ± 12.8	85.7 ± 11.6
t		1.059	13.826	19.213	6.894
p		0.531	<0.001	<0.001	<0.001

Hip Function Recovery

There is no significant difference in Harris score between Group A and Group B preoperative ($p > 0.05$), while the Harris score in patients of Group A at 3, 6, and 12 months postoperative are all significantly higher than those in patients of Group B ($p < 0.05$) (**Table 3**). Furthermore, according to the Harris score at 12 months postoperative, the number of patients in Group A whose hip function was rated as excellent, good, medium, and poor are 15, 25, 8, and 2, respectively. And Group B are 23, 15, 2, and 0, respectively. Importantly, the excellent and good rate of hip function recovery at 12 months postoperative in patient of Group A is significantly lower than that in patients of Group B (80.0% vs. 95.0%, $p < 0.05$) (**Table 4**).

Other Clinical Outcomes

The score of SF-36 (PCS), SF-36 (MCS), and Barthel in patients of Group A at 6 months postoperative are significantly lower than those in patients of Group B, while the score of MMSE in patients of Group A at 6 months postoperative is significantly lower than that patients of Group B ($p < 0.05$) (**Table 5**). At 12 months postoperative, there are no significance in the score of SF-36 (PCS), SF-36 (MCS), Barthel, and MMSE between Group A and Group B ($p > 0.05$) (**Table 6**).

Postoperative Complications

All patients were followed up for 12 months after surgery, there were 1 infection, 3 deep vein thrombosis (DVT), and 1 bedsore in Group A, while 1 infection, 2 built-in loose, 2 DVT, 2 bedsores, and 4 cardiovascular disease occurred in Group B. Namely, the incidence of postoperative complications in Group A was significantly lower than that in Group B (10% vs. 27.5%, $p < 0.05$) (**Table 7**).

DISCUSSION

Hip fracture is the most common fracture in the elderly, accounting for about 3%–4% of the whole-body fracture, which not only seriously affects the daily life of patients, but also increases the risk of death of patients (1, 2). At present, non-surgical conservative treatment, internal fixation surgery, and artificial hip replacement are clinically used for the treatment of patients with different types of hip fractures. Among them, non-surgical conservative treatment is only recommended for patients who cannot tolerate surgical treatment due to its long treatment cycle, poor treatment effect, and long-term bed rest. Surgery is currently the preferred treatment protocol recommended for hip fracture patients (5–7). Internal fixation and artificial hip arthroplasty are the main surgical methods for hip fracture surgical treatment, and the advantages are not only reduced trauma and shortened bed time, but also significantly reduced the incidence of complications, promoted functional recovery of the hip joint and improved the life quality of hip fracture patients (9, 10).

In this study, elderly hip fracture patients received hip arthroplasty or closed reduction proximal femur nail treatment, and we found that compared with hip arthroplasty, closed reduction proximal femur nail treatment had less surgery time, bleeding volume, infusion volume, but higher weight-bearing activity time and first workout time, which suggested closed reduction proximal femur nail treatment is less traumatic for elderly fracture patients, while hip arthroplasty treatment patients recover faster after surgery. In addition, we also found that the postoperative long-term hip function recovery of hip arthroplasty patients was better than closed reduction proximal femur nail treatment, but there was no significant difference in postoperative long-term quality of life and mental state between the two groups.

Artificial hip arthroplasty is the most commonly used surgical treatment in clinical practice, and its advantages are that the postoperative joint mobility is good, the stability is high, and

TABLE 4 | Comparison of hip joint function recovery between two groups of patients [*n* (%)].

Group	*n*	Excellent	Good	Medium	Poor	Rate of excellent and good
Group A	50	15 (30.0)	25 (50.0)	8 (16.0)	2 (4.0)	40 (80.0)
Group B	40	23 (57.5)	15 (37.5)	2 (5.0)	0 (0.0)	38 (95.0)
t						4.327
p						0.038

TABLE 5 | Comparison of life quality and mental state at 6 months postoperative between two group (score, $\bar{x} \pm S$).

Group	*n*	SF-36 (PCS)	SF-36 (MCS)	Barthel	MMSE
Group A	50	35.1 ± 6.8	50.7 ± 7.5	20.5 ± 1.5	83.2 ± 8.3
Group B	40	40.3 ± 6.5	59.2 ± 6.7	26.3 ± 2.4	76.3 ± 8.8
t		9.562	10.319	8.128	1.319
p		<0.001	<0.001	<0.001	0.325

SF-36, the MOS item short form health survey; PCS, standardized physical component; MCS, standardized mental component; MMSE, mini-mental state examination.

TABLE 6 | Comparison of life quality and mental state at 12 months postoperative between two group (score, $\bar{x} \pm S$).

Group	*n*	SF-36 (PCS)	SF-36 (MCS)	Barthel	MMSE
Group A	50	30.3 ± 4.2	42.7 ± 6.1	17.5 ± 1.1	87.4 ± 6.1
Group B	40	31.4 ± 3.9	43.8 ± 5.3	18.2 ± 1.8	85.9 ± 7.2
t		0.912	1.381	0.521	0.289
p		0.139	0.087	0.392	0.169

SF-36, the MOS item short form health survey; PCS, standardized physical component; MCS, standardized mental component; MMSE, mini-mental state examination.

TABLE 7 | Comparison of postoperative complications between the two groups of patients [*n* (%)].

Group	*n*	Infection	Built-in loose	DVT	Bedsores	Cardiovascular diseases	Total rate
Group A	50	1 (2.0)	0 (0.0)	3 (6.0)	1 (2.5)	0 (0.0)	5 (10.0)
Group B	40	1 (2.5)	2 (5.0)	2 (5.0)	2 (5.0)	4 (10.0)	11 (27.5)
t							4.656
p							0.031

DVT, deep vein thrombosis.

the patient can get out of bed early without waiting for the fracture site to heal (16, 17). Bone cement-type and bio-type artificial hip joints are two groups of prostheses commonly used in the clinic, and they have different characteristics when used in the treatment of elderly patients with hip fractures (18, 19). Bone cement artificial hip joint can improve early stability, help get out of bed early, and promote recovery, but different degrees of acute hypotension, hypoxemia, arrhythmia, cardiac arrest, and cardiopulmonary dysfunction may occur (20, 21). The initial stability of the biological artificial hip joint is not ideal, and long-term bed rest is required after the operation (21). Therefore, the effect of short-term follow-up after the operation is not as good as that of the cemented artificial hip joint, but the risk of postoperative unsafe events is relatively low. In the present study, since the subjects included in this study were all elderly patients with hip fracture, osteoporosis, and severe bone loss were common, so a cemented artificial hip joint was selected during the operation to improve the early stability. Proximal femoral nail fixation is a minimally invasive intramedullary fixation procedure based on biomechanical principles using an anti-rotation helical blade to fix the femoral neck. Because the helical blade is very close to the bone, it can prevent fracture rotation and varus deformity, and enhance fracture stability (22–25). As a minimally invasive operation, small surgical incision, small trauma, short operation time, and avoiding periosteum and soft tissue dissection are the inherent advantages of proximal femoral nailing (26, 27).

Postoperative complications are the main risk factors affecting the recovery of elderly patients with hip fracture (28, 29). Bone cement poisoning, including cardiovascular disease, pulmonary dysfunction, and hypotension, is the main postoperative complication of hip arthroplasty (20, 21). In this study, there were 11 postoperative complications in elderly hip fracture patients treated with hip arthroplasty, among which the highest incidence of cardiovascular disease (four cases). Compared with hip replacement, the postoperative complication rate of elderly hip fracture patients treated with proximal femoral nail fixation is lower, only 10%. This is mainly due to the low trauma to patients treated with proximal femoral nail fixation. However, it should be noted that although the postoperative complication rate of patients treated with proximal femoral nail fixation was significantly lower than that treated with hip arthroplasty, patients treated with hip arthroplasty had faster recovery of hip function. This is mainly due to the timely intervention of postoperative complications to reduce their impact on patients' postoperative recovery.

CONCLUSION

Hip arthroplasty and proximal femoral nail fixation have different advantages for elderly patients with hip fractures. The advantages of proximal femoral nail fixation are ease of operation, less trauma, less operative time, and postoperative complication rates, while the advantages of hip arthroplasty are faster postoperative recovery. Therefore, for different elderly hip fracture patients, different surgical treatment methods should be selected according to their actual status.

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 This study was approved by the ethics committee of our hospital. All subjects gave informed consent and signed the informed consent form. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

XZ is mainly responsible for the writing, data analysis, and research design of the article. The corresponding author is XS, and he is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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Effect of High-Quality Whole-Course Care on Psychological Status and Postoperative Pharyngeal Complications in Patients Undergoing Surgery for Hyperparathyroidism Secondary to Chronic Rrenal Failure

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Objective: To observe the effects of high-quality whole-course care on the psychological status and postoperative pharyngeal complications in patients undergoing surgery for secondary hyperparathyroidism (SHPT) to chronic rrenal failure (CRF).

Methods: The clinical data of 62 patients who underwent surgical treatment for CRF-SHPT from April 2018 to October 2021 in our department were retrospectively analyzed. According to the different nursing methods after admission, they were divided into two groups, of which 33 patients who received high-quality whole-course care were the high-quality group, and 29 patients who received routine nursing were the regular group. Compliance, occurrence of pharyngeal complications, improvement of preoperative and postoperative psychological status [Assessed by self-rating anxiety scale (SAS) and self-rating depression scale (SDS)], nursing satisfaction scores, and serum hormone levels [intact parathyroid hormone (iPTH), calcium (Ca), Phosphorus (P)] were compared between the two groups.

Results: The differences between the general conditions and clinical characteristics of the two groups were not significant ($p > 0.05$). After care, the number of cases with good compliance in the high-quality group was higher than that in the regular group, and the number of cases with non-compliance was lower than that in the regular group ($p < 0.05$); the difference in the number of cases with partial compliance after care between the two groups was not significant ($p > 0.05$). There was no significant difference in the incidence of pharyngeal complications such as sore throat, nausea and vomiting, dry throat and hoarseness between the two groups ($p > 0.05$); however, the 24-h postoperative sore throat and dry throat scores in the high-quality group were significantly lower than those in the regular group ($p < 0.05$). Patients in the

high-quality group had higher nursing attitude, nursing skills, nursing safety, nursing quality, and overall nursing satisfaction scores than the regular group ($p < 0.05$). Compared with the pre-care period, SAS and SDS scores decreased in both groups after care, and SAS and SDS scores decreased more in the high-quality group than in the regular group ($p < 0.05$). Serum iPTH, Ca, and P levels decreased in both groups at 1 week after surgery, and iPTH, Ca, and P levels decreased more in the high-quality group than in the regular group ($p < 0.05$).

Conclusion: Through the high-quality whole-course care, full informed participation and active cooperation of CRF-SHPT patients, close medical and nursing collaboration, attention to detail and overall level of treatment can effectively improve patient compliance, psychological status and postoperative serum indicators, promote patient recovery and improve nursing satisfaction.

Keywords: chronic renal failure, secondary hyperparathyroidism, high-quality whole-course care, psychological status, surgery, pharyngeal complications

PREFACE

Secondary hyperparathyroidism (SHPT) is a series of symptoms caused by excessive production and secretion of parathyroid hormone by the parathyroid glands due to chronic renal insufficiency, renal tubular acidosis, vitamin D deficiency, Fanconi syndrome, digestive system reactions, pregnancy and lactation (1, 2). Among the various factors that trigger this disease, SHPT due to chronic renal failure (CRF) is the most common and is an important factor affecting the quality of survival of patients with CRF (3). Medical drug therapy and hemodialysis are currently the main treatment methods for CRF-SHPT patients, but about 50% of them still cannot relieve the clinical symptoms of SHPT after medical drugs or hemodialysis, and can gradually progress to refractory or progressive disease, at which point the patient will require surgical treatment (4, 5). However, these patients undoubtedly increase the risk of surgery due to long-term hemodialysis and combined multisystemic pathologies, such as impaired coagulation mechanisms, hypoproteinemia, and renal anemia (6). In addition, the operation itself is a stressful event for the patient, which often brings greater psychological pressure to the patient. and the patient is prone to negative emotions such as anxiety and depression, which in turn have a negative impact on the patient's postoperative regression (7), so it is necessary to strengthen all aspects of patient care after admission. High-quality whole-course care (8, 9) is a nursing service for the entire surgical treatment process, implemented according to the characteristics of preoperative, intraoperative and postoperative work, so that the patient is in an optimal state at the physical, psychological and spiritual levels.

Due to the complexity of CRF-SHPT patients, numerous perioperative complications and difficult management, the authors have conducted a study on the effect of High-quality care of CRF-SHPT patients throughout the whole process since 2018, and achieved better results in the perioperative management of CRF-SHPT patients.

Information and Methods

Case Collection

The clinical data of 62 patients who underwent surgical treatment for CRF-SHPT in our department from April 2018 to October 2021 were retrospectively analyzed. Patients were admitted to the hospital and were treated surgically, according to the different nursing methods after admission, they were divided into two groups, of which 33 patients who received high-quality whole-course care were the high-quality group, and 29 patients who received routine nursing were the regular group.

Data Review

General clinical data including gender, age, weight, age on dialysis, and other general demographic information were collected from the subjects. All subjects were tested for serum calcium, phosphorus, and whole segment parathyroid hormone (iPTH) before surgery and 1 week after surgery.

Inclusion Criteria

① Patients with indications for surgery (10), such as (i) joint and bone pain and/or skeletal deformities, significant symptoms of muscle weakness, myalgia and skin pruritus; (ii) persistent blood iPTH > 800 ng/L with hypercalcemia or hyperphosphatemia; (iii) Color Doppler ultrasound showed at least 1 or more enlarged parathyroid glands >1 cm in diameter with abundant blood flow; (iv) Failure of internal medicine treatment.
② No severe skeletal deformity and osteoporosis, severe coagulation dysfunction, or combined with serious systemic diseases such as heart, lung, and brain dysfunction.
③ ASA classification of grade I to III.
④ Aged 20–65 years.

Exclusion Criteria

① Patients with recent history of upper respiratory tract infection, cough, or throat discomfort.
② Previous history of pharyngeal surgery.
③ Primary parathyroid disease.
④ Psychiatric disorders, etc., and the presence of physical disabilities.
⑤ The patient or the patient's family gave informed consent to this treatment plan.

Study Methods

Regular Group

Post-admission to Preoperative

Preoperatively, the nursing staff closely observed the patient's blood pressure, heart rate, pulse and other vital signs.

Intraoperatively

Nursing staff should actively cooperate with the physician, closely observe the patient's temperature, pulse and other relevant changes, and promptly notify the physician for treatment if any situation arises. In terms of diet, the patient should be advised to pay attention to diet and daily living habits, and take medication regularly.

Postoperative to Hospital Discharge

The patient was placed in a flat position and nursing staff closely monitored the patient's skin and pulse; if abnormalities occurred, they were recorded and the physician was notified in a timely manner; when anti-infective drugs were administered, the patient's condition was closely monitored and the physician was notified in a timely manner if abnormalities occurred.

High-Quality Group

The High-Quality Whole-Course Care Responsibility Group was Established

The members of the quality treatment responsibility group all received detailed training on quality treatment and knowledge related to CRF-SHPT surgery, and developed scientific and reasonable quality treatment measures.

Quality Management Measures

The treatment problems were determined with regard to the etiology and surgical characteristics of CRF-SHPT, the causes of major perioperative complications, prevention and treatment points, and the specific conditions of patients.

Post-Admission to Preoperative

① Psychological counseling was carried out: As patients suffered from long-term disease as well as lifelong dialysis and expensive medical costs, they were generally in a state of tension and depression before surgery; coupled with a lack of confidence in the upcoming surgery and fear of surgical risks and prognosis, they were more prone to varying degrees of fear and anxiety, so psychological counselling should be carried out. ② Hypercalcemia management: Monitored the patient's serum Ca, P level, when the patient has nausea and vomiting symptoms, should be alert to the occurrence of critical signs. When the patient's blood Ca was greater than 3.2 mmol/L, he (she) should be promptly given a low-calcium diet and drink more water, drinking >1,500 mL/d. Daily intake and output were recorded to maintain the balance of output, and blood potassium was monitored to prevent hypokalemia due to massive urination; when the patient's blood calcium was >3.75 mmol/L, the patient should be resuscitated as hypercalcemic, regardless of the manifestation of hypercalcemic crisis. ③ Preoperative preparation: the last preoperative dialysis was performed with heparin-free or low-molecular heparin dialysis to reduce intraoperative and postoperative bleeding. Trained patients to adapt to shoulder elevation and neck hyperextension position to ensure smooth operation, and patients were instructed to pay attention to safety when moving around, not to fall, prevent falling from bed and avoid fracture.

Intra-Operative

Helped the anesthesiologist to do a good job of anesthesia, and when the anesthesia was successful, we had to position the patient to a safe and comfortable angle, and take 2 mL venous blood specimens for the patient before, 5 minutes and 10 minutes after surgery, and send them to the laboratory for PTH testing. The changes in the patient's blood oxygen saturation, pulse, blood pressure, heart rate and other indicators were closely observed during the operation. The infusion rate should be strictly controlled, and once the patient is found to have hand and foot convulsion symptoms, 10–20 mL of calcium gluconate (concentration of 10%) should be slowly pushed intravenously in a timely manner.

Postoperative to Hospital Discharge

① Strict observation of vital signs: For postoperative patients, vital signs should be strictly observed, especially if there was a tendency of bleeding during dialysis or hypertension with heart failure, notify the doctor immediately and gave symptomatic treatment. Kept a tracheotomy kit at the patient's bedside for 24 h after surgery, and resuscitated the patient in time if he/she was found to have respiratory distress or tendency to suffocate. ② Control of infection: Due to the large amount of toxins that accumulate in the body of CRF-SHPT patients and cannot be eliminated on their own, the water-electrolyte disorders in the body were highly susceptible to infectious diseases such as skin mucosal infections and stomatitis. Some studies concluded that active oral care and skin care were the keys to preventing pressure sores and infections, while ventilating, disinfecting and reducing visits to the ward. Monitor blood count, blood sugar and kidney function at all times so that problems could be notified to the doctor in time for appropriate treatment. ③ Health education was provided to patients and their families to guide them to choose a nutritious diet and to enhance the intake of iron-containing foods. It was important to avoid consuming iron-containing foods while quoted tea and coffee to avoid affecting the absorption of iron in the body, but you could

increase vitamin C-rich vegetables and fruits at the same time with iron-containing foods to promote their absorption.

Observed Indicators

Compliance

The classification of compliance of surgical patients was divided into 3 levels: ① Good compliance: Perioperative patients fully accepted the treatment plan formulated by the physician, complete the complete treatment process, and fully cooperate with all care measures. ② Partial compliance: Perioperative patients accepted the treatment plan developed by their physicians and partially cooperated with the nursing measures. ③ Non-compliance: Perioperative patients did not understand the reactions and side effects that occur and do not cooperate with medical care..

Post-Operative Complications

The occurrence, severity and incidence of sore throat, dry throat, nausea and vomiting, and hoarseness at 24 h after surgery were recorded in the two groups. ① Postoperative sore throat: the degree was evaluated by numerical rating system (NRS) (11): 0 being no pain, and 10 being the most painful. ② Dry throat score: A score of 0 indicated that the patient felt no difference from before surgery and had no symptoms of dry throat. 1 indicated mild discomfort, the patient felt different from before surgery and had symptoms of dry throat, but it was not obvious that there was no feeling of stuffiness and/or constriction and no foreign body sensation in the pharynx. A score of 2 indicated moderate discomfort, mainly dryness of the throat with a feeling of stuffiness and/or constriction, with minimal self-consciousness, no or no foreign body sensation in the throat, occasional throat clearing, no habitual throat clearing, and a score of 3 indicated severe discomfort, with a constant habitual throat clearing to ensure the comfort of the throat, a feeling of stuffiness and/or constriction, and a feeling of reduced mucus secretion in the throat and an obvious foreign body sensation in the throat.

Nursing Satisfaction

A questionnaire designed in-house was used to determine the satisfaction level of nursing care for both groups. The questionnaire was scored on a percentage scale, and the nursing satisfaction score consisted of 20 items in four dimensions: nursing attitude, nursing skills, nursing safety and nursing quality. Assessments were conducted separately before and after care and were rated by the same assessor.

Mental Status

Self-rating anxiety scale (SAS) and self-rating depression scale (SDS) were used to determine the severity of patients' anxiety and depression negative emotions were positively correlated with the scores (12). A final SAS score of <50 indicates no anxiety, with higher scores indicating more severe anxiety. A final SDS score of <53 indicates no depression, with higher scores indicating more severe depression. Assessments were conducted separately before and after care and were rated by the same assessor.

Serological Indicators

The serum iPTH, Ca and P levels of the patients were compared preoperatively and at the 1st postoperative week. Serum iPTH was measured by enzyme-linked immunosorbent assay (The relevant kits were purchased from Shanghai mlbio Co.), and serum Ca and P were measured by fully automated biochemical analyzer(Shandong Boke Biological Industry Co.).

Statistical Methods

SPSS 20.0 was used for data analysis, and the independent sample t-test or Kruskal-Wallis and Mann-Whitney method tests were used for measurement data, and Fisher'S exact probability method was used for count data. $P < 0.05$ was considered a statistically significant difference.

RESULTS

General and Clinical Characteristics

General clinical data of the subjects were collected, including general demographic data and clinical characteristics such as gender, age, height, years on dialysis, and ASA classification, and iPTH, Ca, and P were tested before care. The results of the analysis showed that there was no significant difference between patients in the regular and high-quality group s in terms of gender, age, years on dialysis, weight, preoperative iPTH, Ca, and P levels, and the ratio of ASA classification, intractable pruritus, bone pain, insomnia, muscle weakness, and restless leg syndrome ($p > 0.05$) (**Table 1**).

Adherence

The results of the pre-care measurement showed that there was no significant difference in the distribution of the three levels of good, partial and non-adherence between the regular group and the high-quality group ($p > 0.05$). After care, the number of cases of good compliance was higher, and the number of cases of non-compliance was lower in the high-quality group when compared to the regular group ($p < 0.05$); the difference in the number of cases of partial compliance between the two groups after care was not significant ($p > 0.05$) (**Table 2**).

Throat Complications

We observed and counted the occurrence of pharyngeal complications such as sore throat, nausea and vomiting, dry throat, and hoarseness in the regular group and the high-quality group at 24 h postoperatively, and scored the degree of sore throat and dry throat. The results of the analysis showed that there was no significant difference in the incidence of pharyngeal complications such as sore throat, nausea and vomiting, dry throat and hoarseness between the two groups ($p > 0.05$); however, the scores of sore throat and dry throat in the high-quality group were significantly lower than the regular group 24 h after surgery ($p < 0.05$) (**Table 3** and **Figure 1**).

TABLE 1 | General condition level clinical characteristics of patients before care.

Information		Regular group ($n = 29$)	High-quality group ($n = 33$)	t or χ^2 value	p value
Sex (Male, %)		16 (55.17)	20 (60.61)	0.187	0.665
Age (years; Mean, SD)		46.56 ± 8.45	47.02 ± 8.73	0.210	0.834
Years of dialysis (years; Mean, SD)		7.16 ± 3.46	7.01 ± 3.22	0.177	0.860
Body weight (kg; Mean, SD)		61.80 ± 9.42	62.17 ± 9.93	0.150	0.881
ASA classification (n, %)	Grade II	11 (37.93)	14 (42.42)	0.130	0.719
	Grade III	18 (62.07)	19 (57.58)		
	Intractable pruritus	9 (31.03)	11 (33.33)	0.037	0.847
	Bone pain	20 (68.97)	18 (54.55)	1.353	0.245
Clinical features (n, %)	Insomnia	7 (24.14)	9(24.24)	0.079	0.778
	Myasthenia	16 (55.17)	19 (57.58)	0.036	0.849
	Restless legs syndrome	10 (34.48)	11 (33.33)	0.009	0.924
iPTH (ng/L)		1,738.50 ± 726.20	1,746.36 ± 733.53	0.042	0.966
Ca (mmol/L)		2.76 ± 0.25	2.70 ± 0.27	0.753	0.454
P (mmol/L)		2.30 ± 0.40	2.28 ± 0.31	0.221	0.826

TABLE 2 | Comparison of compliance before and after care between the two groups (n, %).

Group	Good compliance		Partially compliant		Non-compliant	
	Before care	After care	Before care	After care	Before care	After care
Regular group ($n = 29$)	8 (27.59)	10 (34.48)	13 (44.83)	12 (41.38)	8 (27.59)	7 (24.13)
High-quality group ($n = 33$)	10 (30.30)	21 (63.64)*	16 (48.48)	11 (33.33)	7 (21.21)	1 (3.03)*
χ^2 value	0.098	5.248	0.083	0.428	0.342	6.119
p-value	0.754	0.022	0.773	0.513	0.559	0.013

*Note: *Shows the difference with the same group before care, $p < 0.05$.*

TABLE 3 | Comparison of the occurrence of postoperative pharyngeal complications between the two groups (n,%).

Group	Sore throat	Nausea and vomiting	Dry throat	Hoarseness
Regular group ($n = 29$)	4 (13.79)	4 (13.79)	3 (10.34)	2 (6.90)
High-quality group ($n = 33$)	3 (9.09)	2 (6.06)	1 (3.03)	0 (0.00)
χ^2 value	0.341	1.056	1.368	2.272
p-value	0.559	0.304	0.242	0.132

Nursing Satisfaction

The degree of patient satisfaction with nursing care in both groups was determined after nursing care using our in-house designed questionnaire. The results of the analysis showed that the patients in the high-quality group had higher ratings of nursing attitude, nursing skills, nursing safety, nursing quality, and overall nursing satisfaction than the regular group ($p < 0.05$) (**Figure 2**).

Pre- and Post-Care Psychological Status Scores

The SAS and SDS scales were used to assess the patients' anxiety and depression before and after care. The results of the analysis showed that the difference between the SAS and SDS scores of the regular group and the high-quality group before care was not significant ($p > 0.05$). After care, the SAS and SDS scores of both groups decreased, and the SAS and SDS scores of the high-quality group decreased more than the regular group ($p < 0.05$) (**Figure 3**).

Serological Indicators

Serum iPTH, Ca, and P levels were measured pre-op and 1 week post-op, respectively. The results of the analysis showed that the differences between the pre-op serum iPTH, Ca and P levels of the regular group and the high-quality group were not significant ($P > 0.05$). Serum iPTH, Ca, and P levels in both groups decreased at 1 week post-op, and the iPTH, Ca, and P scores in the high-quality group decreased more than those in the regular group ($p < 0.05$) (**Figure 4**).

DISCUSSION

SHPT is one of the common serious complications in CRF patients, especially in patients on long-term maintenance dialysis therapy. In CRF, the stimulation of the parathyroid glands by the imbalance of acid-base balance and various electrolyte metabolism disorders, as well as the presence of

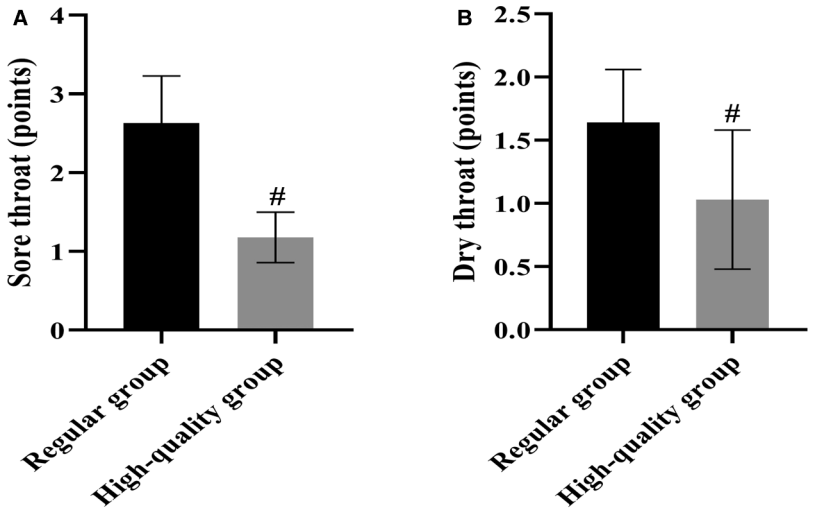

FIGURE 1 | Comparison of the severity of postoperative pharyngeal complications between the two groups (Mean, SD). Note: (**A**) shows the sore throat score and (**B**) shows the dry throat score. # shows the difference with the Regular group, $p < 0.05$.

calcium and phosphorus metabolism disorders and active vitamin D deficiency in the middle and late stages of renal failure promote the secretion of PTH and induce the development of SHPT (13, 14). Studies have shown (15) that hypersecretion of PTH and hyperplasia and hypertrophy of parathyroid glands are characteristic of hyperparathyroidism. Patients with CRF-SHPT tend to present with hypercalcemia, osteoporosis, bone pain, skeletal deformities and pathological fractures, and most patients come to the clinic when they develop persistent bone pain (16). In China, because there are fewer kidney sources available for kidney transplantation and more patients with chronic renal impairment to chronic renal failure due to various reasons, patients with chronic renal failure are treated with hemodialysis or peritoneal dialysis with drug treatment for complications in order to maintain the quality of life of these patients and prolong their life span (17, 18). Over the past 20 years, SHPT has been well controlled due to the development of dialysis technology and early intervention with drugs, but some patients with refractory SHPT still require surgical treatment. However, the condition of these patients is complex, with many complications, and the surgical treatment of general anesthesia with tracheal intubation is an invasive operation, which can easily cause local nerve compression, airway mucosal injury, and vocal cord injury; the damage to the pharyngeal mucosa caused by tracheal intubation can lead to an imbalance in the ratio of the attached local flora, and some bacteria can move down with the catheter, which can increase the risk of infection, and then form harmful irritation and increase the risk of pharyngeal complications such as sore throat and dry throat (19, 20). Therefore, more effort needs to be invested before and after the procedure in CRF-SHPT patients to enable them to safely survive the perioperative period.

In this study, by observing the effect of implementing full quality care for patients undergoing CRF-SHPT surgery, we found that patient compliance, satisfaction with care, and improvement in SAS and SDS scores after care were better in the high-quality group than in the regular group. Although there was no significant difference in the incidence of pharyngeal complications between the two groups at 24 h postoperatively, the sore throat and dry throat degree scores were lower in the high-quality group than in the regular group. This suggests that the whole process of quality care can effectively improve the compliance of patients undergoing CRF-SHPT surgery, reduce patients' bad mood, make patients accept the surgery in a good state of mind, and better cooperate with the treatment and nursing work; it can also reduce the degree of sore throat and dry throat of patients 24 h after surgery to accelerate their postoperative recovery, and improve the recognition and satisfaction of nursing work. In addition, the serum iPTH, Ca, and P levels of patients in the high-quality group were lower than those in the regular group at 1 week postoperatively, suggesting that conventional care enables faster correction of calcium and phosphorus disorders in patients undergoing CRF-SHPT. High-quality whole-course care takes quality care as the main nursing concept and enhances the efficiency of nursing work with a patient-centered service concept in the nursing process. By establishing a professional full quality nursing team, the nursing staff's level of care has been enhanced to provide a comfortable treatment environment for patients undergoing CRF-SHPT, which is conducive to enhancing the comfort level of the patient's organism, thereby increasing patient compliance with treatment (21, 22). Preoperative quality treatment was carried out mainly for patients' psychological stress, hypercalcemia and surgical adaptation exercises, and medical and nursing education measures were further strengthened to give patients a more

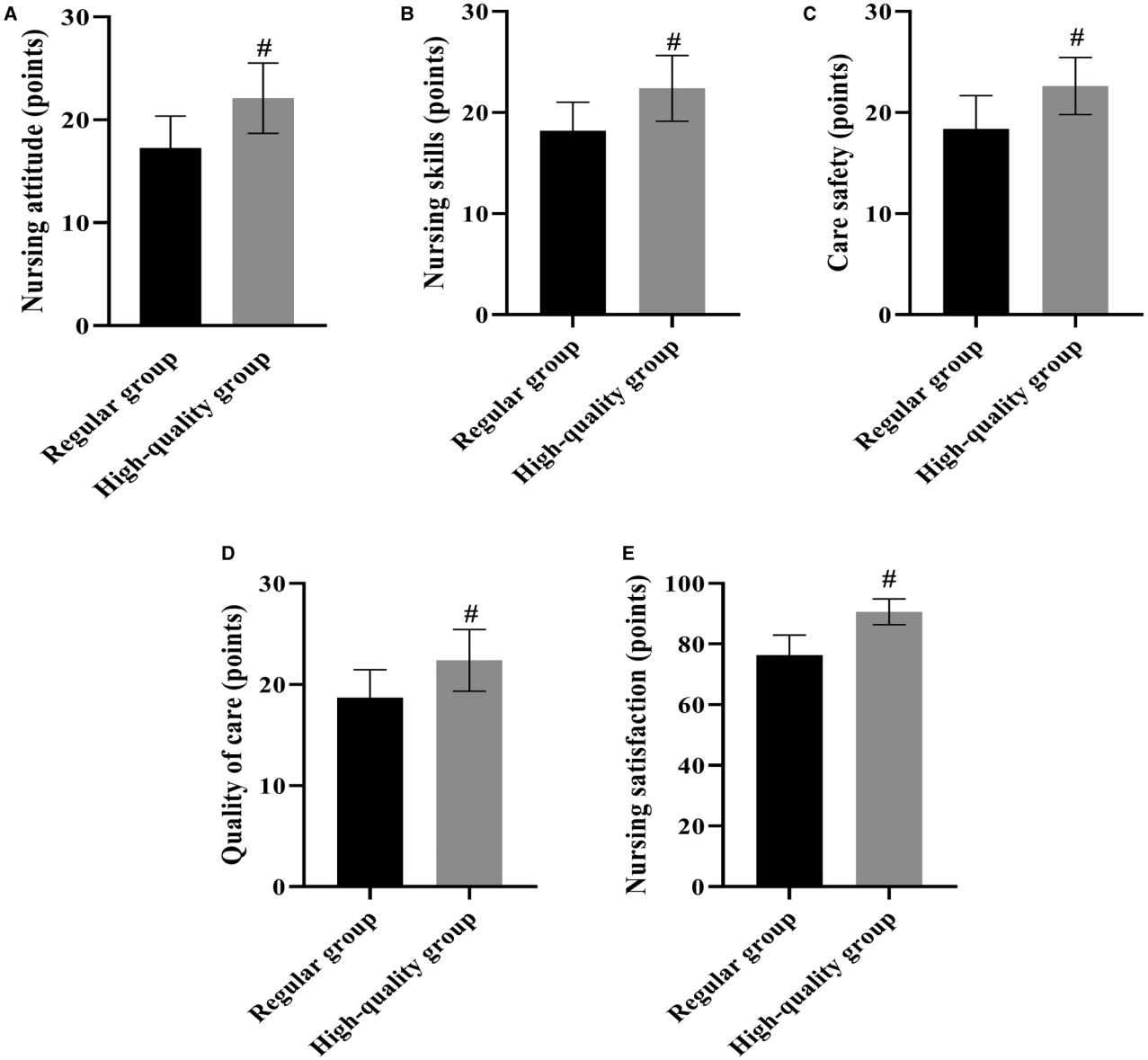

FIGURE 2 | Comparison of various scores of nursing satisfaction after care in the two groups (Mean, SD). Note: (**A**) shows nursing attitude scores, (**B**) shows nursing skill scores, (**C**) shows nursing safety scores, (**D**) shows quality of care scores, and E shows total nursing satisfaction scores. # shows the difference with the Regular group, $p < 0.05$.

comprehensive understanding of the purpose, steps and procedures, and effects of the upcoming surgery, to fully prepare them psychologically, to eliminate their nervousness and concerns, and to reasonably avoid surgical risks (23, 24). Care through intraoperative sign monitoring, position selection, encouragement support and temperature maintenance can ensure a smooth operation. By planning a proper diet and actively taking good oral care and skin care after surgery, patients can reduce the discomfort level of sore throat, dry throat and other throat complications.

CONCLUSION

In conclusion, this study confirms that through the whole process of quality case, fully informed participation and active cooperation of CRF-SHPT patients, close medical and nursing collaboration, attention to detail and overall level of treatment can effectively improve patient compliance, psychological status and postoperative serum indicators, promote patient recovery and increase nursing satisfaction.

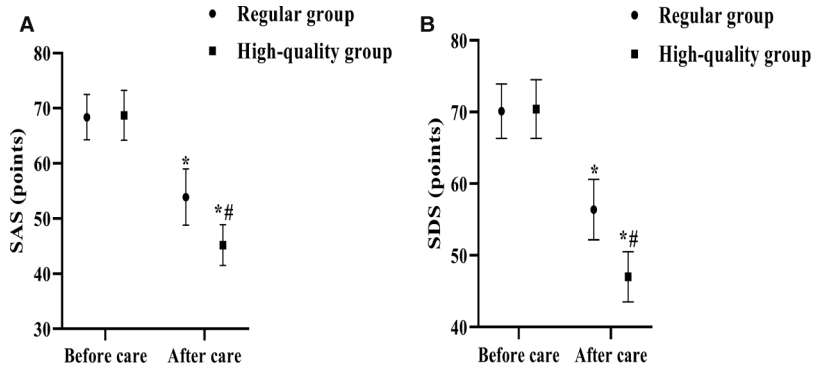

FIGURE 3 | Comparison of psychological status scores between the two groups before and after care. (Mean, SD), Note: (**A**) shows SAS scores, (**B**) shows SDS scores. * shows the difference with the same group before care, $p < 0.05$; # shows the difference with the Regular group, $p < 0.05$.

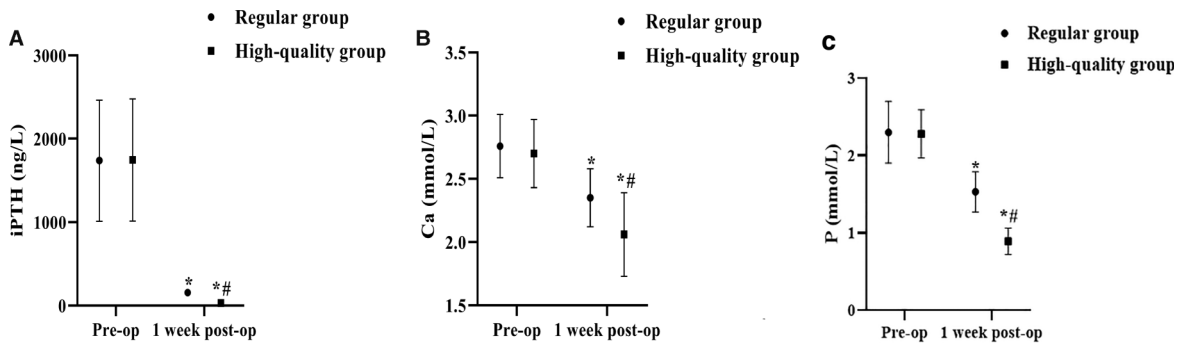

FIGURE 4 | Comparison of iPTH, Ca, and P levels between the two groups before and 1 week after surgery. (Mean, SD). Note: (**A**) shows iPTH levels, (**B**) shows Ca levels, and (**C**) shows P levels. * shows the difference with the same group before care, $p < 0.05$; # shows the difference with the Regular group, $p < 0.05$.

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 This trial was approved by the local ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QL is the mainly responsible for the writing, data analysis. SZ is responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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Efficacy and Safety of Simultaneous Integrated Boost Intensity-Modulation Radiation Therapy Combined with Systematic and Standardized Management for Esophageal Cancer

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Objective: To analyze and compare the efficacy and safety of simultaneous integrated boost intensity-modulation radiation therapy (SIB-IMRT) combined with systematic and standardized management for esophageal cancer.

Methods: From January 2012 to January 2019, 200 patients with esophageal cancer who received radical chemoradiotherapy in our hospital were treated with lymphatic drainage area radiation prevention combined with systematic and standardized management. According to difference in radiotherapy methods, the patients were divided into local lesion 92 patients treated with simultaneous integrated boost intensity-modulation radiation therapy (SIB-IMRT) combined with systematic standardized management (SIB-IMRT group), and late course boost intensity-modulation radiation therapy (LCB-IMRT) combined with systematic standardized management 108 patients (LCB-IMRT group). The short-term eficacy of the two groups were compared. The dose volume parameters of the organ in danger are evaluated based on the dose volume histogram. The related adverse reactions during chemoradiotherapy were compared between two groups. The local control rate and survival rate were compared between the two groups.

Results: The recent total effective rates of rats in the SIB-IMRT group and LCB-IMRT group were 95.65% and 90.74%, respectively, and there was no significant difference between the two groups ($p > 0.05$). The mean doses to left and right lung, heart and spinal cord in the SIB-IMRT group were significantly lower than that in the LCB-IMRT group ($p < 0.05$). There was no significant difference in the incidence of adverse reactions such as radiation esophagitis, radiation pneumonitis, radiation tracheitis, gastrointestinal reaction and bone marrow suppression between the SIB-IMRT group and LCB-IMRT groups ($p > 0.05$). The one-year and three-year overall survival rates in the SIB-IMRT group and LCB-IMRT groups were 82.61%, 42.39% and 77.78%, 34.26%, respectively, and the median survival times were 38 and 29 months,

respectively. The local control rates in the SIB-IMRT group and LCB-IMRT group in one and three years were 84.78%, 56.52% and 75.93%, 41.67%, respectively. The 3-year local control rate in the SIB-IMRT group was higher than that in the LCB-IMRT group ($p < 0.05$), but there was no significant difference in the 1-and 3-year overall survival rates between the two groups ($p > 0.05$).

Conclusion: SIB-IMRT combined with systematic and standardized management in the treatment of esophageal cancer can reduce the amount of some organs at risk and improve the local control rate of the lesion.

Keywords: simultaneous integrated boost intensity-modulation radiation therapy, systematic and standardized management, dose-dependent intensity-modulated radiotherapy, esophageal cancer, efficacy and safe

INTRODUCTION

In recent years, with the constant changes in people's daily life and diet structure, the incidence of esophageal cancer is increasing year by year, and it is more likely to occur in the elderly (1). Early esophageal cancer is mainly treated by surgery, but most patients are in the advanced stage at the time of diagnosis, mainly by concurrent chemoradiotherapy. In addition, radiotherapy is one of the main methods to treat esophageal tumors for patients who can not receive surgical treatment (2–4). Esophageal carcinoma is a dose-dependent malignant tumor. The local control rate of esophageal cancer is positively ralated to the dose of radiotherapy, but many important organs are close to the periphery of the esophagus. Considering that the normal area around the tumor tissue has a certain dose limitation, it is difficult to obtain a more suitable dose distribution in the total tumor volume with conventional radiotherapy (5). Traditional radiotherapy techniques, which is simulated by esophageal barium meal radiography, may not be able to irradiate the tumor tissue and/or there is a low dose area in the tumor tissue, and it is difficult to increase the local dose of esophageal lesions due to the tolerance dose limitation of surrounding normal tissues and organs (6, 7).

With the extensive development of intensity-modulated radiotherapy, the five-year survival rate of esophageal cancer has been significantly improved compared with conventional two-dimensional radiotherapy. At present, the commonly used intensity-modulated radiation therapy commonly used in clinic includes conventional dose intensity-modulated radiation therapy, locally synchronous integrated intensity-modulation radiation therapy (SIB-IMRT), etc. The simultaneous integrated boost intensity-modulation radiation therapy allows different doses to be given to different irradiation areas in the same treatment, which not only increases the irradiation dose of tumor bed area, but also does not increase the tolerance dose of the surrounding normal tissues, and shorten the whole treatment time (8–10).

In the past, traditional clinical management only paid attention to the patients's disease progress and treatment status, and explained the disease and treatment status to the patients orally, while ignoring the influence of psychological and spiritual factors on the disease, which made the treatment effect difficult to achieve clinical expectations. Systematic and standardized management is a newly emerging mode in recent years. It adheres to the service concept of "people-oriented" under the mode of psychological-physiological-social medicine, and implements a series of management interventions according to patients' specific condition, psychology and mental state, so as to meet the their psychological, physiological and social needs and improve their quality of life (11). The purpose of this study was to explore the curative effect of SIB-IMRT combined with systematic and standardized management for the treatment of esophageal cancer, and to provide reference for the individualized plan for comprehensive radiotherapy for esophageal cancer.

DATA AND METHODS

General Information

From January 2012 to January 2019, a total of 200 patients with esophageal cancer who received radical chemoradiotherapy in our hospital were selected, and treated with prophylactic irradiation in lymphatic drainage area combined with systematic and standardized management. According to different radiotherapy methods, the patients were divided into local lesion 92 patients treated with SIB-IMRT combined with systematic standardized management (SIB-IMRT group), and LCB-IMRT combined with systematic standardized management 108 patients (LCB-IMRT group). Inclusion criteria: The first treatment was confirmed as esophageal squamous cell carcinoma by pathology; Fluid food can be fed before radiotherapy, with KPS score ≥70; Receiving radical chemoradiotherapy or radical radiotherapy (dose ≥50 Gy); No signs of esophageal bleeding or perforation before radiotherapy; No other history of malignant tumor; All patients signed informed consent of radiotherapy or chemoradiotherapy. Exclusion criteria: Endoscopic report of a superficial tumor with no obvious esophageal lesion on CT images or endoscopic ultrasonography showing only invasion of the lamina propria and submucosa; Well-differentiated cancer; Esophagus has perforation signs; Esophageal surgery has been performed; There is distant organ metastasis; Incomplete follow-up information or follow-up failure.

Research Methods

Radiotherapy

All the patients received radiotherapy through 6MV-X-ray of Elekta accelerator (Meda, Sweden). The patient took the supine position, and lay flat on the positioning bed. The positioning membrane was used to fix the body position. The scans were performed under a CT analog positioner. The scanning range from the cricoid cartilage to the celiac trunk was selected according to the different lesion sites. The whole neck should be scanned for patients with cervical esophageal cancer. The scanning layer was 5 mm thick and was transmitted digitally to the Treatment Planning System (TPS) for three-dimensional image reconstruction. Diagnostic criteria for a primary tumor were a thickness of the esophageal wall >0.5 cm or a diameter of the airless esophageal lumen >1.0 cm. The diagnostic criteria of metastatic lymph nodes were as follows: short diameter of lymph nodes in mediastinum ≥1.0 cm, and long diameter of paraesophageal, tracheoesophageal groove, pericardial horn and abdominal lymph nodes ≥0.5 cm.

Gross tumor volume delineation: The gross tumor volume (GTV) consists of the primary esophageal tumor and the metastatic lymph nodes (GTVnd); is delineated separately if the metastatic lymph nodes are far from the esophageal lesion); The clinical target volume (CTV) is the axial abduction of the primary tumor GTV by 0.8–1.0 cm, and up and down by 2.0–3.0 cm, with appropriate modifications based on the anatomical barrier. CTVnd refers to the uniform outward expansion of GTVnd of 0.5–0.8 cm in all directions. The planned target volume (PTV) and PTVnd were expanded evenly by 0.5–1.0 cm over the CTV and CTVnd.

The prescription doses of SIB-IMRT (different doses in different target areas but with the same irradiation times) were 58.05–65.10 Gy for 95%PTV and 95%PTVnd, with 28–31 times, and a single dose of 1.95–2.15 Gy; The prescription dose of LCB-IMRT was 46–54 Gy for 95%PTV in 23–27 times with a single dose of 1.8–2.0 Gy, and 10–16 Gy for PTV and PTVnd in 5–8 times to 58–66 Gy in 29–33 times with a single dose of 2 Gy.

Systemic Normative Management and Treatment

Pre-radiotherapy preparation: Health education and individual assessment before radiotherapy can improve patients' cognition of the disease and radiotherapy, realize the importance of radiotherapy and self-care, correct patients' biased understanding of radiotherapy, meet patients' psychological needs, alleviate patients' adverse psychological reactions, and ensure the smooth progress of chemotherapy treatment. The contents of education included: concept of radiotherapy, preparation before radiotherapy, adverse reactions of radiotherapy, cooperation during radiotherapy, psychological guidance, etc. Individual evaluation contents include patients' condition, psychological condition, family and social support, disease cognition, disease behavior ability, etc. In addition, we should also pay attention to the psychological counseling of patients' families to get their understanding and cooperation.

Quality control in radiotherapy: The problems existing in patients during interviews were taken as the guidance for patients to formulate systematic and standardized management plan. Patients were regularly screened for risk during chemotherapy, and nutritional support treatment was given based on the screening results in combination with patients' relevant blood indicators. After chemotherapy, the responsible nurse completes the continuous evaluation list of radiotherapy education, including the systematic evaluation and treatment of patients' adverse reactions, such as gastrointestinal reactions and bone marrow suppression, and puts forward the corresponding nursing measures and continuous improvement.

Quality management after chemotherapy: A personal file was established when the patient was discharged from hospital. In addition to the basic information such as the patient's condition, home address, and contact information, the interview records were also recorded in the file. Subsequently, for each follow-up visit, the time and method of follow-up visit, patients' various problems and improvements need to be continuously recorded in personal files. All patients were followed up for 3 consecutive years, one month after the end of treatment, every 3 months for 2 years, and every 6 months for 3 years. A patient communication area was established through WeChat, and the WeChat contact information was established for each patient. Face-to-face conversation guidance was provided to patients during outpatient re-examination or when they came to our hospital for radiation therapy. Contact the relevant physicians for the individual problems of the patients, and formulate the improvement plan for the patients. According to the patients' cultural level and understanding ability, health education manuals, videos, pictures and case presentations were used to guide the patients to cultivate healthy behavior and self-care ability.

Observation Indicators

Comparison of Short-Term Efficacy of Patients Between the Two Groups

The short-term efficacy is evaluated one month after radiotherapy, and the lesion retraction is evaluated according to the reexamination of chest CT changes before and after treatment. The short-term efficacy is divided into complete response, partial response, stability, and progression. Complete remission: the known lesions completely disappeared, and no new lesions appeared, which lasted for at least 4 weeks; Partial remission: the sum of the largest diameters of lesions decreased by ≥30% and maintained for at least 4 weeks; Stability: the sum of the maximum diameters of target lesions is reduced to the standard of partial remission, or increased to the standard of disease progression; Disease progression: The sum of the maximum diameters of target lesions increased by at least ≥20%, and their absolute values increased by at least 5 mm, or new lesions appeared. Total effective rate = (complete response + partial response)/total cases × 100%.

According to the dose-volume histogram, the dose-volume parameters of organs in danger were evaluated, including the average radiation doses of left and right lungs, heart and spinal cord.

Comparison of adverse reactions related to radiltherapy and chemotherapy between the two groups. The patients' condition were recorded weekly during radiotherapy, and evaluated by RTOG standard classification according to the existence of acute radiation injury in patients who were followed up after radiotherapy.

Comparison of Local Control Rate and Survival Rate Between the Two Groups

Survival time was calculated from the date of diagnosis until death or end of follow-up. The deadline for follow-up is January 2022. Within 6 months after radiotherapy, local uncontrolled lesions appeared at the original lesion site, and tumor recurrence is defined as lesion lasting more than 6 months.

Statistical Methods

SPSS22.0 software was used for processing. The measurement data of the experimental data were expressed as mean standard ± deviation ($\bar{x} \pm s$), and t test was used for pairwise comparison. The enumeration data were expressed as (%) and the comparison was conducted by χ^2 test. Kaplan-Meier method was used for survival analysis. The Kaplan-Meier method was used to calculate the local control rate and survival rate at 1 and 3 years. 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 and lesion length between the two groups ($p > 0.05$). See **Table 1**.

TABLE 1 | Comparison of general data of patients.

Project	SIB-IMRT group ($n = 92$)	LCB-IMRT group ($n = 108$)	t/χ^2	p
Gender			0.466	0.495
Male	63	69		
Woman	29	39		
Age (years)	60.28 ± 6.37	59.92 ± 6.18	0.405	0.686
Lesion length (cm)	4.71 ± 1.16	4.92 ± 1.59	1.051	0.295
Food intake			0.060	0.806
Common food	27	30		
Semi/liquid food	65	78		
Hoarseness			1.047	0.306
Yes	5	10		
No	87	98		
Lesion site			0.322	0.570
Cervical segment	8	12		
Thoracic segment	84	96		
Clinical t staging			0.029	0.864
T1	33	40		
T2–4	59	68		
Clinical n-staging				
N0	32	38	0.004	0.953
N1–2	60	70		
Chemotherapy			0.363	0.547
Yes	55	60		
No	37	48		

Comparison of Short-Term Efficacy Between the Two Groups

The recent total effective rates of the SIB-IMRT group and the LCB-IMRT group in the same period were 95.65% and 90.74%, respectively, and there was no significant difference between the two groups ($p > 0.05$). See **Table 2**.

TABLE 2 | Comparison of short-term efficacy between the two groups (n,%).

	Complete remission	Partial response	Stable condition	Disease progression	Total effective rate
SIB-IMRT group ($n = 92$)	31	57	3	1	95.65%
LCB-IMRT group ($n = 108$)	28	70	6	4	90.74%
χ^2					1.841
p					0.175

Comparison of Exposure of Endangered Organs Between the Two Groups

The average radiation doses to left and right lung, heart and spinal cord in the same period of the SIB-IMRT group were significantly lower than those in the LCB-IMRT group, and the differences were statistically significant ($p < 0.05$). See **Figures 1–4**.

Comparison of the Incidence of Adverse Reactions Between the Two Groups

The incidences of radiation esophagitis, radiation pneumonitis, radiation tracheitis, gastrointestinal reaction and bone marrow suppression in the SIB-IMRT group and the LCB-IMRT group were 80.43% and 79.63%, 9.78% and 10.19%, 17.39% and 25.93%, 33.70% and 34.26%, 59.78% and 62.04%, respectively. There was no significant difference in the incidence of adverse reactions between the two groups ($p > 0.05$). See **Figure 5**.

Comparison of Long-Term Efficacy Between the Two Groups

The one-year and three-year overall survival rates in the SIB-IMRT group and the LCB-IMRT group were 82.61%, 42.39% and 77.78%, 34.26%, respectively, and the median survival times were 38 and 29 months, respectively. The local control rates in the SIB-IMRT group and the LCB-IMRT group in

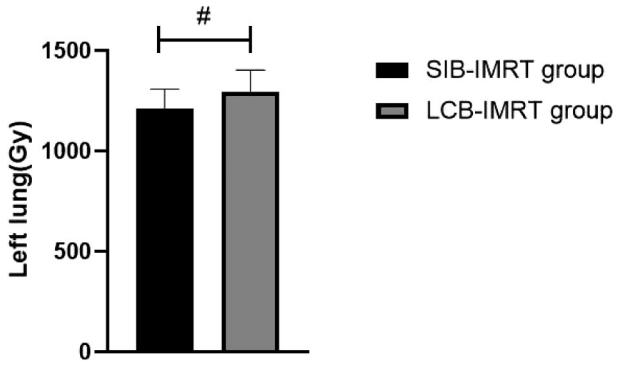

FIGURE 1 | Comparison of average left lung exposure between the two groups. Note: Compared with the LCB-IMRT group, $^{\#}p < 0.05$.

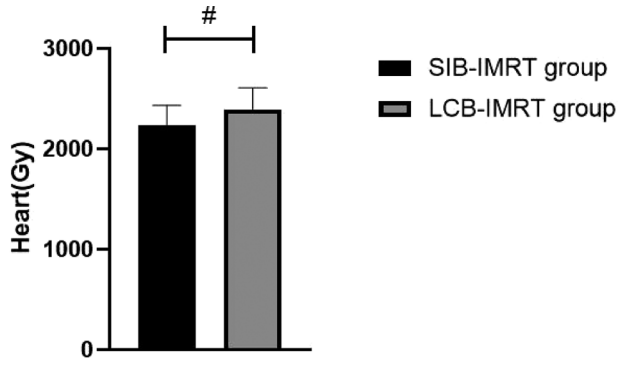

FIGURE 3 | Comparison of average heart exposures between the two groups. Note: Compared with the LCB-IMRT group, $^{\#}p < 0.05$.

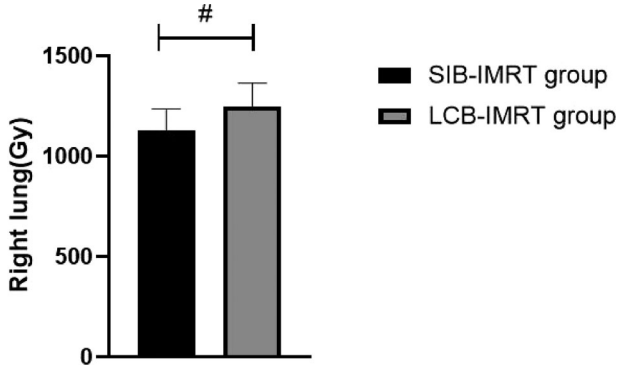

FIGURE 2 | Comparison of average right lung exposure between the two groups. Note: Compared with the LCB-IMRT group, $^{\#}p < 0.05$.

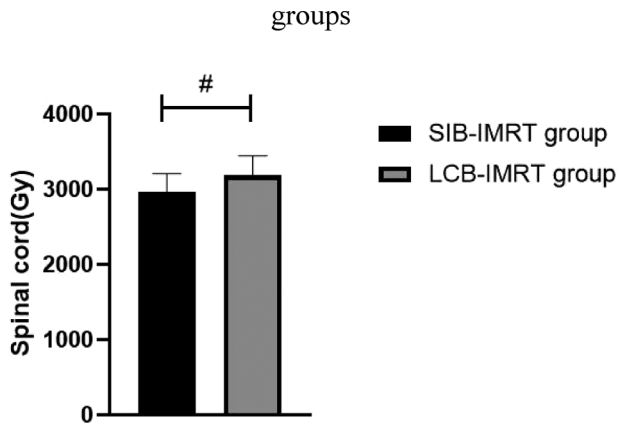

FIGURE 4 | Comparison of average spinal cord exposures between the two groups. Note: Compared with the LCB-IMRT group, $^{\#}p < 0.05$.

one-year and three-year were 84.78%, 56.52% and 75.93%, 41.67%, respectively. The three-year local control rate in the SIB-IMRT group was higher than that in the LCB-IMRT group ($p < 0.05$), but there was no significant difference in the one-year and three-year overall survival rates between the two groups ($p > 0.05$). See **Figures 6** and **7**.

DISCUSSION

Esophageal cancer is one of the common digestive tract cancers in China. Most patients have no obvious clinical symptoms in the early stage. Therefore, when seeing a doctor, most patients are in the advanced stage, and most of them are elderly patients. And surgical radiotherapy and chemotherapy are the main treatment methods (12, 13). Although intensity-modulated radiation therapy has been increasingly used in the treatment of esophageal cancer in recent years, local uncontrolled and recurrence are still the main methods of treatment failure. Therefore, it may be an important method to improve the curative effect of esophageal cancer by using the maximum dose in the tumor area and reducing the irradiated dose to the surrounding normal tissues (14–16).

The target area of the cervical and upper thoracic esophagus is large and irregular in shape, which makes it difficult to complete a single plan of conformal radiotherapy technology, requiring segmental irradiation. In addition, due to the limitation of normal tissue dose, the local dose in the target area is relatively low (17). However, the local dose increase of esophageal cancer should be carefully considered, especially the single dose which is prone to perforation and bleeding. In addition, the esophagus is located in the chest cavity, adjacent to the lung, heart, spinal cord and other important organs, with limited local stress increase (18–20). In this study, we compared the short-term efficacy of patients in the two groups who received SIB-IMRT and LCB-IMRT. The results showed that there was no significant difference between the two groups. However, the average exposure of left and right lung, heart and spinal cord in patients treated with SIB-IMRT was lower than that of LCB-IMRT. The SIB-IMRT not only has the advantages of highly conformal dose distribution of

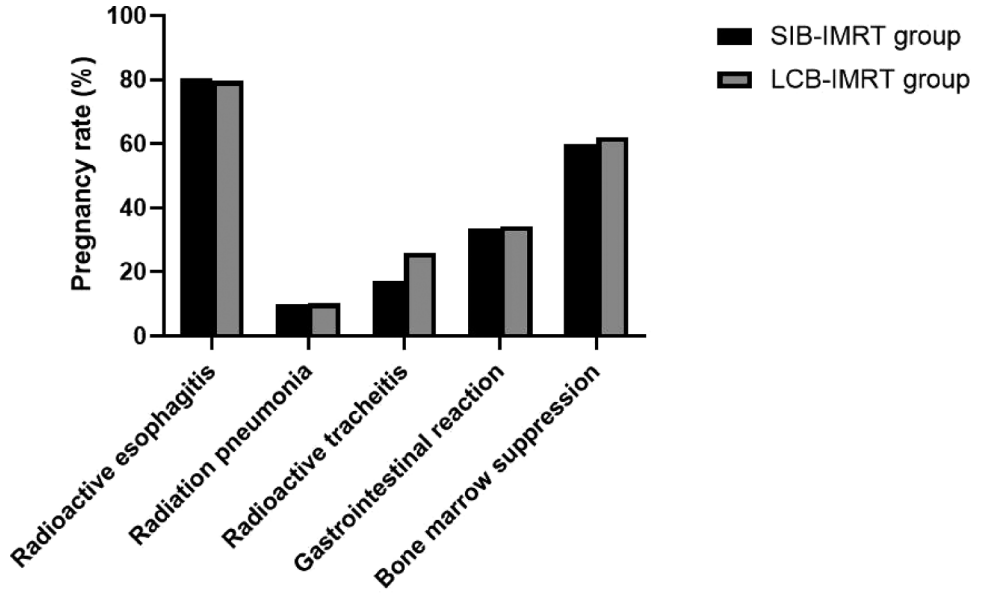

FIGURE 5 | Comparison of the incidence of adverse reactions between the two groups.

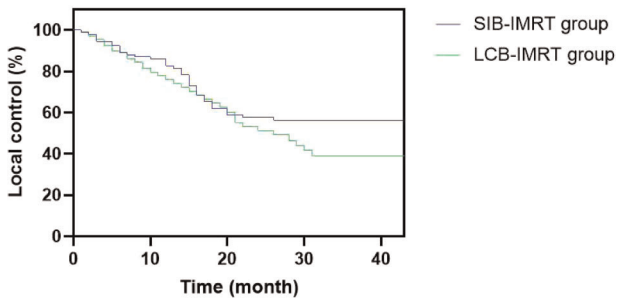

FIGURE 6 | Comparison of local control curves between the two groups.

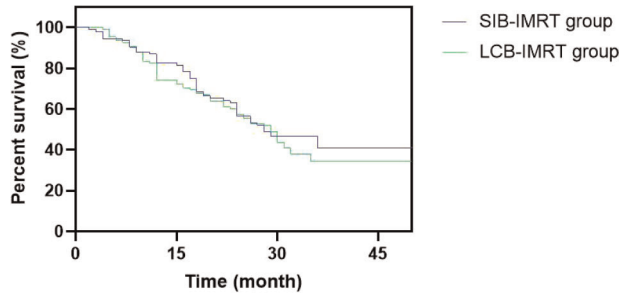

FIGURE 7 | Comparison of survival curves of patients between the two groups.

intensity-modulated radiotherapy and effective protection of surrounding normal organs, but also has the advantages of high efficiency, accuracy, high biological effect and satisfactory dose distribution in the target area by using field-in-field irradiation technology, so as to reduce the dose to some dangerous organs, especially to better protect heart and lung (21–24).

This study showed that there was no significant difference between the two groups in the incidence of adverse reactions such as radiation esophagitis, radiation pneumonia, radiation tracheitis, gastrointestinal reactions and bone marrow suppression. Concurrent chemotherapy will inevitably aggravate treatment-related adverse reactions, especially acute radiation esophagitis, which often leads to the delay or interruption of radiotherapy plans (25). Compared with the traditional LCB-IMRT, the SIB-IMRT can achieve the purpose of receiving different doses in different target areas at the same time, shorten the timeof radiotherapy and improve the intensity and efficiency of treatment. From the perspective of radiobiology, the increase of a single dose can make the total tumor volume obtain a higher equivalent biological dose, thereby improving the radiobiological effects and reducing the radiation dose to the surrounding organs (26–29).

Chemotherapy is an effective method for the clinical treatment of advanced esophageal cancer. However, as a strong stressor, it will directly invade the patient's immune system, causing serious trauma to the body, resulting in negative psychology such as anxiety and depression, further affecting the patient's immune system, reducing the body's immunity to tumor cells, and even failing to successfully complete chemotherapy. Systematic and standardized management of patients with esophageal cancer undergoing chemotherapy can meet the nursing requirements at all stage of chemotherapy. At the same time, paying attention to

individualzed nursing, strengthens psychological nursing, improving patients' compliance with treatment, and having strong clinical applicability are of great significance to ensure the normal progress of patients' chemotherapy (30).

In this study, systematic and standardized management was selected, while the advantages of SIB-IMRT were fully utilized, in an attempt to kill the subclinical lesions and well control the local lesion and metastatic lymph nodes within the limited treatment time. The results showed that the local control rate during the same period of three years by SIB-IMRT group was superior to that by the LCB-IMRT group. These results suggest that SIB-IMRT may be a better option for improving long-term local control. Although the overall survival rates of the patients in the two groups are similar, the survival curve of the concurrent dosed intensity-modulated radiotherapy shows a significant increase trend compared with the sequential dosed intensity-modulated radiotherapy, and the survival curve remains at about 50%. The effect of SIB-IMRT in radical chemoradiotherapy for esophageal cancer was confirmed.

To sum up, the SIB-IMRT group can reduce the exposure of some dangerous organs and has certain advantages in improving the local control rate of esophageal cancer. However, this study still has certain limitations. The individualized treatment plan with sub-layers needs long-term results of multi-centers and more cases in the future to be canfirmed.

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 Consent for this study was approved by our medical ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WD, WS and XZ are the mainly responsible for the writing. JS is mainly responsible for data analysis. CS, JX and XZ are responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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Intensity-Modulated Radiotherapy and Three-Dimensional Conformal Radiotherapy Combined with Intracavitary Posterior Radiotherapy for the Treatment of Medium-Term and Advanced Cervical Cancer: Efficacy, Safety and Prognostic Factors

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Objective: To explore the efficacy, safety, and prognostic factors of intensity modulated radiation therapy (IMRT) and three dimensional conformal radiation therapy (3D-CRT) combined with intracavitary posterior radiotherapy for medium-term and advanced cervical cancer.

Methods: Retrospectively analyze the clinical data of 104 patients with medium-term and advanced cervical cancer who were treated in the radiotherapy department of our hospital from September 2015 to March 2017. According to the different radiotherapy techniques, they were divided into the IMRT combined with intracavitary posterior radiotherapy group ($n = 52$) and the 3D-CRT combined with intracavitary posterior radiotherapy group ($n = 52$). Observe and compare the short-term efficacy, occurrence of adverse reactions and overall survival rate of the two groups. The clinicopathological characteristics of the survival group and the death group were compared, and univariate analysis and multiple logistic regression models were used to analyze the relationship between the clinicopathological characteristics and the patient's prognosis.

Results: The total effective rate of IMRT combined with intracavitary posterior radiotherapy group was 96.15%, which was higher than that of 3D-CRT combined with intracavitary posterior radiotherapy group (88.46%), but the difference was not statistically significant ($p > 0.05$). The incidence of digestive system injury, thrombocytopenia, and radiation proctitis in the IMRT combined intracavitary posterior radiotherapy group was lower than that of the 3D-CRT combined intracavitary posterior radiotherapy group, and the differences were statistically significant ($p < 0.05$). The prognosis and survival of the two groups of patients were similar, and the

difference was not statistically significant ($p > 0.05$). Pathological classification, clinical stage, and lymph node metastasis are independent influencing factors of 3-year prognosis in patients with medium-term and advanced cervical cancer ($p < 0.05$).

Conclusion: IMRT combined with intracavitary posterior radiotherapy is equivalent to 3D-CRT combined with intracavitary posterior radiotherapy, but it can reduce the incidence of adverse reactions in patients with medium-term and advanced cervical cancer, and has higher safety. Pathological typing, clinical staging, Lymph node metastasis were independent factor affecting the prognosis of patients. In clinical treatment, IMRT combined with intracavitary posterior radiotherapy is more recommended as a treatment plan for patients with medium-term and advanced cervical cancer.

Keywords: medium-term and advanced cervical cancer, intensity modulated radiation therapy, three-dimensional conformal radiotherapy, efficacy, prognosis

INTRODUCTION

Cervical cancer is one of the most common malignant tumors in women. Early stage cervical cancer is usually treated with surgery, while radiotherapy and chemotherapy are the main treatments in the medium-term and advanced stages (1). At present, external irradiation combined with intracavitary posterior radiotherapy and concurrent chemotherapy is the standard method for the treatment of medium-term and advanced cervical cancer. Traditional radiotherapy methods such as four-field box-type and front-to-back penetrating irradiation have been used earlier and are widely used, but their damage to the digestive tract, urinary tract and hematopoietic systems is relatively serious (2, 3). Intensity modulated radiation therapy (IMRT) and three dimensional conformal radiation therapy (3D-CRT) are new radiotherapy techniques, and there is no unified understanding on the specific effects of these two techniques. However, studies have confirmed that these two techniques can increase the irradiation dose of target area and effectively reduce the irradiation dose of surrounding normal tissues and organs, effectively control tumors and reduce damage to the body (4, 5). Whether IMRT and 3D-CRT can replace traditional radiotherapy in the treatment of medium-term and advanced cervical cancer is worth looking forward to. Therefore, in this study, IMRT combined with intracavitary radiotherapy was used to treat patients with medium-term and advanced cervical cancer, and compared with 3D-CRT combined with intracavitary posterior radiotherapy, in order to provide theoretical support for the efficient treatment of patients with medium-term and advanced cervical cancer. The specific research is shown as follows.

MATERIALS AND METHODS

General Information

A total of 104 patients with medium-term and advanced cervical cancer who were admitted to our hospital from September 2015 to March 2017 were selected. All patients met the diagnostic criteria for medium-term and advanced cervical cancer (6); Diagnosed by pathological and imaging examinations; tumor FIGO stage was IIB–IVA; Bian's score was ≥70 points; expected survival >3 months; abnormal liver and kidney function and other organ diseases were excluded. According to the treatment method, the patients were divided into IMRT and 3D-CRT combined with intracavitary posterior radiotherapy groups, with 52 patients in each group. The age of IMRT combined with intracavitary posterior radiotherapy group was 32–77 years old, with an average age of (55.03 ± 7.14) years; 32 cases of IIB, 10 cases of IIIA, 9 cases of IIIB, and 1 case of IVA; 49 cases of squamous cell carcinoma and 3 cases of adenocarcinoma; 30 patients had tumor diameter ≥4 cm, and 22 patients had tumor diameter <4 cm. The age of 3D-CRT combined with intracavitary posterior radiotherapy group was 33–78 years old, with an average of (54.86 ± 7.25) years old; 34 cases of IIB, 9 cases of IIIA, 8 cases of IIIB, and 1 case of IVA; 50 cases of squamous cell carcinoma and 2 cases of adenocarcinoma; 29 patients had tumor diameter ≥4 cm, and 23 patients had tumor diameter <4 cm. There was no statistical difference in general clinical data such as age, FIGO stage, pathological classification and tumor diameter between the two groups ($p > 0.05$), which were comparable.

Research Methods

In terms of the IMRT combined with intracavitary posterior radiotherapy group: One day before localization, the patients underwent bowel preparation by oral administration of Meglumine. Before localization, the patients' bladder was filled and the rectum was emptied. The joints were fixed with vacuum pad and thermoplastic film, and CT scan was performed. Clinical target volume (CTV): including the primary area of cervical tumor (parametrial triangle, cervix, vagina, etc.) and pelvic metastatic area (parametrium, paravaginal tissue, pelvic lymphatic area, etc.). Planned target volume (PTV): CTV was expanded by 5 mm in the S/I, A/P, and R/L directions, respectively. Gross tumor target volume (GTV): the cervical mass and lymph node metastases that have been diagnosed by imaging or definite diagnosis. Lymph node area delineation: The lymph node area and corresponding blood vessel area were delineated along the

lymph node area and the corresponding blood vessel area in patients diagnosed with lymph node metastasis, followed by delineation of the para-aortic lymph nodes, anterior iliac, external iliac, internal iliac, common iliac and obturator foramen. The range was from the fifth lumbar vertebra to the obturator foramen. The PTV dose was 1.8 Gy/time, and the total dose was 48.60–50.40 Gy/27–28, 5 times a week. PTV adopted 7-field intensity-modulated irradiation, and was irradiated with an isodose curve of 95% of PTV, and the minimum and maximum doses of the target area were within the range of ±10% of the prescribed dose. After 25 times of external irradiation, the irradiation was stopped, intracavitary posterior radiotherapy was performed once a week, 6–7 Gy/time, with a total dose of 30–36 Gy/5–6 f. The radiation doses of the small intestine, rectum and bladder were V45 < 20%, V45 < 40% and V45 < 30%, respectively.

In terms of the 3D-CRT combined with intracavitary posterior radiotherapy group: the positioning and target delineation methods were the same as above. The target area was irradiated by four-field box type, 6MV-X-ray, 180–200 cGy/time, the total dose was 4,500–5,000 cGy. Conventional segmentation irradiation, 5 times a week. The method of intracavitary posterior radiotherapy was the same as above.

Observation indicators: The short-term efficacy and adverse reactions of the two groups of patients were recorded, analyzed and compared, and the adverse reactions included acute and chronic radiation injury. Acute and chronic radiation injuries were divided into grades I, II, III, and IV. The higher the grade, the more severe the adverse reaction. Acute radiation injury included digestive tract, blood, and urinary system injury; chronic radiation injury was mainly intestinal and urinary system injury, including radiation cystitis and proctitis. After radiotherapy, consolidation chemotherapy was performed according to the specific conditions of the patients. During hospitalization, the patients were regularly checked for blood routine every week. In the event of an acute chemoradiotherapy reaction, medical staff need to timely treat the symptoms according to the specific conditions of the patient.

Efficacy evaluation: The changes in tumor size were observed by CT or MRI, and graded according to the WHO efficacy evaluation criteria. including disease progression (PD): the product of the largest vertical diameter and the largest diameter of the lesion (the product of the two diameters) increased by more than 25% compared with that before radiotherapy, and time continued more than 30 days; stable disease (SD): the two-dimensional product of the lesion decreased by less than 50% or increased by less than 25% compared with that before radiotherapy, and lasted for more than 30 days; partial remission (PR): the two-dimensional product of the lesion decreased by at least 50% compared with that before radiotherapy, duration of more than 30 days; complete remission (CR): the lesions completely disappeared, the duration of more than 30 days. Total effective rate = (PR + CR) / total number of cases × 100%.

Follow-up: Patients were regularly followed up every 3 months by outpatient or telephone, all patients were followed up for 3 years. The follow-up contents included patient survival time and adverse reactions. Survival time was calculated from the time of diagnosis to the date of death or the end of follow-up.

Statistical Methods

SPSS 22.0 software was used for processing. The measurement data conforming to normal distribution were expressed as mean ± standard deviation, and t test was used for comparison. Count data were expressed as (%), and χ^2 test was used for comparison. Survival curves were drawn by using the Kaplan-Meier method. The test level was $\alpha = 0.05$, and $p < 0.05$ was considered statistically significant.

RESULTS

Comparison of Short-Term Curative Effect between Two Groups of Patients

The results showed that the total effective rate of IMRT combined with intracavitary posterior radiotherapy group was 96.15%, which was higher than that of 3D-CRT combined with intracavitary posterior radiotherapy group (88.46%), but the difference was not statistically significant ($p > 0.05$), as shown in **Table 1**.

Comparison of Adverse Reactions of the Two Groups of Patients

The results showed that the incidence of digestive system injury, thrombocytopenia, and radiation proctitis in the IMRT combined with intracavitary posterior radiotherapy group were 28.85%, 9.62%, and 19.23%, respectively, which were lower than those in the 3D-CRT combined with intracavitary posterior radiotherapy group (55.77%, 40.38%, 48.08%), the differences were statistically significant ($p < 0.05$). There was no significant difference in the incidence of hemoglobin reduction, leukopenia, urinary system injury and radiation cystitis between the two groups ($p > 0.05$), as shown in **Table 2**.

Comparison of Prognosis and Survival between the Two Groups of Patients

The results showed that during the 3-year follow-up, the total number of deaths was 32 cases. Among them, the mortality rate of IMRT combined with intracavitary posterior radiotherapy was 25.00% (13/52) lower than that of 3D-CRT

TABLE 1 | Comparison of effective rates between the two groups of patients (*n*, %).

Group	PD	SD	PR	CR	PR + CR
IMRT combined with intracavitary posterior radiotherapy group	0	2	27	23	50 (96.15)
3D-CRT combined with intracavitary posterior radiotherapy group	0	5	26	20	46 (88.46)
χ^2	–	–	–	–	2.167
p	–	–	–	–	0.141

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

Classification	Adverse reaction	IMRT combined with intracavitary posterior radiotherapy group	3D-CRT combined with intracavitary posterior radiotherapy group	χ^2	*p*
Acute	Digestive damage	15 (28.85)	29 (55.77)	7.721	0.005
	Thrombocytopenia	5 (9.62)	21 (40.38)	13.128	0.001
	Decreased hemoglobin	24 (46.15)	26 (50.00)	0.154	0.695
	Leukopenia	35 (67.31)	34 (65.38)	0.043	0.836
	Urinary system damage	8 (15.38)	11 (21.15)	0.580	0.446
Chronic	Radiation proctitis	10 (19.23)	25 (48.08)	9.689	0.002
	Radiation cystitis	3 (5.77)	6 (11.54)	1.095	0.295

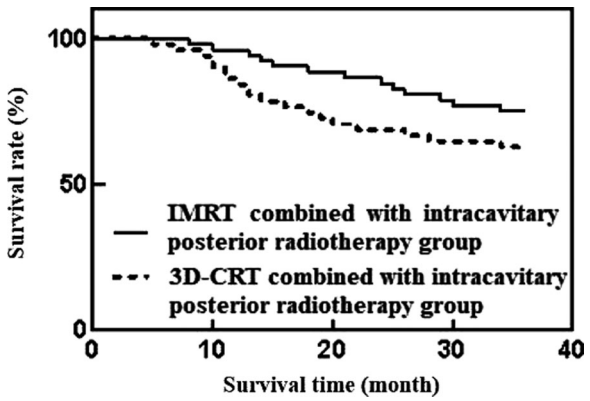

FIGURE 1 | Comparison of prognosis and survival between the two groups of patients.

combined with intracavitary posterior radiotherapy group, which was 36.54% (19/52), and the median survival time of both groups was 36 months. The difference was not statistically significant ($p > 0.05$), as shown in **Figure 1**.

Analysis of Prognostic Factors of Patients with Medium-Term and Advanced Cervical Cancer

The results showed that there were significant differences in case type, clinical stage, tumor diameter, and lymph node metastasis between the survival group and the death group ($p < 0.05$). There was no statistically significant difference in age ($p > 0.05$) as shown in **Table 3**.

Multivariate Analysis of Prognosis of Patients with Medium-Term and Advanced Cervical Cancer

Logistic regression analysis showed that pathological type, clinical stage and lymph node metastasis were independent influencing factors of 3-year prognosis of patients with medium-term and advanced cervical cancer ($p < 0.05$), while tumor diameter had no significant effect on 3-year prognosis of patients ($p > 0.05$), as shown in **Tables 4** and **5**.

DISCUSSION

The incidence of cervical cancer is increasing year by year, and the patients tend to be younger. Therefore, it is particularly important to reduce the mortality rate of cervical cancer and control the development of cervical cancer (7). External beam radiation combined with intracavitary radiotherapy and concurrent chemotherapy in the treatment of medium-term and advanced cervical cancer can prevent tumor metastasis and local recurrence. The scope of external irradiation not only includes the uterus, paracyngeal tissues, cervix and vagina, but also needs to cover the pelvic lymphatic drainage area (8, 9). Traditional external irradiation techniques are relatively backward, and the incidence of various complications has increased, which has been gradually replaced by IMRT, 3D-CRT and other new radiotherapy technologies (10).

3D-CRT is based on the reconstruction of three-dimensional image of human body structure, and can accurately distinguish normal tissue and tumor tissue. The radiation dose of the rectum, bladder and other organs at risk can be reduced by adjusting the radiation direction and changing the radiation dose (11). IMRT is an in vitro three-dimensional irradiation method developed through improved 3D-CRT technology. By adjusting the output dose, the radiation shape in all three-dimensional directions can be kept consistent with the target area, and the radiation dose of organs at risk and normal tissues around the target area can be reduced. so as to effectively treat and control tumors (12). Compared with 3D-CRT technology, IMRT technology can better adapt to irregularly shaped tumors, and at the same time, by controlling the dose intensity, a high-dose target area can be concentrated in the target area (13). IMRT can reduce the acute myelosuppression and other reactions caused by concurrent chemotherapy, which can reduce the harm to surrounding tissues and reduce the occurrence of various complications.

IMRT and 3D-CRT are widely used in cancer treatment. Guillemin et al. (14) used IMRT and 3D-CRT in the treatment of non-small cell lung cancer and found that IMRT can more effectively reduce the radiation dose to the surrounding organs at risk of patients. In cervical cancer, Contreras' team (15) found that IMRT can reduce the amount of rectal and bladder tissue around the tumor, ensure the coverage of tumor tissue, and alleviate complications caused by radiotherapy. This study found that the total effective rate of IMRT combined with intracavitary posterior radiotherapy was higher than that of 3D-

TABLE 3 | Analysis of prognostic factors of patients with medium-term and advanced cervical cancer (*n*, %).

Influencing factors	Survival group (*n* = 72)	Death group (*n* = 32)	χ^2	*p*
Age (Years)				
≥55	35 (48.61)	14 (43.75)	0.210	0.647
<55	37 (51.39)	18 (56.25)		
Pathological typing				
Squamous cell carcinoma	71 (98.61)	28 (87.50)	5.976	0.015
Adenocarcinoma	1 (1.39)	4 (12.50)		
Clinical stage				
II B	41 (56.94)	25 (78.12)	4.286	0.038
III–IV	31 (43.06)	7 (21.88)		
Tumor diameter (cm)				
≥4	46 (63.89)	13 (40.62)	4.85	0.027
<4	26 (36.11)	19 (59.38)		
Lymph node metastasis				
Yes	32 (44.44)	26 (81.25)	12.166	0.001
No	40 (55.56)	6 (18.75)		

TABLE 4 | Assignment table.

Influencing factors	Assignment
Pathological typing	Squamous cell carcinoma = 1, Adenocarcinoma = 2
Clinical stage	II B = 1, III ~ IV = 2
Tumor diameter	≥4 cm = 1, <4 cm = 2
Lymph node metastasis	Yes = 1, No = 2

TABLE 5 | Multivariate analysis of prognosis of patients with medium-term and advanced cervical cancer.

Influencing factors	*B*	*SE*	*Walds*	df	Sig.	Exp(B)
Pathological typing	2.615	1.034	6.398	1	0.027	5.492
Clinical stage	1.569	0.523	8.741	1	0.015	6.937
Tumor diameter	1.037	0.594	3.317	1	0.0145	2.459
Lymph node metastasis	1.375	0.509	7.321	1	0.023	6.558

CRT combined with intracavitary posterior radiotherapy, but the difference was not statistically significant. There was no significant difference in the overall survival rate and median survival time between the two groups. The results showed that the treatment efficacy of the two regimens were equivalent. However, the incidences of gastrointestinal tract injury, thrombocytopenia and subsequent radiation proctitis in the IMRT combined with intracavitary posterior radiotherapy group were significantly lower than those in the 3D-CRT combined with intracavitary posterior radiotherapy group. This suggested that when all conditions of intracavitary posterior radiotherapy were the same, IMRT can relieve gastrointestinal and hematological injury, with higher safety.

The results of this study showed that pathological type, clinical stage and lymph node metastasis were independent prognostic factors for patients with medium-term and advanced cervical cancer. Among them, patients with squamous cell carcinoma, late clinical stage, and lymph node metastasis have higher mortality rates. This may be related to the fact that the cancer cells of squamous cell carcinoma patients have invaded into the muscle layer, the distance from the radiation source is far, patients with advanced staging have increased tumor uncontrollability, and patients with lymph node metastasis have wider tumor distribution (16, 17). Yüksel et al. (18), Ramlov et al. (19) found that case typing, tumor size, lymph node metastasis, etc. are all risk factors for the prognosis of patients with medium-term and advanced cervical cancer. However, this study showed that tumor size was not a prognostic factor for patients with medium-term and advanced cervical cancer, which was partially deviated from previous studies. This may be related to the small sample size and short follow-up time in this study. It is necessary to expand the sample size and extend the follow-up time in the future to improve the credibility of the research results.

In conclusion, IMRT combined with intracavitary posterior radiotherapy has the same curative effect as 3D-CRT combined with intracavitary posterior radiotherapy, but it can reduce the incidence of adverse reactions of patients with medium-term and advanced cervical cancer and has higher safety. Pathological type, clinical stage, and lymph node metastasis are independent factors affecting the prognosis of patients. In clinical treatment, IMRT combined with intracavitary posterior radiotherapy is more recommended as the treatment plan for patients with medium-term and advanced cervical 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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by This study was approved by the ethics committee of our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The first author is KY, he is responsible for the writing, research design, data analysis of the article. LZ is responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Er,Cr:YSGG Laser Therapy for Drug-Induced Gingival Overgrowth: A Report of Two Case Series

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Background: Drug-induced gingival overgrowth is common but neglected in patients with systemic disease medications until it seriously affects the quality of life.

Methods: Initial periodontal treatment, combined with water laser surgery, was performed sequentially in two cases.

Results: The therapeutic effect was good, and there was no recurrence along with good oral hygiene.

Conclusion: Water laser equipment surgery, as well as initial periodontal treatment, required that surgeons are trained specifically. A tool was devised for various oral diseases, and it was safer, more efficient and more comfortable than others.

Keywords: laser therapy, drug-induced gingival overgrowth (DIGO), surgery, aesthetics, oral health

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INTRODUCTION

Predisposing drugs for gingival enlargement mainly fall into three types: antiepileptic drugs (such as Phenytoin), immunosuppressive agents (such as Cyclosporin), and calcium channel antagonists (such as Nifedipine), while its severity can be modified by the degree of primary gingival inflammation and oral hygiene conditions (1). Gingival enlargement may lead to chewing and pronunciation difficulties regardless of oral facial aesthetics, and the major managements are initial periodontal treatment and surgical periodontal therapy. In the past few years, increasing studies have revealed the superiority of laser therapy over conventional surgical treatment, which manifested as less infection, better hemostatic effect, clearer surgical field, shorter operative time, less anesthetic dosage, and less postoperative discomfort with remarkable therapeutic effect (2). The water laser technique, other than having the above advantages, overcomes the deficiency of heat production caused by conventional laser techniques owing to its unique therapeutic mechanism, allowing its wide applicability in the treatment of diseases of oral soft and hard tissues. Here, we report the cases of two patients who underwent water laser-based gingivectomy for drug-induced gingival overgrowth (DIGO) following initial periodontal treatment. The patients suffered from slight bleeding and discomfort during the operation, with no postoperative pain or bleeding and showed rapid recovery. The gingiva of the patients gradually recovered to normal after 1 year of follow-up, and there were no signs of recurrence. Written informed consent was obtained from the patients for the publication of any potentially identifiable images or data included in this article.

CASE DESCRIPTION 1

General Information

The first patient who was a male and 42 years old complained of 1 year of gingival overgrowth with bleeding from brushing at his first visit. Three years prior to this diagnosis, the patient underwent a kidney transplant in another hospital and took Tacrolimus and Felodipine after this. He had a history of kidney disease and hypertension but no allergies to medications or food.

Examinations

Intraoral Examination (Figure 1)

The patient's oral hygiene was in a poor condition, which manifested as a dental calculus (++), with a large amount of materia alba, swelling and tumor-like overgrowth of the gingiva, obtuse morphology, a nodular gingival enlargement of the anterior teeth covering more than 2/3 of the crown with a wide base, a barely noticeable pedicle, little mobility and a tough and substantial texture, PD: 4–6 mm, BI: 3–4.

Extraoral Examination

The patient had facial symmetry, no obvious deformity or defects, normal mouth opening and shape, and no enlargements of bilateral cervical or submandibular lymph nodes.

Auxiliary Examination (Figure 1)

Cone beam computed tomography (CBCT) showed a slightly horizontal alveolar bone absorption of full teeth and a slightly vertical alveolar bone absorption of the bilateral posterior teeth. The periodontal examination tables show the presence of deep pockets around the periodontium.

Diagnosis

DIGO and chronic periodontitis were diagnosed.

Treatment Plan

Oral hygiene education; initial periodontal treatment; surgical periodontal therapy; periodontal maintenance therapy.

Treatment Procedure

Initial Periodontal Treatment

Oral hygiene education was imparted for this patient. The patient was informed of the correct control methods for dental plaque and was advised to develop good oral hygiene habits. Complete supragingival and subgingival scaling and root planning were recommended successively (cleansing with hydrogen peroxide after treatment followed by local iodophenol application). Regular re-examination was required.

Surgical Periodontal Therapy

A total of 4–6 weeks after the periodontal therapy, the gingival overgrowth of the upper and lower anterior teeth reduced, while aesthetics, mastication, and oral hygiene maintenance were still affected. Er,Cr:YSGG laser was used for the removal of the enlarged gingiva at labial (palate) 13–23 and 33–43 based on the external oblique incision. The gingival morphology was trimmed and hemostasis was performed. Postoperative anti-inflammatory treatment and chlorhexidine gargle rinse were managed for 5 days.

Periodontal Maintenance Therapy (Figure 3)

One year after the operation, the patient's oral hygiene was in good condition upon re-examination, with less plaque and pigmentation. The mouth gingiva was pinkish in color, with a tough texture and an improved gingival morphology, and

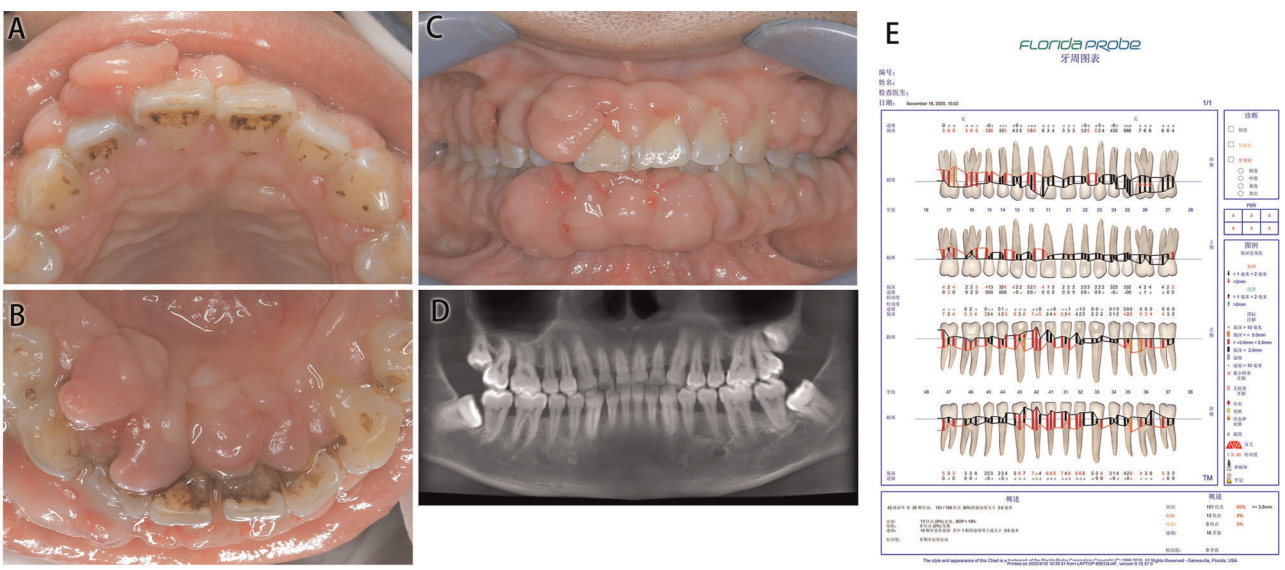

FIGURE 1 | Medical information on Case 1 at first diagnosis (before treatment). (**A**) Maxillary view. (**B**) Mandibular view. (**C**) Frontal view images. (**D**) Radiological images. (**E**) Periodontal examination tables.

there was no recurrence. The enlarged gingiva of the posterior teeth was not managed by periodontal surgery, but it greatly reduced after treatment.

CASE DESCRIPTION 2

General Information

The second patient who was a female and 67 years old gradually developed gingival swelling with bleeding 6 years ago and visited our hospital for a recent difficulty in food intake. The patient suffered from diabetes, coronary heart disease and hypertension for more than 10 years. She had well-controlled blood glucose and pressure by daily oral administration of Metformin Hydrochloride tablets and Amlodipine Besylate tablets.

Examination

Intraoral Examination (Figure 2)

This patient had poor oral hygiene, a large amount of plaque and materia alba and dental calculus (+++). The whole gingiva was bright red in color and manifested as spherical gingival enlargements covering more than 2/3 of the crown surface, with a tough texture and a tendency to bleed on touching. The upper and lower anterior teeth were spread, and teeth 31 and 41 were dislocated with 3° loosening.

Auxiliary Examination (Figure 2)

CBCT presented an alveolar bone absorption of teeth 31 and 41 to the apical part, and an absorption of teeth 32 and 42 to the 1/3 apical part. Full mouth examination was referred to the periodontal specialist examination table.

Diagnosis

DIGO was diagnosed.

Treatment Plan

Oral hygiene education; initial periodontal treatment; surgical periodontal therapy; supportive periodontal therapy.

Treatment Procedure

Initial Periodontal Treatment

Oral hygiene education was imparted. Complete supragingival and subgingival scaling and root planning were recommended to be performed consecutively. Inflammation was basically controlled in 4–6 weeks and regular re-examination was required.

Surgical Periodontal Therapy

Gingival swelling greatly subsided after initial treatment. The laser technique was used to generate a gingival physical appearance favorable for follow-up self-cleaning, by performing gingivectomy on 16–26 and 36–46 based on external oblique incision. The gingival morphology was trimmed and hemostasis was performed. The incision was protected by a periodontal pack. The patient was informed of postoperative precautions and asked to orally take antibiotics followed by chlorhexidine gargle rinse.

Supportive Periodontal Therapy (Figure 3)

In 1 week after the operation, the gingival swelling subsided significantly, and basically, a normal scallop-shaped gingiva was revealed.

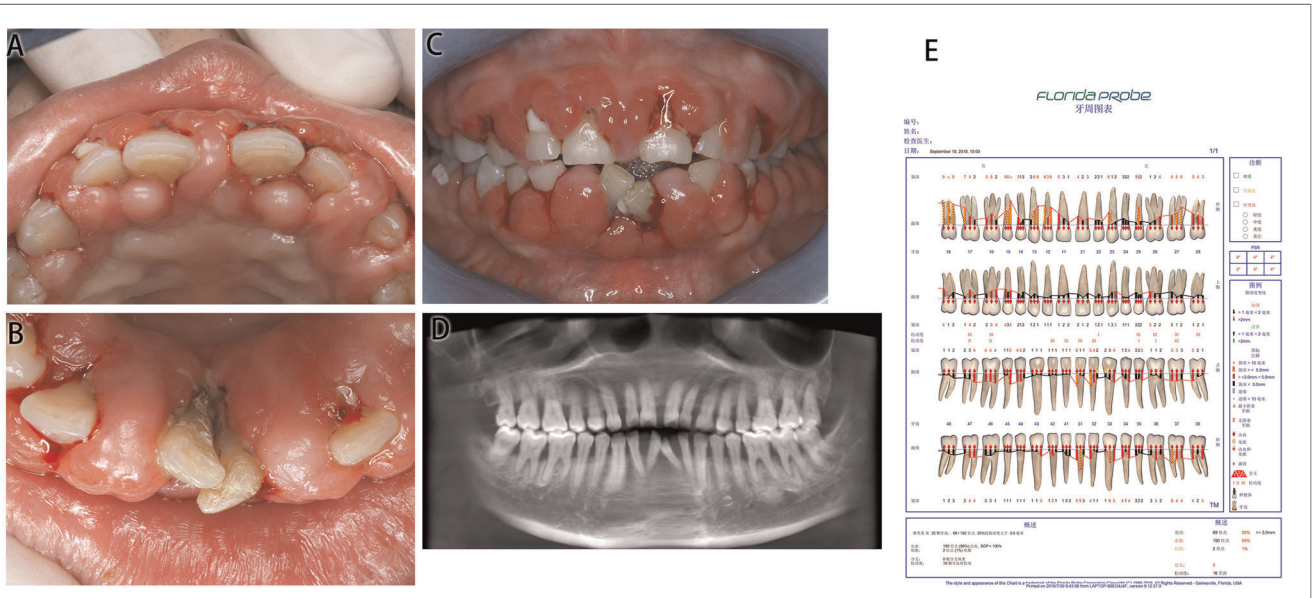

FIGURE 2 | Medical information on Case 2 at first diagnosis (before treatment). (**A**) Maxillary view. (**B**) Mandibular view. (**C**) Frontal view images. (**D**) Radiological images. (**E**) Periodontal examination tables.

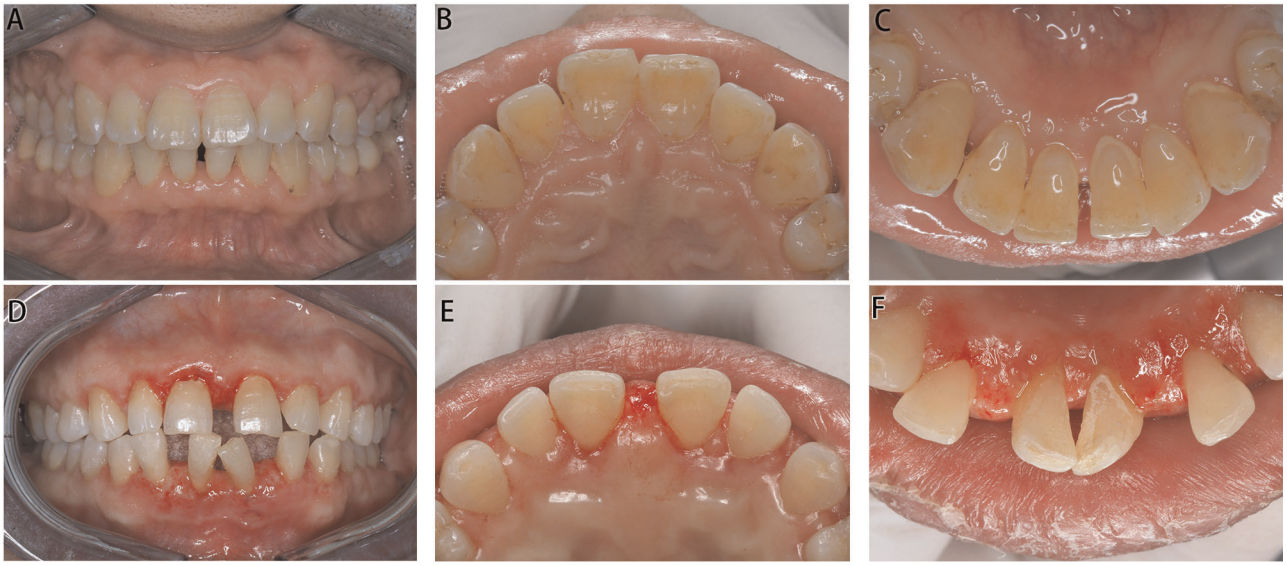

FIGURE 3 | Intraoral images of Cases 1 and 2 post operation. (**A**–**C**) Images of Case 1 in 1 year post operation. (**D**–**E**) Images of Case 2 in 1 week post operation.

DISCUSSION

A transplant operation often requires the use of immunosuppressants such as Cyclosporine and Tacrolimus to reduce the rejection of recipients (3). Renal hypertension is prone to become a complication requiring a regular use of antihypertensive drugs, which is significantly associated with DIGO (4–6). Such disease is reported to occur at a probability range of 8%–70% (7), modified by a patient's age, drug dosage, duration of action, combination therapy, and other factors (8). Drugs of different types function behind diverse mechanisms. Phenytoin mainly causes gingival fibrosis, Cyclosporine is mainly associated with inflammatory responses with less effect on gingival fibrosis, while Nifedipine induces both fibrosis and inflammation, resulting in gingival overgrowth (9). Additionally, plaque microorganisms play an important role in the occurrence and development of DIGO (10, 11). Therefore, initial periodontal treatment is a necessity that can greatly control gingival enlargement-related inflammation by removing plaque and calculus, decreasing stimulation on periodontal tissue and reducing periodontal inflammation.

Predominantly, DIGO is managed by flap surgery, gingivectomy, and laser resection (12). Conventional gingivectomy involves a 45° oblique incision with a scalpel under anesthesia, which generates greater pain post operation (13) compared with flap surgery but preserves more aesthetic gingival morphology (14). However, the risks of anesthesia pain and accident, postoperative swelling and pain and infection cannot be negated. Besides, the surgical field of surgeons might be stained with the effects of massive bleeding during operation, and postoperative complications are prone to develop. Laser-guided gingival resection is emerging as an alternative with many advantages such as less infection, better hemostatic effect, clearer surgical field, shorter operative time, less anesthetic dosage, and less postoperative discomfort with remarkable therapeutic effect (2). Such a technique, on the one hand, makes up for the disadvantages in conventional gingivectomy, contributing to easier hemostasis, clearer surgical field and favorable therapeutic effect and prognosis. On the other hand, postoperative morphological recovery of gingiva is more aesthetic in nature owing to the procedure of oblique incision. Mavrogiannis et al. (13) compared the efficacy of traditional gingivectomy with laser resection on DIGO and postoperative recurrence, and they indicated that laser resection was superior in terms of hemostasis and the reduction of recurrence rates. Another compelling evidence by Campos et al. (15) also revealed that, in two recurrent cases of DIGO by laser treatment, only slight bleeding and discomfort occurred during operation with no postoperative pain, bleeding or recurrence signs in 1 year of follow-up. This indicated that laser treatment might be associated with increased therapeutic efficacy and favorable outcome of DIGO.

Currently, the main laser types available for gingivectomy are semiconductor diode laser, CO_2 laser, Nd:YAG laser, Er:YAG laser, and Er,Cr:YSGG laser (16–19). Among these types, except the first one (semiconductor diode laser), the others are all capable of performing soft-tissue cutting and function to achieve hemostasis and sterilization (17, 20).

Er,Cr:YSGG laser therapy involves the release of a laser light of 2,780 mm in wavelength to activate water molecules and convert them into particles with high-speed kinetics, which enables the cutting function, and then causes the energy-released water to re-condense into normal water droplets. This allows the laser to perform its cutting function while protecting normal tissue and removing heat and debris from damaged tissue, which is in contrast to conventional surgery and the working of other laser

types. The Er,Cr:YSGG laser during treatment can produce a kind of morphine-like electrical biological stimulation at the surgical site, which blocks nerve conduction and achieves analgesia (21). This can contribute to a reduction of pain during treatment, which is particularly suitable for those who are sensitive to pain, such as children and the elderly, and those incapable of tolerating pain. The patients in this report had poor pain tolerance due to DIGO induced by immunosuppressants and antihypertensive drugs after a kidney transplant. Er,Cr:YSGG laser resection was then managed for gingival enlargements, resulting in obvious discomfort during and after operation. The patients actively cooperated with the doctors and recovered well post operation. Soares et al. (22) applied the Er,Cr:YSGG laser to treat the case of gingival enlargement in a child, which showed remarkable results. Besides, favorable gingival healing was observed upon oral examination in 1 week and 3 months of follow-up visits. This is also in agreement with the views mentioned earlier. Current studies have identified that the Er,Cr:YSGG laser, apart from being used for the resection of an enlarged gingiva, is also used for soft tissue mass resection of gingiva and for the treatment of oral mucosal diseases and hard tissue diseases with favorable therapeutic effects.

Patient Perspective

Due to its advantageous characteristics of efficient cutting function, less heat generation, less pain, active hemostasis, and coagulation, the Er,Cr:YSGG laser has been widely seen in oral and maxillofacial surgery, bone and soft tissue repair, and other oral surgeries (23). In addition, because of the safe, painless and comfortable treatment process, the fear of patients with regard to postoperative pain can be greatly alleviated, making it particularly suitable for children, the elderly and those incapable of tolerating pain. This also supports its promising application prospect. Although Er,Cr:YSGG laser equipment, as well as treatment cost, is huge, and surgeons are required to be trained specifically in its use, it is a tool that is safer, more efficient and more comfortable than others for the treatment of various oral diseases.

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 the institutional review board and human subject ethics board of Xiangya Stomatological Hospital of Central South University. Written informed consent was obtained from the patients 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. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Pediatric Critical Illness Score, Clinical Characteristics and Comprehensive Treatment of Children with Severe Mycoplasma Pneumoniae Pneumonia

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Objective: To investigate the clinical characteristics of children with severe Mycoplasma pneumoniae pneumonia (SMPP) and the correlation with pediatric critical illness score (PICS), and to explore the effect of combined treatment with antibiotics and glucocorticoids.

Methods: The medical records of 120 children with SMPP admitted to our hospital from January 2020 to June 2021 were retrospectively analyzed. Children with a PICS score greater than 80 within 24 h of admission were included in the non-critical group, those with a score of 71–80 were included in the critical group, and those with a score of ≤70 were included in the extremely critical group. The relevant clinical data and examination indicators of the three groups of children were intercepted and compared. Univariate and multifactorial logistic regression analyses were performed to analyze the correlation between clinical characteristics of children with SMPP and PICS. According to the different treatment methods, the children were subdivided into the control group ($n = 54$) who received antibiotics alone and the comprehensive group ($n = 66$) who received antibiotics combined with glucocorticoid therapy. The erythrocyte sedimentation rate (ESR), inflammation and immune indexes, symptom relief or disappearance time, hospitalization days, and clinical efficacy were compared between the two groups before and after treatment.

Result: Within 24 h of admission, among the 120 children with SMPP, 79 had PICS >80, 32 had PICS 71–80, and 9 had PICS ≤70. Before discharge, among the 120 children with SMPP, 99 had PICS >80, 17 had PICS 71–80, and 4 had PICS ≤70. Univariate analysis showed that there were no significant differences in gender ratio, ratio of fever duration >10 days, age and WBC among the three groups ($p > 0.05$), the differences in the ratio of abnormal ECG, the ratio of ≥2 pathogenic infections, the ratio of ≥2 systemic damages, CRP levels, and D-dimer levels were statistically significant when compared among the three groups ($p < 0.05$). Multivariate Logistic regression analysis

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showed that the number of Co-systemic damages and the level of D-dimer were negatively correlated with PICS classification ($p < 0.05$). After medication, ESR, CRP, IL-6, and CD8+ levels decreased and CD4+ and CD4+/CD8+ levels increased in both the control and comprehensive groups, and all changes were significant in the comprehensive group compared with the control group ($p < 0.05$). The antipyretic time, cough relief time, disappearance time of lung rales and hospitalization days in the comprehensive group were shorter than those in the control group ($p < 0.05$). The total effective rate of the comprehensive group (95.45%) was better than that of the control group (83.33%) ($p < 0.05$).

Conclusion: PICS can effectively reflect the clinical characteristics of children with SMPP. The comprehensive treatment effect of azithromycin combined with glucocorticoid is significantly better than that of azithromycin alone. It can effectively reduce the level of inflammation in children with SMPP, improve the immune function of children, and accelerate clinical recovery. It has promotion value.

Keywords: severe Mycoplasma pneumoniae pneumonia, pediatric critical illness score, clinical characteristics, antibiotics, glucocorticoids, comprehensive treatment

INTRODUCTION

Mycoplasma pneumoniae pneumonia (MPP) has gradually become one of the most common manifestations of community-acquired pneumonia in children. It refers to respiratory disease caused by Mycoplasma pneumoniae (MP) infection in children that are mostly mild and self-limiting, or respond well to macrolide antibiotics (1, 2). However, in recent years, pathogen resistance due to long-term antimicrobial drug therapy has increased, and the number of cases of severe Mycoplasma pneumoniae pneumonia (SMPP) has been increasing, with children having special clinical manifestations, obvious immune disorders, and poor efficacy of macrolide antibiotic therapy alone. Severe cases can cause necrotizing pneumonia (3), hepatitis (4), encephalitis (5), myocarditis (6), hemophagocytic syndrome (7), and even life-threatening in children. Early detection of severe cases and appropriate treatment can prevent or reduce the occurrence of serious sequelae or death.

Pediatric critical illness score (PICS) selects 10 indicators to score critical cases in children, all of which use quantitative data or objective indicators obtained from laboratory examination or physical examination, and the first score can accurately reflect the severity of children's illness, has a certain judgment value for the prognosis of the disease (8).

At present, there are few reports on the correlation between clinical features of SMPP and PICS, and there is also a lack of objective indicators and reports that can alert disease progression. In this study, 120 children with SMPP were included and grouped by PICS, and the relevant clinical data and examination indicators of different groups were retrospectively analyzed, in order to systematically evaluate the clinical characteristics of children with SMPP and their correlation with PICS scores, and to further clarify the guiding significance of PICS for the diagnosis and treatment of SMPP. In addition, some scholars have reported that the combination of drugs has a significant effect. This study conducted a secondary group analysis. According to the different treatment methods, the children were divided into the control group who received antibiotics alone and the comprehensive group who received antibiotics combined with glucocorticoid therapy. The erythrocyte sedimentation rate (ESR), inflammatory and immune indexes, symptom relief or disappearance time, hospitalization days, and clinical efficacy were analyzed and compared between the two groups before and after medication. The summary and analysis are as follows.

MATERIALS AND METHODS

Research Object

This study was a retrospective study, and the subjects were the medical records of 120 children with SMPP admitted to our hospital from January 2020 to June 2021. Inclusion criteria: ≤12 years old. Complete medical records. The symptoms and related examinations of the children met the diagnostic criteria for MPP in the "Handbook of Diagnosis and Treatment of Common Respiratory Diseases in Children", and on this basis met the following points: ① With symptoms of dyspnea and tachycardia; ② Accompanying hypoxemia; ③ Fever (armpit temperature) >38.5°C for more than 1 week; ④ Complications such as pleural effusion and atelectasis occured, and imaging data showed that more than two-thirds of the thoracic segments were involved; ⑤ Incorporate at least one system damage. With antibiotics or combined glucocorticoids in hospital. All children were evaluated by PICS within 24 h of admission. Exclusion criteria: Children with congenital developmental defects or immunodeficiency. Children with severe blood disease or cardiovascular disease. Children who had undergone tracheotomy, tracheal

intubation, and mechanically assisted ventilation before admission. Severely malnourished children.

Research Method

Through literature search, we collected and sorted out the clinical characteristics that may affect PICS in children with SMPP. Including gender, abnormal ECG, whether or not with ≥2 pathogenic infections, whether with ≥2 kinds of systemic damages, duration of fever, age, C-reactive protein (CRP), white blood cell count (WBC), plasma D-dimer level. Univariate analysis and multivariate Logistic regression analysis were performed to analyze the correlation between the above indicators and PICS in children with SMPP.

All the children were divided into the control group ($n = 54$) who received antibiotics alone and the comprehensive group ($n = 66$) who received antibiotics combined with glucocorticoids according to the different treatment methods. Among them, the children in the control group received azithromycin (Shenyang No. 1 Pharmaceutical Factory of Northeast Pharmaceutical Group, H20000426) 10 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$ intravenous drip for 7 days on the basis of routine phlegm-relieving, cough-relieving and symptomatic and supportive treatment. The comprehensive group received methylprednisolone sodium succinate (Pfizer Pharmaceutical Co., Ltd., H31020310) 10 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$ intravenous drip for 5 days on the basis of the control group. The improvement of ESR, inflammation and immune indexes, time of symptom relief or disappearance, length of hospitalization, and clinical efficacy of the two groups were collected and sorted. Through analysis and comparison, the comprehensive therapeutic effect of antibiotics and glucocorticoids was discussed.

Research Indicators

PICS grouping: PICS of children within 24 h of admission and before discharge were collected and collated, including heart rate, pH, blood sodium, blood potassium, blood pressure, hemoglobin, respiratory rate, urea nitrogen, creatinine, and oxygen saturation 10 items, each with 10 points, totaling 100 points (9). Children with a PICS score >80 within 24 h of admission were included in the non-critical group, those with a score of 71–80 were included in the critical group, and those with a score ≤70 were included in the extremely critical group. Criteria for determining abnormal ECG: The ECG examination within 72 h of admission was collected and collated, and if the ECG indicated atrial fibrillation, ventricular fibrillation, paroxysmal tachycardia and other arrhythmic signs, the ECG was determined to be abnormal.

Criteria for determining pathogenic infection and systemic damage: Blood culture of pathogenic bacteria (including adenovirus, influenza A virus, Mycoplasma pneumoniae, herpes simplex virus, IgM antibody, Chlamydia pneumoniae, etc.), sputum culture and drug sensitivity test results within 24 h of admission were collected and collated, and if the cumulative number of viral or bacterial infections was ≥2, the child was judged to have a combination of ≥2 pathogenic infections. The types of systemic damage (including electrolyte disorders, liver function damage, gastrointestinal bleeding, myocarditis, central nervous system infection, etc.) that appeared within 72 h of admission were collected and collated, and if the cumulative systemic damage was ≥2, the child was judged to have a combination of ≥2 systemic damages.

Serological indexes: The results of venous blood sampling before drug administration were collected and collated, including CRP (rate scattering turbidimetric method, determined by Mérieux VIDAS automatic immunoassay analyzer), WBC (blood cell count method, determined by Mindray BC-5120 automatic blood cell analyzer), plasma D-dimer (immunoturbidimetric method, determined by Hysenmecom CA-1500 automatic coagulometer, Japan), ESR (measured by PUC-2068A hematocrit meter, purchased from Beijing Pulang New Technology Co., Ltd.), interleukin-6 (IL-6) (immunofluorescence method, kit purchased from Guangzhou Baochuang Biotechnology Co., Ltd.), immunological indicators: $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ (measured by BD FACSCalibur multicolor flow cytometer, mouse anti-human CD4-R D1, CD8-ECD monoclonal antibodies were purchased from Beckman). The venous blood results of the children after 14 days of medication were collected and sorted, including ESR, CRP, IL-6, $CD4^+$, $CD8^+$, $CD4^+/CD8^+$.

Symptoms resolution: The fever reduction time, cough relief time, pulmonary rales disappearance time, and hospitalization days of children receiving different treatment plans were collected and sorted.

Clinical efficacy: The clinical efficacy of the children after 14 days of medication were compared, The judgment criteria were evaluated with reference to the "Guidelines for Clinical Research on Antibacterial Drugs". Healed: Symptoms, signs, sputum culture, chest X-ray, WBC and other indicators have returned to normal; Markedly effective: symptoms and signs basically disappeared, sputum culture returned to negative, X-ray showed that the inflammation was basically absorbed, and WBC returned to normal, etc.; Effective: symptoms and signs improved significantly, and WBC returned to normal; ineffective: no obvious improvement or aggravation of the condition.

Statistical Method

The analysis software was SPSS22.0. All relevant data were in accordance with normal distribution by K-S test. The enumeration data were expressed as percentage (%), and the continuous correction χ^2 test was performed. The normally distributed measurement data were expressed as mean ± standard deviation ($M \pm SD$), the t-test was used for comparison between groups. Variables with statistically significant differences between multiple groups in univariate analysis required further multivariate logistic regression analysis. Statistical difference was expressed as $p < 0.05$.

RESULT

PICS Classification of 120 Children with SMPP

Within 24 h of admission, among the 120 children with SMPP, 79 had PICS >80, 32 had PICS 71–80, and 9 had PICS ≤70.

Before discharge, among the 120 children with SMPP, 99 had PICS >80, 17 had PICS 71–80, and 4 had PICS ≤70. As seen in **Figure 1**.

Analysis of Clinical Characteristics of 120 Children with SMPP

Univariate analysis showed that there were no significant differences in gender ratio, ratio of fever duration >10 days, age and WBC among the three groups ($p > 0.05$), the differences in the ratio of abnormal ECG, the ratio of ≥2 pathogenic infections, the ratio of ≥2 systemic damages, CRP levels, and D-dimer levels were statistically significant when compared among the three groups. As seen in **Table 1**.

Multivariate Logistic Regression Analysis of PICS Classification and Clinical Characteristics in 120 Children

Multivariate Logistic regression analysis showed that the number of Co-systemic damages and the level of D-dimer were negatively correlated with PICS classification ($p < 0.05$). As seen in **Table 2**.

Analysis of ESR, CRP and IL-6 Levels in 120 Children

After medication, ESR, CRP, and IL-6 levels decreased in both groups, with significant changes in the comprehensive group compared to the control group ($p < 0.05$). As seen in **Figure 2**.

Analysis of Immune Indexes in 120 Children

After medication, CD4+ and CD4+/CD8+ levels increased and CD8+ levels decreased in both groups, with significant changes in the comprehensive group compared to the control group ($p < 0.05$). As seen in **Figure 3**.

Analysis of Symptom Resolution in 120 Children

The antipyretic time, cough relief time, disappearance time of lung rales and hospitalization days in the comprehensive

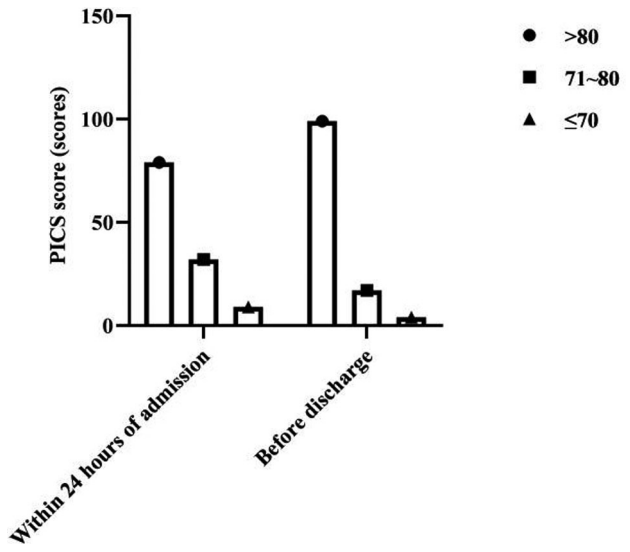

FIGURE 1 | PICS classification of 120 children with SMPP.

TABLE 2 | Multivariate Logistic regression analysis of PICS classification and clinical characteristics in 120 children.

Indicator	*r*	*p*	Assignment	PICS classification
ECG examination	0.520	0.187	1 = normal, 2 = sometimes abnormal, 3 = abnormal	Grade A: PICS > 80, non-critical; Grade B: PICS 71–80, –critical, Grade C: PICS ≤70, extremely critical
Co-pathogenic infections	−0.80	0.101	1 = 1 type, 2 = 2 types, 3 = 3 types and more	
Co-systemic damages	−1.53	0.023	1 = none, 2 = 1 type, 3 = 2 types, 4 = 3 types and more	
CRP	−0.90	0.085	1 ≤ 8. 20 mg/L, 2 = 8. 20–40. 00 mg/L, 3 ≥ 40. 0 mg/L	
D-Dimer	−1.44	0.030	1 ≤ 0. 20 mg/L, 2 = 0. 20–2. 00 mg/L, 3 ≥ 2. 00 mg/L	

TABLE 1 | Analysis of clinical characteristics of 120 children with SMPP.

Indicator	Non-critical group (*n* = 79)	Critical group (*n* = 32)	Extremely critical group (*n* = 9)	χ^2/F	*p*
Male /Female	43/36	19/13	5/4	0.226	0.893
Abnormal ECG (*n*, %)	11 (13.92)	11 (34.38)	6 (66.67)	15.538	<0.001
≥2 pathogenic infections (*n*, %)	10 (12.64)	12 (37.50)	6 (66.67)	18.070	<0.001
≥2 systemic damages (*n*, %)	29 (36.71)	25 (78.13)	9 (100.00)	24.468	<0.001
Fever duration >10 days (*n*, %)	7 (8.86)	4 (12.50)	3 (33.33)	4.725	0.094
Age (years old)	5.63 ± 1.47	5.63 ± 1.34	5.67 ± 1.41	0.003	0.997
CRP (mg/L)	45.14 ± 9.12	60.01 ± 14.21	72.56 ± 18.56	35.810	<0.001
WBC ($\times 10^9$/L)	14.24 ± 3.32	15.92 ± 4.48	15.65 ± 4.50	2.541	0.083
D-dimer (mg/L)	3.21 ± 0.86	8.46 ± 0.90	12.41 ± 1.20	694.400	<0.001

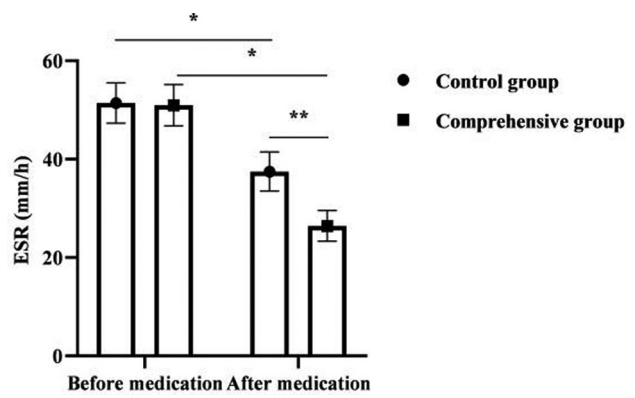

FIGURE 2 | Analysis of ESR, CRP and IL-6 levels in 120 children. Note: * was $p < 0.05$ for the comparison before and after medication; ** was $p < 0.05$ for the comparison after medication.

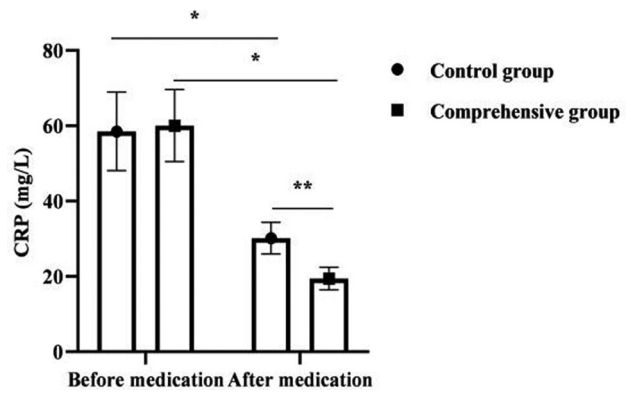

FIGURE 3 | Analysis of immune indexes in 120 children. Note: * was $p < 0.05$ for the comparison before and after medication; ** was $p < 0.05$ for the comparison after medication.

group were shorter than those in the control group ($p < 0.05$). As seen in **Figure 4**.

Clinical Efficacy Analysis of 120 Children

The total effective rate of the comprehensive group (95.45%) was better than that of the control group (83.33%) ($p < 0.05$). As seen in **Table 3**.

DISCUSSION

Children are susceptible to MPP, and their clinical manifestations vary. If the disease is not effectively controlled in a timely manner, the disease may continue to progress to SMPP or may involve multiple organs and systems throughout the body, seriously threatening their life safety (10). As such,

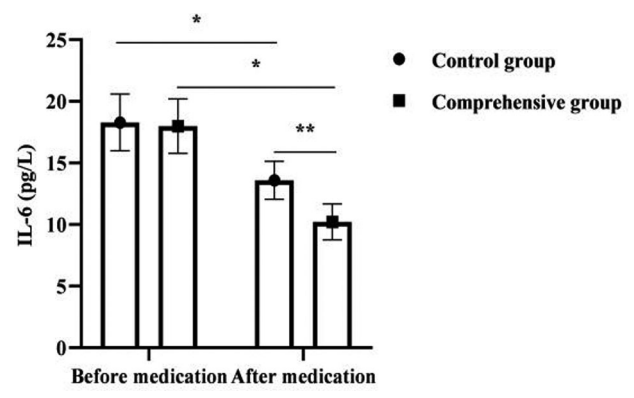

FIGURE 4 | Analysis of symptom resolution in 120 children. Note: * was $p < 0.05$ for comparison between groups.

TABLE 3 | Clinical efficacy analysis of 120 children.

Group	Healed	Markedly effective	Effective	Ineffective	Total effective
Control group ($n = 54$)	30 (55.56)	8 (14.81)	7 (12.96)	9 (16.67)	45 (83.33)
Comprehensive group ($n = 66$)	44 (66.66)	14 (21.21)	5 (7.58)	3 (4.55)	63 (95.45)
χ^2	1.551	0.812	0.958	4.849	4.849
p	0.213	0.368	0.328	0.028	0.028

how to quickly and effectively assess the condition of MPP and promptly diagnose and treat it has become a hot issue in pediatric clinics. PCIS can effectively reflect the severity of the child's condition through a comprehensive evaluation of 10 indicators, such as heart rate and pH etc. Wang et al. (11), a domestic scholar, used PCIS to evaluate the criticality of severe pneumonia in infants and children and found that PCIS could accurately determine the progression of the child's disease, and the lower the score, the greater the proportion of multi-organ damage occurred, and by dynamically observing the PCIS score, there was a significant correlation between the improvement of the patient's condition and the PCIS score. In addition, some authors (12) found that the PCIS score can be used to assess the condition of children with hand, foot and mouth disease complicated with encephalitis, in which heart rate, blood pressure and renal function can effectively predict the risk of death with a high specificity and sensitivity. However, with the widespread development of clinical applications, the lack of coagulation indicators and poor sensitivity to the severity of the disease have become increasingly prominent in PICS, making it questionable whether the PICS score can comprehensively assess the severity of SMPP.

This study investigated the clinical characteristics of children with SMPP and their correlation with PICS. By comparing the

clinical characteristics of children with different PICS score groups, it was found that the number of combined systemic damage and the level of D-dimer were negatively correlated with PICS classification. The incidence of MPP infection in children with other pathogens is as high as 50%, and it can enhance the virulence of bacteria and viruses, resulting in SMPP (13). Song et al (14) found that the proportion of mixed infection in children with SMPP in Beijing was significantly higher than that in children without SMPP. Among them, 25% were infected with two pathogens; the occurrence of mixed infections often leads to prolonged disease course, increased drug use, and greatly increases the risk of developing multi-system and multi-organ damage. This study suggests that the number of combined systemic damage is negatively correlated with the PICS classification, which needs to be paid attention to in clinical practice. With the aggravation of MPP, the thrombin and fibrin in the children's body are continuously activated, leading to an imbalance between the coagulation and anticoagulation systems, resulting in a hypercoagulable state, which further leads to clinical symptoms and aggravates the damage to other system functions (15). D-dimer is an important indicator reflecting coagulation function. It is a sensitive marker of thrombus formation in the vascular circulatory system and can reflect the activity of thrombin and plasmin (16). This study found that the level of D-dimer was negatively correlated with the PICS classification, indicating that children with SMPP have different degrees of blood hypercoagulation, and the PCIS score can effectively reflect the coagulation function of children with SMPP and thus determine the progress of the disease. For example, one study (17) reported that Mycoplasma pneumoniae infection causes vascular embolism in children and that a hypercoagulable state of the blood is its main cause. This is important to guide the anticoagulation treatment and prognostic assessment of the child. Inflammatory mediators play an important role in the pathogenetic progression of MPP. Among them, CRP, an acute phase-responsive protein, can be extremely increased in case of infection or inflammation and is associated with criticality of the disease (18). However, the present investigation showed no correlation between PCIS scores and CRP levels, which may be related to the younger age of the children included in the study and the weaker CRP synthesis ability.

It is reported that the comprehensive treatment of antibiotics and glucocorticoids can significantly improve the clinical effect of MPP in children (19). Glucocorticoids are commonly used clinical immunomodulators, which can play a variety of pharmacological effects such as immunomodulation, anti-allergy, and anti-inflammatory. The present results showed that the combined group treated with combined glucocorticoids had significantly lower ESR, CRP, IL-6, and $CD8^+$ levels and significantly higher $CD4^+$ and $CD4^+$ /$CD8^+$ levels than the control group after medication. As a typical marker of disease activity and inflammatory infection, ESR can directly reflect the dynamic changes and development of the disease (20), and the ESR of SMPP children is significantly higher than that of ordinary MPP children. In the present results, after treatment, the ESR of the comprehensive group was significantly lower than that of the control group, indicating that the combined treatment of the two was beneficial to disease control. It was previously believed that the pathogenesis of SMPP is mainly related to the direct action of pathogens and the indirect action of pathogens stimulating inflammatory immune responses (21). When the organism is infected with pneumonia, mycoplasma enters the lung through the airway and stimulates macrophages at the alveoli, producing inflammatory cytokines such as CRP and IL-6, and then stimulates various cytokines in the lungs and induces inflammatory cells in the peripheral circulation to enter the alveoli and interstitium, which in turn produce a large number of cytokines and inflammatory mediators, further aggravating the inflammatory response of the organism (22). Mei Yuxia (23) found that azithromycin combined with glucocorticoids for SMPP resulted in a significant reduction in inflammatory factor levels, and the present results also showed this effect. In addition, mycoplasma is capable of causing disruption of the normal ratio of T lymphocyte subsets and inducing reduced and disturbed cytokine production (24). It is common that the dynamic balance between CD4+ and CD8+ is disrupted, leading to pathological immune damage. The improvement of immune function was more significant in the comprehensive group after medication in this result, suggesting that the combination of both treatments is more helpful in the correction of the organism's immune dysfunction. The results of this study also showed that the time to fever resolution, cough relief, disappearance of pulmonary rales and days of hospitalization were shorter in the comprehensive group than in the control group. The total effective rate of the comprehensive group was better than that of the control group. It indicates that the combination of antibiotics and glucocorticoids can promote the improvement of clinical manifestations in children with SMPP, thus reducing their suffering and increasing their tolerance.

CONCLUSION

PICS can effectively reflect the clinical characteristics of children with SMPP. The comprehensive treatment effect of azithromycin combined with glucocorticoid is significantly better than that of azithromycin alone. It can effectively reduce the level of inflammation in children with SMPP, improve the immune function of children, and accelerate clinical recovery. It has promotion 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

This study was approved by the Ethics Review Committee of our Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CF and YM are the mainly responsible for the writing of the article. MJ is mainly responsible for research design. CF is mainly responsible for data analysis. WY and YM are responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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Expression and Predictive Value of Serum NLR, PLR Combined with SAA in Patients with Different Stages of Colorectal Cancer

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Colorectal cancer (CRC) is one of the major causes of death in the world, and has become a serious threat to human life. The prognosis of CRC patients in different pathological stages is quite different, so it is necessary to evaluate the clinical stages of CRC patients before surgery. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), serum amyloid A (SAA) and other indicators have been widely proved to play the role of early diagnosis and prognosis monitoring in chronic inflammatory diseases and cancers. In this study, we collected clinical data of 103 patients with CRC confirmed by pathology in Yiwu Central Hospital from January 2019 to December 2021. In addition, it aims to explore the expression and predictive value of NLR, PLR combined with SAA in patients with different stages of CRC, so as to provide reference for patients to choose a reasonable treatment plan. The results show that serum NLR, PLR combined with SAA can predict CRC staging effectively, which has certain auxiliary value for clinical decision-making.

Keywords: colorectal cancer, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, serum amyloid A, predictive value

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INTRODUCTION

In 2020, colorectal cancer (CRC) is the third most common malignant tumor in the world (1.93 million), with 940,000 deaths. In 2020, CRC is the second most common malignant tumor in China (560,000), with 290,000 deaths. CRC is a serious threat to human health worldwide, and it has become a heavy global public health burden (1, 2). In recent years, medical technology has maintained rapid development, people's understanding of CRC has been greatly improved. At present, surgery, radiotherapy, chemotherapy, molecular therapy and targeted drug therapy have made great achievements in the field of CRC. Surgical tumor resection is the fundamental method for the treatment of CRC, which greatly improves the survival rate of patients (3). However, in China, with the improvement of social level and the change of people's living habits, the probability of CRC patients diagnosed every year is still at a high level. The prognosis of CRC patients in different pathological stages is quite different, so it is necessary to evaluate the clinical stages of CRC patients before surgery. For early-stage CRC patients,

clarifying the clinical stage of the patients is helpful for formulating subsequent treatment plans and monitoring the recurrence of patients. For patients with advanced CRC, the judgment of clinical stages can improve the level of treatment and improve the treatment effect (4). Although the clinical stage of CRC patients can be determined by needle biopsy, local infiltration, lymph node metastasis and distant metastasis, these methods are traumatic (5). Therefore, in order to more comprehensively assess the prognosis, monitor the development of diseases, and improve the survival and prognosis of patients, it is clinically necessary to find more effective and minimally invasive prediction indicators to predict the stages of CRC.

Studies have shown that in tumor patients, after inflammatory mediators are released by tumor cells, they will promote the proliferation and migration of tumor cells, and inflammatory indicators may indicate tumor staging (6). As the main components of anti-inflammation and immune surveillance, the role of neutrophil (NEU), platelets (PLT) and lymphocyte count (LYM) in the occurrence and development of tumors has received increasing attention. NEU can reflect the inflammatory state of the body, and LYM can reflect the stress state of the body (7). Neutrophil to lymphocyte ratio (NLR) can reflect the systemic inflammation, and the imbalance of NLR may be related to the occurrence and development of tumors (8). Platelet to lymphocyte ratio (PLR) is a relevant marker reflecting the changes of PLT and LYM counts, which can assess the severity of infectious diseases, and also reflect or evaluate the degree of thrombosis and inflammatory response in the body. When the body's PLR level increases, it may indicate that the body's immune homeostasis is destroyed and the risk of tumor metastasis may increase (9). Serum amyloid A (SAA) is an acute apolipoprotein reactant, mainly produced by liver cells and regulated by inflammatory cytokines. When the body is damaged by infection, trauma, inflammatory response, cancer, etc., the serum SAA level can be significantly increased (10).

NLR, PLR, SAA and other indicators have been widely proved to play the role of early diagnosis and prognosis monitoring in chronic inflammatory diseases and cancers, but so far, there is no report on the correlation analysis between NLR, PLR, SAA and CRC patients. Therefore, we aim to discuss the expression and predictive value of NLR, PLR combined with SAA in patients with different stages of CRC, so as to provide reference for patients to choose a reasonable treatment plan.

MATERIALS AND METHODS

Research Object

From January 2019 to December 2021, the clinical data of 103 patients with CRC confirmed by pathology in Yiwu Central Hospital were collected. Inclusion criteria: Patients underwent radical resection or palliative care for CRC after admission; The patient had not received any treatment for CRC before admission; Within 2 weeks before admission, the patients did not take anti-inflammatory, anticoagulation, glucocorticoid, immunosuppressants and other drugs. Exclusion criteria: CRC patients without surgery; Patients with signs such as acute infection, blood diseases and high fever before surgery; CRC patients with metastases from other organs; Patients with recurrence of colorectal tumors undergoing reoperation; No drugs that might have influenced the study results were administered preoperatively; Patients with severe heart and lung diseases; There were autoimmune diseases; Patients with other malignant tumors; Incomplete clinical data.

Methods

Puncture biopsy was performed on CRC patients, the puncture path was determined, the needle was inserted to the edge of the tumor, the material was collected, and sent to the pathology department for pathological examination. CRC specimens were divided into 4 stages according to TNM stage (11): I-II, III and IV. As the stage increases, the symptoms of cancer also worsen.

When the patient was admitted to hospital, 4 mL of elbow venous blood was taken in the morning, centrifuged for 15 min, and the upper serum was taken and frozen in the refrigerator, prepared for subsequent use. PLT was detected by direct current impedance method of sheath fluid, and white blood cells (NEU, LYM) were detected by fluorescence staining flow cytometry. Automatic blood cell analyzer (Sysmex XE-5000) was used to test the blood within 2 h after blood collection. NLR = NEU/LYM、PLR = PLT/LYM. SAA was detected by immune timing nephelometry, and detected by automatic biochemical analyzer (BECKMAN DxI 800) within 2 h after blood collection. Tests were carried out in strict accordance with the requirements, and the quality control of the project was carried out.

Statistical Methods

SPSS 22.0 was used to process the data. Measurement data conforming to a normal distribution was expressed by mean ± standard deviation. ANOVA test was used for comparison among multiple groups, and SNK-q test was used for pairwise comparison. Counting data was expressed by ratio, and χ^2 test was used for pairwise comparison. ROC curve was drawn, and AUC was used to predict the diagnostic value of serum NLR, PLR and SAA levels in staging of CRC patients. AUC value >0.7 had good predictive value. $p < 0.05$ was statistically significant.

RESULTS

Basic Information of CRC Patients in Different Stages

Among 103 CRC patients, 22 cases (21.36%) were in stage I–II, 49 cases (47.57%) were in stage III and 32 cases (31.07%) were in stage IV. There was no significant difference in age, gender and body mass index among CRC patients in different stages ($p > 0.05$). See **Table 1**.

TABLE 1 | Basic information of CRC patients in different stages.

Group	Age (years)	Gender		Body mass index (kg/m^2)
		Male	Female	
Stage I-II ($n = 22$)	65.94 ± 4.25	14 (63.64%)	8 (36.36%)	23.91 ± 3.17
Stage III ($n = 49$)	66.16 ± 4.28	33 (67.35%)	16 (32.65%)	24.62 ± 3.04
Stage IV ($n = 32$)	68.20 ± 4.57	24 (75.00%)	8 (25.00%)	24.34 ± 3.09
χ^2/*t value*	2.591	0.896		0.406
p value	0.080	0.639		0.667

Serum NLR, PLR and SAA Levels of CRC Patients in Different Stages

The levels of serum NLR and SAA in patients with stage IV were higher than those in patients with stage I–II and stage III, and those in patients with stage III were higher than those in patients with stage I–II ($F = 30.937$, $F = 264.814$, $p < 0.05$). There was no significant difference in serum PLR levels among CRC patients in different stages ($F = 2.7986$, $p > 0.05$). See **Figure 1**.

Value of Serum NLR, PLR and SAA Levels in Predicting Patients with Stage I-II CRC

The AUC of serum NLR, PLR and SAA levels in predicting CRC patients with stage I-II was 0.770, 0.593 and 0.931 respectively, and the AUC of combination of the three in predicting CRC patients with stage I-II was 0.989. See **Table 2** and **Figure 2**.

Value of Serum NLR, PLR and SAA Levels in Predicting Patients with Stage III CRC

The AUC of serum NLR, PLR and SAA levels in predicting CRC patients with stage III was 0.640, 0.556 and 0.638 respectively, and the AUC of combination of the three in predicting CRC patients with stage III was 0.706. See **Table 3** and **Figure 3**.

Value of Serum NLR, PLR and SAA Levels in Predicting Patients with Stage IV CRC

The AUC of serum NLR, PLR and SAA levels in predicting CRC patients with stage IV was 0.874, 0.638 and 0.931 respectively, and the AUC of combination of the three in predicting CRC patients with stage IV was 0.973. See **Table 4** and **Figure 4**.

DISCUSSION

CRC is one of the major causes of death in the world, and has become a serious threat to human life. In recent years, despite the rapid development of surgery, chemotherapy and molecular therapy, the prognosis of CRC patients is not good due to the fact that tumors tend to be deeper local infiltration, lymph node metastasis, and some patients are accompanied by cardiovascular diseases and immune system diseases (12). Since the staging system is related to the prognosis of CRC patients, it is necessary to find serum biological indicators that can effectively assess tumor staging, and research in this area has received more and more attention.

NEU is the white blood cell with the largest content in peripheral blood, accounting for 40%–60% of leukocytes. NEU is mainly involved in innate immunity, that is, nonspecific inflammatory reaction (13). NEU plays an key role in host protection against infection and inflammation. It can cause tissue damage, provide signals to epithelial cells, macrophages and other immune cells, and then increase LYM, thus regulating the subsequent inflammatory response (14). NEU promotes the formation of blood vessels and tumor growth by secreting vascular growth factors; It is also possible to accelerate tumor progression by promoting the release of proteins such as epidermal growth factor and platelet-derived growth factor in extracellular matrix (15, 16). Granot's team found that some NEU can kill tumor cells through direct cytotoxicity or antibody-dependent cell-mediated cytotoxicity (17). LYM accounts for 20%–40% of peripheral white blood cells, which is an important cell of human immune response and participates in adaptive immunity. LYM is an important part of anti-tumor immunity, which plays an immune surveillance role. When the body suffers from severe immune dysfunction and immunosuppression, it will cause a series of pathophysiological changes (18). LYM can specifically recognize and directly kill tumors or release a series of cytokines to activate anti-tumor immunity, which plays a key role in the production of cytokines that inhibit tumor proliferation and metastasis (19). NEU and LYM are objective indicators reflecting the inflammatory response and immune status of the body. However, a single indicator is greatly affected by physiology and stress, and the detection results have a large fluctuation range and low stability. NLR can stably reflect the relationship between multiple factors and the interaction of inflammatory response, immune system in the body (20). In this study, CRC staging is positively correlated with NLR. The possible reasons are as follows: with the increase of stage, the body's inflammatory response increases, and the level of NEU in CRC patients increases. At the same time, there may also be a decrease in the body's immune function and LYM level, so NLR increases. With the increase of CRC staging and the deepening of tumor invasion, lymph node metastasis and distant metastasis may occur, thus stimulating the growth-promoting effect of NEU on tumor and reducing anti-tumor cellular immune response mediated by LYM. NLR has the characteristics of convenient sampling, low cost, simplicity and rapidity, and can be used as an indicator to observe systemic inflammatory response.

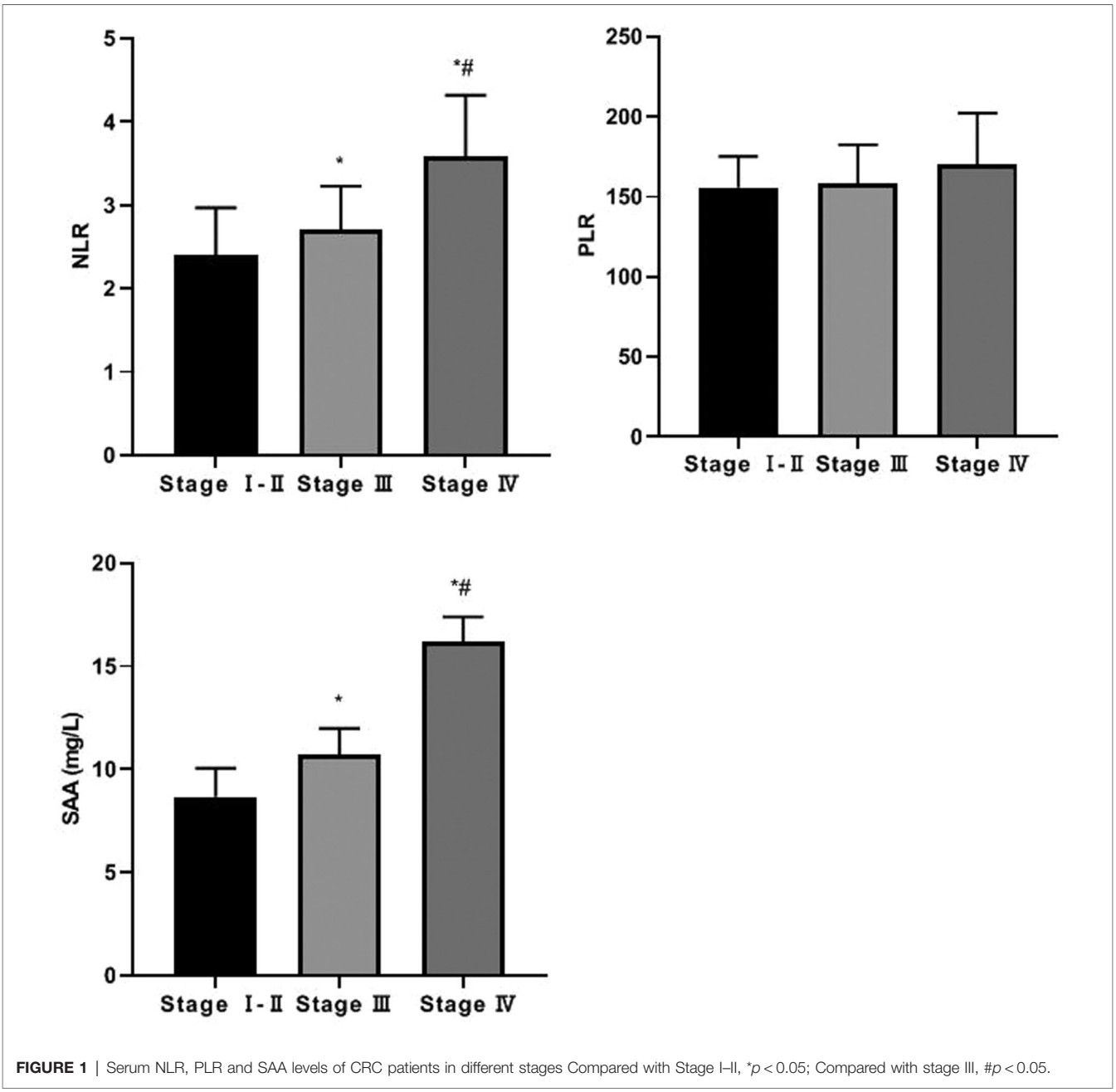

FIGURE 1 | Serum NLR, PLR and SAA levels of CRC patients in different stages Compared with Stage I–II, $*p < 0.05$; Compared with stage III, $\#p < 0.05$.

TABLE 2 | Value of serum NLR, PLR and SAA levels in predicting patients with stage I–II CRC.

Variable	AUC	Standard error	*p* value	Asymptotic 95% CI	
				Lower limit	Upper limit
NLR	0.770	0.054	0.000	0.665	0.875
PLR	0.593	0.060	0.184	0.474	0.711
SAA	0.931	0.031	0.000	0.871	0.991
NLR + PLR + SAA	0.989	0.008	0.000	0.974	1.000

PLT plays an key role in the regulation of hemostasis, wound healing, inflammatory response, immune response and tumor development (21). After tumor cells are detected, PLT will be rapidly activated, and start to drive the inflammatory response, directly regulate the activity of NEU, LYM and endothelial cells, and promote the aggregation of various adhesion molecules and chemokines to the tissue injury site. In addition, PLT is involved in the growth and metastasis of tumor cells by releasing platelet-derived growth factors and many angiogenic proteins. At the same time, tumor cells can induce PLT aggregation and manipulate PLT activity to

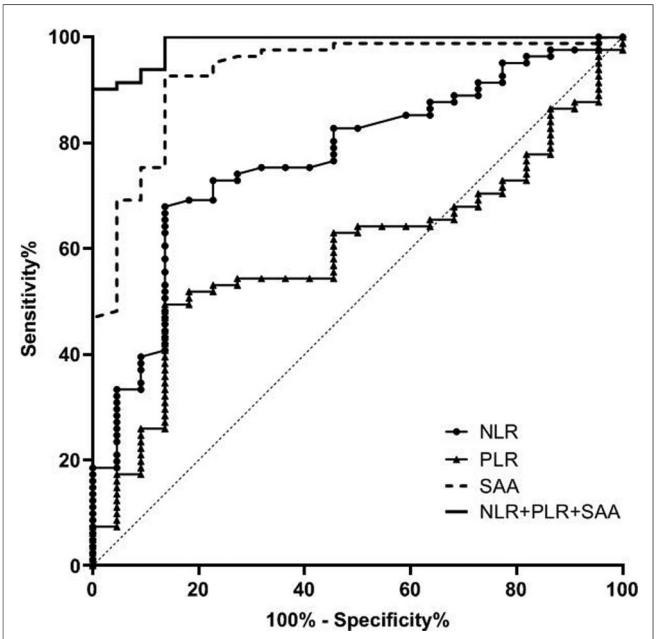

FIGURE 2 | Value of serum NLR, PLR and SAA levels in predicting patients with stage I-II CRC.

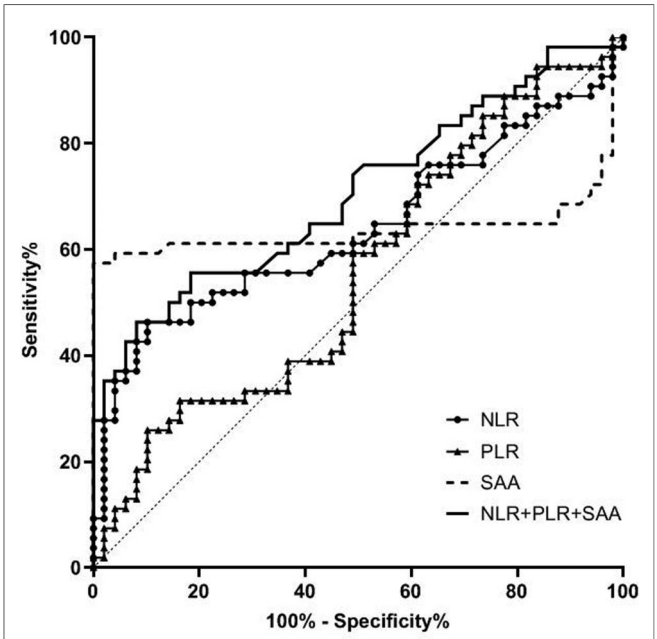

FIGURE 3 | Value of serum NLR, PLR and SAA levels in predicting patients with stage III CRC.

TABLE 3 | Value of serum NLR, PLR and SAA levels in predicting patients with stage III CRC.

Variable	AUC	Standard error	*p* value	Asymptotic 95% CI	
				Lower limit	Upper limit
NLR	0.640	0.055	0.015	0.531	0.748
PLR	0.556	0.057	0.325	0.444	0.668
SAA	0.638	0.063	0.016	0.516	0.761
NLR + PLR + SAA	0.706	0.051	0.000	0.607	0.806

TABLE 4 | Value of serum NLR, PLR and SAA levels in predicting patients with stage IV CRC.

Variable	AUC	Standard error	*p* value	Asymptotic 95% CI	
				Lower limit	Upper limit
NLR	0.874	0.039	0.000	0.796	0.952
PLR	0.638	0.062	0.025	0.515	0.761
SAA	0.931	0.030	0.000	0.873	0.989
NLR + PLR + SAA	0.973	0.018	0.000	0.937	1.000

promote tumor progression (22). PLR can be used to assess the dynamic balance between anti-tumor immunity in vivo. When PLR is high, there is an immune imbalance between anti-tumor and tumor-promoting (23). Catal's team research shows that PLT supports the formation of blood vessels in tumor tissues, the growth and diffusion of cancer cells and subsequent secondary lesions; PLR is related to the size and degree of tumor invasion (24). However, some reports suggest that PLR is not an independent predictor of CRC staging (25). Our study also found that there was no significant difference in serum PLR levels among patients with different stages of CRC, and the AUC of PLR in predicting CRC patients with different stages was smaller. Therefore, the value of PLR in predicting CRC in different stages is still controversial, which requires scholars to conduct further experiments to explore the reasons.

SAA is a substance synthesized and induced by tumor necrosis factor, interleukin −1 and interleukin −6. When the body is stimulated by inflammation or infection, the serum levels of SAA can increase abnormally (26). Davis' team reported that the progress and metastasis of CRC are closely associated with inflammatory response (27). It is speculated that the detection of serum SAA level may play a certain role in predicting the clinical stage of CRC patients. In this study, with the increase of CRC stage, the level of serum SAA increased. The results suggest that SAA has certain evaluation value for the staging of CRC patients. As an inflammatory factor, SAA can participate in the process of inducing gene mutation, change the tumor microenvironment and promote the occurrence and development of tumors. In addition, the synthesis of SAA is regulated by a variety of inflammatory factors, and the up-regulation of these factors can further promote tumor proliferation and accelerate tumor progression.

In addition, the ROC curve results of this study found that the AUC of serum NLR, PLR and SAA levels in predicting CRC staging was higher, and the AUC of combination of the three in predicting CRC patients with stage I-II, stage III and stage IV was 0.989, 0.706 and 0.973 respectively. Compared

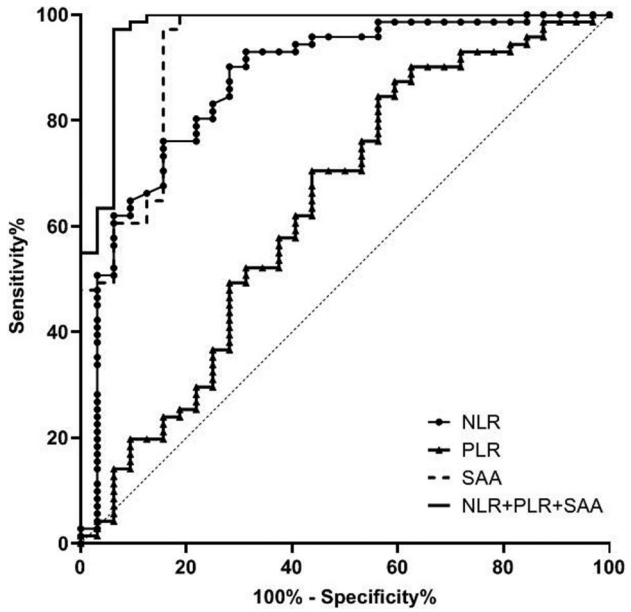

FIGURE 4 | Value of serum NLR, PLR and SAA levels in predicting patients with stage IV CRC.

with a single detection index, the AUC of NLR, PLR combined with SAA in predicting CRC staging was significantly higher. This further indicates that the combined detection of NLR, PLR and SAA can effectively evaluate the clinical stage of CRC patients and make up for the defect of low sensitivity of single marker to CRC. Therefore, the detection of NLR, PLR combined with SAA can provide some auxiliary value for the surgical preparation and prognosis of CRC patients.

CONCLUSION

To sum up, serum NLR, PLR combined with SAA can predict CRC staging effectively, which has certain auxiliary value for clinical decision-making. This study has the following shortcomings: it is a retrospective study, a small sample size, a single-center trial, and there is potential selection bias. In addition, this study only considered the serum NLR, PLR, and SAA levels of CRC patients on admission, and did not monitor the changes of these indicators in patients who underwent radical surgery. We need to further improve the research plan 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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Yiwu Central Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QY is the mainly responsible for the writing of the article. CS is mainly responsible for research design. QY is mainly responsible for data analysis. LZ is responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Clinical Efficacy of Modified Small Incision Thyroidectomy and Analysis of Influencing Factors of Postoperative Hypocalcemia

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Objective: Analyze the clinical effect of modified small incision thyroidectomy and evaluate the influencing factors of hypocalcemia (EH) in patients after operation.

Methods: A total of 220 patients with thyroid cancer in our hospital from October 2019 to October 2021 were selected. The patients were randomly divided into a control group and an observation group, with 110 patients in each group. The control group were treated with traditional thyroidectomy, while the observation group were treated with modified small incision surgery. The perioperative indicators of the two groups were compared. The thyroid hormone indexes of the two groups were meansured before operation and 7 days after operation, and the incidence of complications was compared between the two groups. Serum calcium was detected 7 days after operation in both groups. According to the level of blood calcium, patients were divided into EH group and normal group. The data of two groups were compared, and the related factors affecting the occurrence of EH after operation were analyzed.

Results: The operation time, incision length and intraoperative bleeding volume of patients in the observation group were significantly lower than those of patients in the control group ($p < 0.05$). There was no significant difference in drainage time and postoperative drainage volume between the two groups ($p > 0.05$). The postoperative PTH level of patients in the observation group was significantly higher than that in the control group ($p < 0.05$), but there was no significant difference in FT3, FT4 and TSH levels ($p > 0.05$). The incidence of postoperative complications in the observation group (11.82%) was significantly lower than that in the control group (34.55%). Logistic regression analysis showed that bilateral lymph node dissection, parathyroidectomy and decreased PTH were the independent risk factors for EH in our patient after operation ($p < 0.05$).

Conclusion: The modified small incision operation can effectively reduce the occurrence of surgical trauma and related complications. Bilateral lymph node dissection,

parathyroidectomy and PTH decrease are the risk factors for postoperative EH in patients with thyroid cancer. Taking corresponding measures to improve the metabolic function of patients during perioperative period will help to reduce the incidence of postoperative EH in patients with thyroid cancer.

Keywords: thyroid cancer, modified small incision, efficacy, hypocalcemia, risk factor

INTRODUCTION

Thyroid cancer is a common malignant tumor in the head and neck, and its incidence is increasing year by year in recent years. The local lump caused by thyroid cancer can lead to swallowing dysfunction, and reduce the quality of life of patients, and seriously threaten their life and health (1–3). Thyroidectomy is the main method to treat thyroid cancer. The effectiveness of traditional excision has been widely confirmed in clinic, but it requires a 6–8 cm long incision, which leads to high risk of postoperative complications and obvious scars, thus increasing the physical and mental burden of patients. Surgery can also cause hoarseness, hypocalcemia (EH) and other complications, which is not conducive to the patient's recovery (4, 5). How to reduce postoperative complications of thyroid cancer is a difficult problem faced by surgeons. With the development of minimally invasive surgery, the improved mini-incision thyroidectomy has increased the technique of endoluminal instruments, reducing the difficulty of operation, and made some progress in the surgical treatment of thyroid cancer. Modified small incision surgery can reduce the incision to about 2 cm, which has the characteristics of low incidence of postoperative complication and minimal trauma (6–8).

Although surgery can bring a certain radical effect, postoperative complications have a negative impact on the recovery of patient's physical function. EH is a common complication after thyroidectomy. Acupuncture-like numbness or limb twitching occurs locally in the patients's body, which has a serious impact on the patient's neurological function, cardiovascular system and bone. In addition, a few patients even suffer from permanent EH, which leads to body function decline and long-term quality of life decrease (9, 10). The ability of doctors' to predict EH after thyroid surgery is very important for postoperative management. Early detection of high blood pressure risk would eliminate unnecessary laboratory tests. In this study analyzed the clinical effects of modified small incision thyroidectomy in the treatment of thyroid cancer, evaluated the influencing factors of postoperative EH, aimed to finding a suitable surgical treatment method for thyroid cancer, and discussed the correlation between different factors and EH.

DATA AND METHODS

General Information

A total of 220 patients with thyroid cancer in our hospital from October 2019 to October 2021 were selected. The patients were randomly divided into a control group and an observation group with 110 patients in each group. The control group were treated with traditional thyroidectomy, while the observation group were treated with modified small incision surgery. In the control group, there were 39 males and 71 females aging (51.93 ± 6.94) years old, with tumor locations on the left side 52 patients and the right side 58 patients. In the observation group, there were 37 males and 73 females, and they were aged (52.08 ± 7.14) years old. The tumor locations were shown in the left side 56 patients and the right side 54 patients. There was no significant difference in general information such as gender, age and tumor location between the two groups ($p > 0.05$), indicating that they were comparable. This study was reviewed and approved by the Ethics Committee of our hospital, and the patients and their families informed consent.

Inclusion criteria: ① All patients met the diagnostic criteria for thyroid cancer, and were diagnosed by CT/pathological biopsy; ② All patients suffered from unilateral involvement, and there was no respiratory and vocal dysfunction; ③ Tumor stage I–III; ④ All patients met the indications of thyroid surgery and had no history of thyroid surgery; ⑤ If there is no serious complication of cardiovascular and cerebrovascular diseases, liver, kidney, lung and other organ and tissue diseases.

Exclusion criteria: ① Metastasis of thyroid carcinoma; ② Patients suffering from serious diseases of the blood system, immune system or other endocrine system; ③ Patients with incomplete clinical data or incomplete postoperative follow-up data; ④ The expected survival time is <6 months.

Research Methods

Traditional thyroidectomy was used in the control group. The patient was oprated under general anesthesia with endotracheal intubation. The opration was performed in a supine position, with his head tilted back on the operating table. An incision was made through the anterior sternal notch of the neck of the patient. The length of the arc cut is 6–8 cm. The skin, subcutaneous and zonal muscles and other tissues were peeled off. The white line of the neck and the lateral fascia were cut open to fully expose the thyroid to the surgical field. The thyroid suspensory ligament is separated from the upper pole blood vessel, and then the middle vein was ligated to free the lower pole of the gland, which is used to ligate the lower artery and vein after excision. The thyroid gland is separated between the internal and external fascia, and is ligated, stopped bleeding, and removed. According to the situation, clean the peripheral lymph node, and pay attention to protecting of the superior laryngeal nerve and recurrent laryngeal nerve. After successful hemostasis and

confirmation of correct operation, the drainage tube was routinely retained and sutured.

The observation group were treated with modified small incision surgery. The patient received general anesthesia with intubation, and the shoulder should be properly raised to expose the operation area. A transverse incision (about 2 cm in length) was made through the sternal notch at the lower edge of the thyroid gland to dissect the skin, platysma and other tissues, and a surgical cavity similar to the conventional thyroidectomy was constructed to ensure that the required parts of the neck surgery were fully exposed with the traction of the retractor. At the same time, the white line of the neck was cut, the inferior polar artery and vein were raised, and the fascia tissue and parathyroid gland below the inferior polar artery and vein were free. During this period, the injuries of cervical venous plexus and muscle group were avoided. The isthmus of the pretracheal space was severed and the thyroid was towed sufficiently away from the suspensory ligament before the middle vein was severed. separate the recurrent laryngeal nerve and move it to the vicinity of the larynx, where the upper pole was ligated. After resection of the upper parathyroid gland, the thyroid gland is pulled out of the incision. After thyroidectomy, thyroidectomy or subtotal thyroidectomy was performed, and lymph node dissection was performed according to the circumstances. After successful hemostasis and confirmation of correct operation, the drainage tube was routinely retained and sutured.

The operation time, intraoperative bleeding volume, incision length, drainage time, and postoperative drainage volume of the two groups were compared.

The thyroid hormone indexes of the two groups were detected before operation and seven days after operation. Fasting venous blood was collected and centrifuged at 3,500 r/min × 10 min. The levels of free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH) and parathyroid hormone (PTH) were detected by electrochemical luminescence immunoassay using Roche chemiluminescence immunoassay instrument.

The incidence of complications such as recurrent laryngeal nerve injury, hoarseness, dysphagia, and incision infection 14 days after surgery was compared between the two groups.

Blood calcium of patients in the two groups was detected 7 days after surgery. According to the blood calcium levels of patients, they were divided into EH group and normal group. Biochemical EH: serum calcium level <2.15 mmol/L, with or without EH symptoms; EH symptoms occur, and calcium supplementation is required regardless of EH. The data of the two groups were compared and the related factors affecting the postoperative blood calcium levels were analyzed.

Statistical Methods

SPSS22.0 software was used for processing. Experimental data were normally distributed, and measurement data were expressed as mean standard deviation ($\bar{x} \pm s$), and enumeration data were expressed as (%). *t*-test analysis was used for pairwise comparison of measurement data between groups. The count data were tested by χ^2 test. Comparison of single factor differences affecting postoperative blood calcium levels was performed using t test or χ^2 test, and multivariate analysis was performed using Logistic model. The test level was $\alpha = 0.05$, and $p < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of Perioperative Conditions Between the Two Groups

The operation time, incision length and intraoperative bleeding amount of patients in the observation group were significantly lower than those of patients in the control group ($p < 0.05$). There was no significant difference in drainage time and postoperative drainage between the two groups ($p > 0.05$). As showns in **Figures 1–4**.

Comparison of Thyroid Hormone Levels Before and After Operation Between the Two Groups

There was no significant difference in preoperative FT3, FT4, TSH and PTH levels between the two groups ($p > 0.05$). The

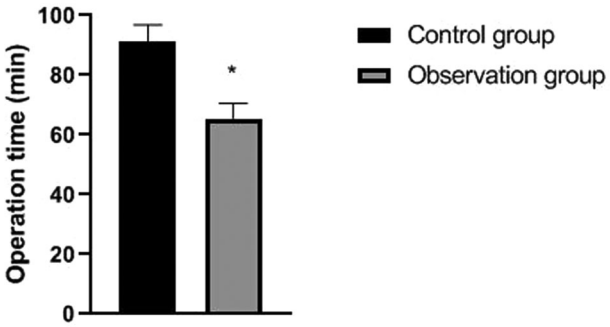

FIGURE 1 | Comparison of operation time between the two groups. Note: compared with the control group, *$p < 0.05$.

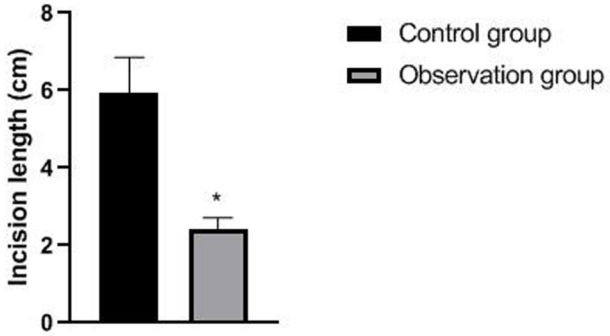

FIGURE 2 | Comparison of incision lengths between the two groups. Note: compared with the control group, *$p < 0.05$.

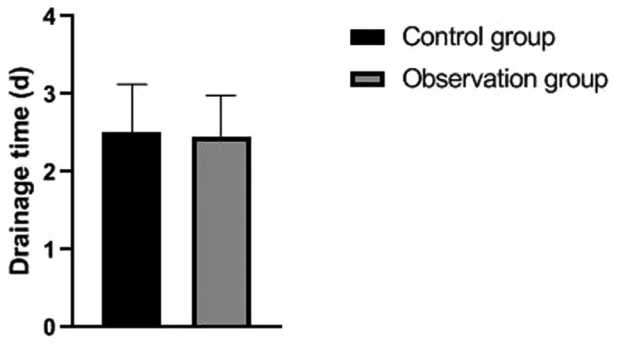

FIGURE 3 | Comparison of drainage time between the two groups.

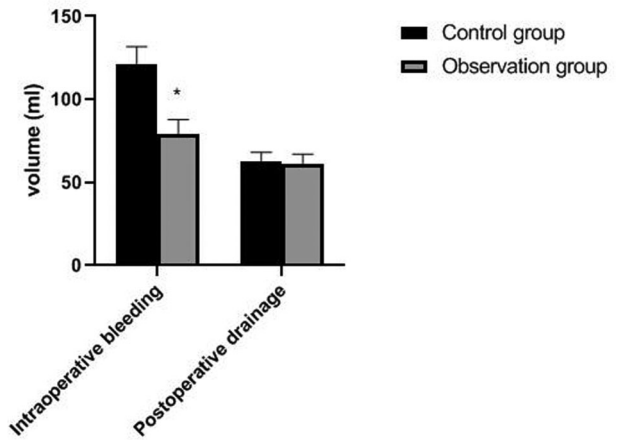

FIGURE 4 | Comparison of intraoperative bleedingv and postoperative drainage between the two groups. Note: compared with the control group, $^{*}p < 0.05$.

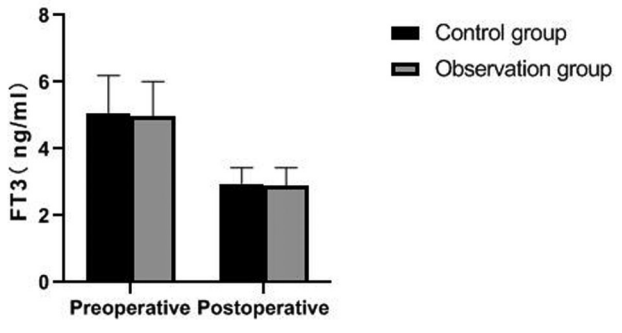

FIGURE 5 | Comparison of FT3 levels between the two groups.

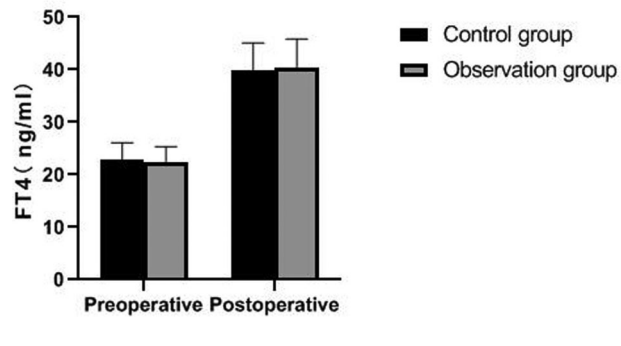

FIGURE 6 | Comparison of FT4 levels between the two groups.

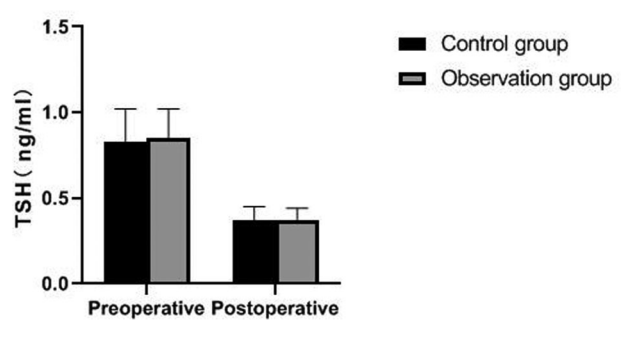

FIGURE 7 | Comparison of TSH levels between the two groups.

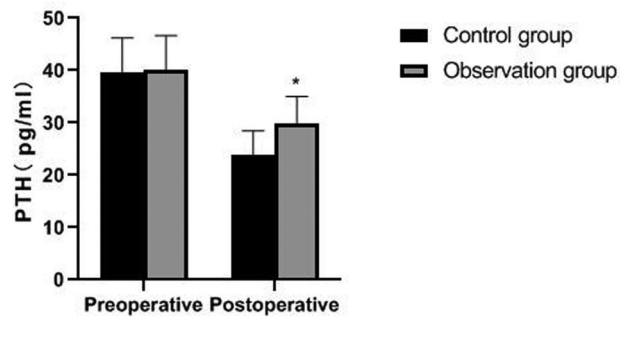

FIGURE 8 | Comparison of PTH levels between the two groups. Note: compared with the control group, $^{*}p < 0.05$.

postoperative PTH level of patients in the observation group was significantly higher than that in the control group ($p < 0.05$), but there was no significant difference in FT3, FT4 and TSH levels ($p > 0.05$). As showns in **Figures 5–8**.

Comparison of the Incidence of Postoperative Complications Between the Two Groups

The incidence of postoperative complications in the observation group (11.82%) was significantly lower than that in the control group (34.55%) ($p < 0.05$). As showns in **Figure 9**.

Univariate Analysis of Patients With EH After Surgery

Significant differences were found in the scope of lymph node dissection, parathyroid resection or not, number of cancer foci, operation method, calcitonin and PTH level between the patients with and without EH ($p < 0.05$). As showns in **Table 1**.

Multi-Factor Analysis of Postoperative EH in Patients

Logistic regression analysis showed that range of lymph node dissection, parathyroidectomy and decreased PTH were the independent risk factors for EH in our patient after surgery ($p < 0.05$). As showns in **Tables 2**, **3**.

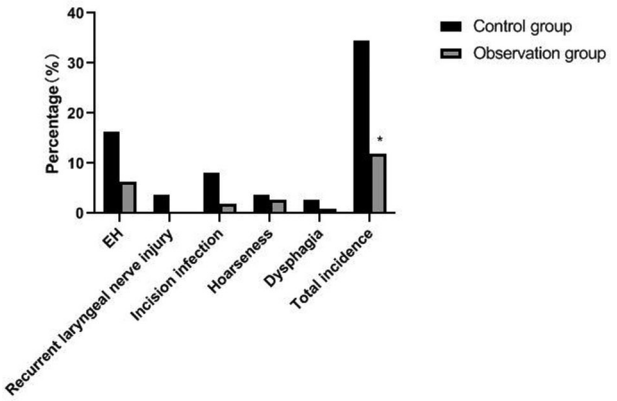

FIGURE 9 | Comparison of incidence of postoperative complications between the two groups. Note: compared with the control group, $^*p < 0.05$.

DISCUSSION

Once thyroid cancer occurs, it can seriously affect the metabolism, nervous and cardiovascular function of the body. Cancerous tissue masses can lead to swallowing and language dysfunction, which poses a great threat to the health of patients (11–13). Surgical thyroid cancer is the most commonly used treatment, especially for high-risk groups. Thyroidectomy can not only prolong the life of patients, but also effectively avoid the oppression and

TABLE 2 | Assignment for multivariate logistic regression analysis.

Factors	Variables	Assignment
Range of lymph node dissection	X1	Unilateral = 0, Bilateral = 1
Parathyroidectomy	X2	No = 0, yes = 1
Number of cancer foci	X3	Single = 0, Multiple = 1
Surgical approach	X4	Traditional excision = 0, Modified small incision = 1
Calcitonin	X5	Continuous variable
PTH	X6	Continuous variable

TABLE 3 | Multivariate analysis of postoperative EH in patients.

Variables	*B*	S.E	Walds	*p*	OR	95% CI
Range of lymph node dissection	0.983	0.378	6.763	0.016	2.672	1.274–5.606
Parathyroidectomy	1.024	0.351	8.511	0.009	2.784	1.399–5.540
Number of cancer foci	0.537	0.279	3.705	0.064	1.711	0.990–2.956
Surgical approach	0.471	0.327	2.075	0.127	1.602	0.843–3.040
Calcitonin	0.453	0.319	2.017	0.268	1.573	0.842–2.939
PTH	1.153	0.327	12.433	0.007	3.168	1.669–6.013

TABLE 1 | Univariate analysis of postoperative EH in patients.

Group	Gender		Age (years)		Range of lymph node dissection		Parathyroidectomy	
	male	woman	≥45	<45	unilateral	bilateral	yes	no
EH group ($n = 25$)	9	16	19	six	3	22	14	11
Normal group ($n = 195$)	67	128	174	23	103	92	170	25
t value	0.026		2.967		14.789		15.740	
p value	0.871		0.085		<0.001		<0.001	

Group	Lymph node metastasis		Number of cancer foci		Surgical approach		Calcitonin (pg/mL)	PTH (pg/mL)
	yes	no	single	multiple	traditional excision	modified small incision		
EH group ($n = 25$)	5	20	10	15	18	7	3.67 ± 0.84	22.25 ± 4.94
Normal group ($n = 195$)	59	136	149	46	92	103	1.49 ± 0.32	27.45 ± 5.58
t value	1.130		14.659		5.461		24.977	4.440
p value	0.288		<0.001		0.019		<0.001	<0.001

invasion of surrounding tissues by tumors. However, thyroidectomy needs to cut off the anterior cervical muscle and platysma muscle. Severe intraoperative trauma is easy to cause massive bleeding. Incision bleeding and hematoma may cause compression of trachea and esophagus, and even asphyxia.. At the same time, it will damage the recurrent laryngeal nerve and parathyroid gland, resulting in insufficient secretion of parathyroid hormone, lowering of blood calcium content, and even inducing hypocalcemia convulsion, which seriously affecting the postoperative recovery quality (14–17). Therefore, how to carry out effective and low injury resection is an important topic in the treatment of thyroid cancer.

In the past, thyroidectomy was often used in clinical operation, and the injury of recurrent laryngeal nerve was reduced by ligating the upper and lower polar vessels. However, this operation easily damaged the blood supply to parathyroid in patients, which then induced hypoparathyroidism, hypocalcemia and other complications. With the gradual development and improvement of surgical instruments and minimally invasive techniques, as well as the enhancement of people's health awareness, major changes have taken place in the surgical mode, and various new surgical methods have been continuously promoted. The modified small incision surgery reduced the traditional surgical size from 6–8 cm to about 2 cm, avoided damage to the cervical flap, muscle, blood vessel and nerve, and achieved meticulous thyroid vessel ligation. Resection of the gland lobe while retaining the original position of parathyroid gland has little effect on blood perfusion and thyroid function (18–20). The results of this study showed that the operation time, incision length and intraoperative bleeding volume of patients in the observation group were significantly lower than those of patients in the control group. Compared with the traditional conventional incision group, the modified small incision group has certain advantages in reducing the amount of intraoperative blood loss and the operation time, because it reduces the size of incision and the invasion of surrounding tissues.

Traumatic surgery is easy to cause damage to the surrounding tissues, especially the recurrent laryngeal nerve has no fixed connection with thyroid artery, so it is difficult to determine the specific location of the recurrent laryngeal nerve during the surgical operation. In addition, the distribution of the inferior polar vein vessels in the body is complex and fragile, and bleeding symptoms may occur during the separation process, which will induce various complications (21, 22). Serum PTH is an important index reflecting parathyroid function, while TSH and FT3 are indicators reflecting thyroid function (23, 24). The results of this study showed that the postoperative PTH level of patients in the observation group was significantly higher than that in the control group, but there was no significant difference in FT3, FT4 and TSH levels. From the incidence of postoperative complications in the two groups, the incidence of postoperative EH and recurrent laryngeal nerve injury in the observation group were lower than that in the control group. It indicated that the damage to thyroid caused by the two operations is similar, and the modified small incision operation was more beneficial to protect the parathyroid gland and recurrent laryngeal nerve. Because the operation of a small incision is to pull out the thyroid lobe, then separate, ligate and disconnect it, the difficulty of operation is greatly reduced. Reduce accidental damage to parathyroid gland and recurrent laryngeal nerve.

Calcium plays an important physiological role in the human body, and it involves in nerve transmission, muscle contraction, hormone release and blood coagulation. EH refers to serum total calcium level <2.15 mmol/L or serum free calcium level <1.12 mmol/L (25). The study have pointed out that EH caused by thyroid surgery poses a great threat to patients' postoperative recovery and quality of life (26). Logistic regression analysis in this study showed that bilateral lymph node dissection, parathyroidectomy and parathyroid hormone lowering were the independent risk factors for EH in our patient after surgery. The extent of lymph node dissection is an independent factor leading to postoperative hypocalcemia. Bilateral lymph node dissection may damage blood vessels and affect the blood supply of parathyroid gland because of its wide range of dissection. Parathyroid cells are very sensitive to the concentration of calcium in the blood. The secretion of PTH increased when the concentration of blood calcium decreased. However, PTH can act on bone cells, increase the permeability of bone cell membrane for calcium ions, and make a large amount of calcium ions in bone cells quickly enter the blood through the bone cell membrane, thus increasing the concentration of calcium ions in the blood (27, 28).

In summary, the modified small incision approach can effectively reduce blood loss, operation time, incision length and other operation-related indexes of patients with thyroid cancer, and reduce the occurrence of surgical trauma and related complications. Bilateral lymph node dissection, parathyroidectomy and the decrease of PTH level are the risk factors for EH in patients with thyroid cancer after operation. It is helpful to reduce the incidence of EH in patients with thyroid cancer after surgery by comprehensive imaging examinations and taking measures to improve the metabolic function 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 This study was approved by the ethics committee of our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JZ is the mainly responsible for the writing of the article. HJ is mainly responsible for research design. HM is mainly responsible for data analysis. QD is responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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Risk Factors of Ischemia Reperfusion Injury After PCI in Patients with Acute ST-Segment Elevation Myocardial Infarction and its Influence on Prognosis

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Purpose: To explore the risk factors of ischemia reperfusion injury (IRI) after percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction (STEMI) and its influence on prognosis.

Methods: The clinical data of 80 patients with STMEI undergoing PCI in our hospital from June 2020 to June 2021 were collected. According to whether IRI occurred after PCI, STMEI patients were divided into IRI group and non-IRI group. The basic information, clinical characteristics, examination parameters and other data of all patients were collected, and the prognosis of the two groups was observed. Risk factors were analyzed by fitting binary Logistic regression model. The survival prognosis was analyzed by Kaplan-Meier survival curve.

Results: Logistic regression analysis showed that type 2 diabetes mellitus (T2DM), pre-hospital delay time (PHD) and door-to-balloon expansion time (DTB) were the influencing factors of IRI in patients with STMEI ($p < 0.05$). MACE occurred in 11 cases (32.35%) in the IRI group and 13 cases (28.26%) in the non-IRI group. Log-rank test showed $p = 0.503$, indicating no statistically significant difference.

Conclusion: T2DM, PHD and DTB were the influencing factors of IRI in patients with STMEI, and IRI will not reduce the prognosis of patients.

Keywords: ST-segment elevation myocardial infarction, percutaneous coronary intervention, ischemia reperfusion injury, risk factors, prognosis

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is mainly caused by unstable plaque detachment in coronary artery to form thrombus, which leads to acute myocardial ischemia and necrosis. The main clinical symptoms are persistent ischemic chest pain, elevated serum myocardial injury markers and elevation of ST segment of electrocardiogram (1). STEMI has an acute onset and rapid onset. Patients may suffer from myocardial injury and necrosis in a short

period of time, even death in severe cases, which poses a serious threat to the life and health of patients (2). With the continuous development of medical technology, the early mortality of STEMI in clinic has dropped significantly, from 13% in 1986 to <4% in 2000, which is mainly due to the application of early opening of infarction-related vascular technology (3). Percutaneous coronary intervention (PCI) is the most common method for the treatment of STEMI. It can recanalize infarct-related arteries, restore myocardial perfusion and restore blood supply, and has been widely carried out in China (4). However, with the deepening of relevant research, scholars have found that effective reperfusion therapy may not only restore the forward blood flow of infarct-related arteries, but also lead to the further aggravation of myocardial ischemic injury, that is, ischemia reperfusion injury (IRI) (5). IRI can be manifested as severe slow arrhythmia, malignant ventricular arrhythmia, cardiac insufficiency and sudden drop of blood pressure after vascular opening, resulting in acute and chronic organ failure, even sudden death, which affects postoperative recovery, so it has been widely valued by doctors in recent years (6). Therefore, it is particularly important to identify the risk factors of IRI in STEMI patients as early as possible clinically. We aim to observe the influencing factors of IRI in STEMI patients after PCI, and whether the occurrence of IRI affects the prognosis of patients.

MATERIALS AND METHODS

Research Object

The clinical data of 80 patients with STMEI undergoing PCI in our hospital from June 2020 to June 2021 were collected. According to whether IRI occurred after PCI, STMEI patients were divided into two groups: 34 cases in IRI group and 46 cases in non-IRI group. Inclusion criteria: Patients meet the diagnostic criteria of STMEI (7); The duration of onset of chest pain ≥30 min; The patient can accurately tell the doctor the specific time of onset; Complete clinical data. Exclusion criteria: those who failed to receive PCI treatment within 12 h of onset due to various reasons; Coronary angiography confirmed incomplete occlusion of criminals' blood vessels; Patients who died during PCI or 24 h after PCI; Patients with active visceral hemorrhage, cardiogenic shock; Liver and renal insufficiency; Combined with malignant tumor.

The diagnostic criteria of IRI were as follows: ① Severe bradycardia, hypotension and frequent premature ventricular contractions within minutes after opening coronary artery vessels during interventional therapy; ② Serious ventricular arrhythmias still occur after drug therapy and/or electrocardioversion and electrodefibrillation; ③ coronary angiography detected coronary angiography TIMI ≤ grade 2, combined with thrombus, dissection or spasm.

Research Methods

All patients received comprehensive treatment measures before operation such as oxygen inhalation, sedation, analgesia, ECG monitoring. The patients were treated with nitrates, β-blockers, heparin and angiotensin converting enzyme inhibitors. Within 12 h of onset, PCI was completed under the guidance of angiography system. Routine percutaneous puncture of the radial artery or femoral artery, coronary angiography was performed, and after the coronary artery disease was identified, the location of the infarction-related artery disease was determined, stent placement was performed, and PCI treatment was completed immediately. PCI was performed by experienced physicians. All patients were treated with double antiplatelet aggregation therapy after operation. If there were no contraindications, nitrates, β -blockers and other drugs were added.

The clinical data of all patients were collected, including: ① age, sex, hypertension, type 2 diabetes mellitus (T2DM), hyperlipidemia, smoking history (>20 cigarettes/day) and alcoholism history (>150 mg/day); ② Admission systolic blood pressure, admission diastolic blood pressure, admission heart rate, pre-hospital delay time (PHD) and door-to-balloon expansion time (DTB); ③ White blood cell count (WBC), platelet count (PLT), total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C) at admission.

Telephone and outpatient follow-up were conducted 6 months after operation to record the prognosis of patients, including major adverse cardiovascular events (MACE) such as readmission, recurrent myocardial infarction, revascularization, fatal arrhythmia, heart failure, stroke, bleeding of vital organs and cardiogenic death. Patients who died or lost follow-up during the follow-up period were excluded.

Statistical Methods

Used SPSS 22.0 software to process. The measurement data was expressed by mean ± standard deviation, and the comparison was made by t test. The count data are expressed by ratio, and the comparison is made by χ^2 test. Risk factors were analyzed by fitting binary Logistic regression model. The survival prognosis was analyzed by Kaplan-Meier survival curve, and the comparison was made by Log-rank test. Inspection level $\alpha = 0.05$.

RESULTS

Basic Information of Patients

There were significant differences in hypertension and T2DM between IRI group and non-IRI group ($p < 0.05$) (**Table 1**).

Clinical Characteristics of Patients

There were significant differences in PHD and DTB between IRI group and non-IRI group ($p < 0.05$) (**Table 2**).

Examination Parameters of Patients

There was no significant difference in WBC, PLT, TC and LDL-C between IRI group and non-IRI group ($p > 0.05$) (**Table 3**).

TABLE 1 | Basic information of patients (*n*,%).

Items	non-IRI group (*n* = 46)	IRI group (*n* = 34)	χ^2 value	*p*-value
Age (years)			1.507	0.220
≤60	28 (60.87%)	16 (47.06%)		
>60	18 (39.13%)	18 (52.94%)		
Sex			0.101	0.751
Male	30 (65.22%)	21 (61.76%)		
Female	16 (34.78%)	13 (38.24%)		
Hypertension			3.942	0.047
With	13 (28.26%)	17 (50.00%)		
Without	33 (71.74%)	17 (50.00%)		
T2DM			4.557	0.033
With	10 (21.74%)	15 (44.12%)		
Without	36 (78.26%)	19 (55.88%)		
Hyperlipoidemia			0.001	0.969
With	12 (26.09%)	9 (26.47%)		
Without	34 (73.91%)	25 (73.53%)		
Smoking history			0.077	0.782
With	27 (58.70%)	21 (61.76%)		
Without	19 (41.30%)	13 (38.24%)		
Alcoholism history			0.621	0.431
With	15 (32.61%)	14 (41.18%)		
Without	31 (67.39%)	20 (58.82%)		

TABLE 2 | Clinical characteristics of patients (n, $\bar{x} \pm$ s, %).

Items	non-IRI group (*n* = 46)	IRI group (*n* = 34)	t/χ^2 value	*p* value
Admission systolic blood pressure (mmHg)	139.64 ± 14.29	135.64 ± 13.88	1.399	0.165
Admission diastolic blood pressure (mmHg)	78.92 ± 10.34	76.50 ± 10.16	1.042	0.300
Admission heart rate (times /min)	83.84 ± 11.39	87.73 ± 10.60	1.554	0.124
PHD (h)			7.020	0.008
≤6	30 (65.22%)	12 (35.29%)		
>6	16 (34.78%)	22 (64.71%)		
DTB(min)			9.934	0.007
<90	16 (34.78%)	2 (5.88%)		
90–180	24 (51.17%)	23 (67.65%)		
>180	6 (13.04%)	9 (26.47%)		

Multivariate Analysis of IRI in Patients with STMEI

Logistic regression analysis showed that T2DM, PHD and DTB were the influencing factors of IRI in patients with STMEI ($p < 0.05$) (**Tables 4**, **5**).

TABLE 3 | Examination parameters of patients (n, $\bar{x} \pm$ s).

Items	non-IRI group (*n* = 46)	IRI group (*n* = 34)	*t* value	*p* value
WBC($\times 10^{12}$/L)	11.35 ± 1.54	11.08 ± 1.69	0.743	0.459
PLT($\times 10^{9}$/L)	201.66 ± 30.74	208.81 ± 28.57	1.059	0.293
TC(mmol/L)	4.75 ± 0.72	4.98 ± 0.76	1.379	0.171
LDL-C(mmol/L)	2.71 ± 0.50	2.92 ± 0.63	1.661	0.100

TABLE 4 | Multi-factor assignment.

Independent variable	Assignment
Hypertension	With = 1, Without = 2
T2DM	With = 1, Without = 2
PHD	≤6 h = 1, >6 h = 2
DTB	<90 min = 1, 90–180 min = 2, >180 min = 3

TABLE 5 | Multivariate analysis of IRI in patients with STMEI.

Variable	*B* value	*SE* value	*Walds* value	*OR* value	*95%CI*	*p*-value
Hypertension	0.468	0.242	3.739	1.596	0.993–2.566	0.872
T2DM	0.339	0.157	4.662	1.403	1.031–1.909	0.038
PHD	0.591	0.185	10.205	1.806	1.256–2.595	0.031
DTB	0.654	0.163	16.098	1.923	1.397–2.647	0.015

Follow-up of Patients

As of January 2022, all patients were followed up. MACE occurred in 11 cases (32.35%) in the IRI group and 13 cases (28.26%) in the non-IRI group. Log-rank test showed $p = 0.503$, indicating no statistically significant difference (**Figure 1**).

DISCUSSION

STEMI can cause arrhythmia, myocardial injury and other symptoms, and severe conditions can endanger the patient's life. PCI can open infarct-related vessels and restore distal myocardial perfusion, which is an efficient and safe treatment for STEMI (8). PCI for STEMI patients can restore the effective blood supply of coronary artery as soon as possible. However, reperfusion therapy after ischemia may further cause myocardial injury, which can seriously affect the surgical efficacy and prognosis. The main mechanisms of IRI are oxidative stress, intracellular calcium overload, destruction of microvascular structure and function, and opening of mitochondrial membrane permeability transformation pores (9, 10). Therefore, exploring the related factors of IRI has becomes an important issue to prevent the occurrence of IRI in STEMI patients after PCI.

This study found that T2DM is the influencing factor of IRI in patients with STMEI. Literature reports at home and abroad show that there are inconsistent research results on the issue of

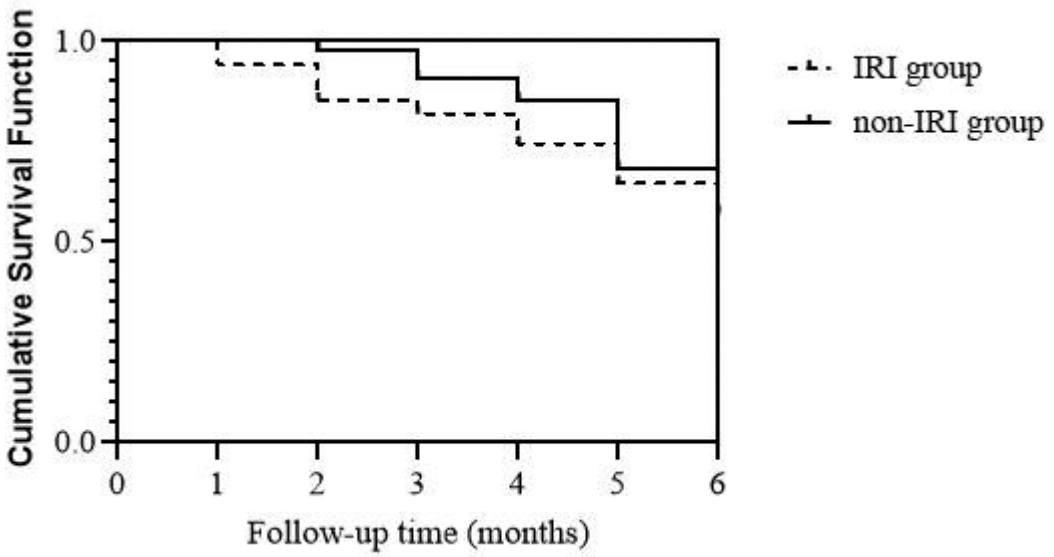

FIGURE 1 | Follow-up of patients.

DM on IRI. Dia's team research showed that patients without DM often fail to establish a good collateral circulation before acute occlusion due to their previous health and lack of long-term chronic myocardial ischemia preconditioning before acute occlusion of criminals' blood vessels. Therefore, compared with STEMI patients with DM, patients without DM have stronger reaction to acute ischemic injury and are more prone to IRI (11). Muráriková' s team believed that because the heart of DM patients may adapt to the changes caused by DM and increase tolerance to ischemic injury, the recovery of DM patients after IRI is better than that of patients without DM, with fewer cardiovascular events (12). However, there are also different research results on the relationship between DM and IRI in clinic. Badalzadeh's team found that STEMI patients with DM have a higher risk of IRI, which may be due to the combined effects of changes of glucose and lipid energy metabolism based on insulin resistance, enhanced oxidative stress and systemic inflammatory responses and ion channel dysfunction (13). Some scholars also believe that long-term chronic hyperglycemia can affect the function and structure of platelets, damage vascular endothelial cells, cause microvascular lesions, and weaken the repair ability of vascular endothelial cells, leading to coronary circulation disorder. DM is one of the main causes of IRI (14). In addition, it has been reported that T2DM has a series of metabolic syndromes caused by insulin resistance, while T1DM does not have insulin resistance in the early stage, and with the prolongation of the disease course, T1DM also gradually develops insulin resistance. Clinically, DM patients with STEMI undergoing PCI often have a long course of disease, and almost all of them have insulin resistance, so the IRI is seriously damaged (15, 16).

In this study, under the condition of PHD $\leq$ 6 h and DTB < 90 min, the probability of IRI in patients with STMEI is small, while when PHD exceeds 6 h and DTB exceeds 180 min, the probability of IRI is significantly increased. Guidelines have shown that opening occluded blood vessels within 12 h of onset of STMEI patients can have beneficial effects on the patient (17). There is a time window from acute coronary artery occlusion to transmural myocardial necrosis, which is about 6 h. Recanalization of coronary arteries within this time window can save ischemic myocardium on the verge of necrosis, promote the body to recover the forward blood flow and occlude blood vessels as soon as possible, and improve the myocardial microcirculation perfusion level (18, 19). The delay in the visit of patients with STMEI can seriously affect the follow-up cardiac function, and early seeing a doctor can provide patients with the opportunity to obtain a good prognosis. In addition, the earlier the treatment of the first balloon dilatation is performed, the greater the benefit of patients. Bruce's team conducted a long-term follow-up of patients with acute myocardial infarction who underwent PCI. The results found that prolongation of DTB could increase the risk of in-hospital death and late death, and DTB > 2 h was an independent risk factor of death (20). De Luca's team showed that with the delay of DTB, the one-year mortality rate of patients with STMEI increased, and the relative risk of death was 1.08 for every 30 min increase in DTB (21, 22). Scholars at home and abroad believe that DTB < 90 min is the best time for the first balloon dilatation, and the shortest DTB can greatly reduce the incidence of short-term and long-term adverse cardiac events after PCI (23, 24). Prehospital delays mainly include patient delays and transport delays. The patient delay is due to the patient's lack of awareness of the visit to the clinic, which leads to the extension of PHD.

Transport delay is due to the large number of patients in the hospital, which leads to a delay in the time of transfer and treatment. In clinical practice, out-of-hospital ECG can greatly shorten PHD and DTB, which is beneficial to quickly determine whether IRI occurs in STMEI patients, so as to make correct treatment decisions. At the same time, an in-hospital emergency service system composed of well-trained ambulance teams is also crucial. The development of the in-hospital emergency service system can avoid the transition of wards or coronary heart disease care units, thereby shortening the time for transferring patients in the hospital and further reducing DTB. In addition, medical staff need to strengthen the people's awareness of STEMI, and identify and treat IRI in patients with STMEI as soon as possible.

In addition, we also found that the occurrence of IRI has no significant influence on whether there is MACE in patients with STMEI. The results suggest that although IRI may have some adverse effects on patients with STMEI, it is a pathophysiological change in a short time during myocardial reperfusion, and IRI in STMEI patients after PCI will not reduce the prognosis of patients. Medical staff need to improve the ability to identify the risk of IRI, and to carry out risk prevention and effective treatment for high-risk factors, without changing the treatment strategy due to IRI.

CONCLUSION

To sum up, T2DM, PHD and DTB were the influencing factors of IRI in patients with STMEI, and IRI will not reduce the prognosis of patients. This study is a single-center, small-sample study, and there is a lack of longer follow-up for patients. We need to improve the research scheme 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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by This study was approved by the ethics committee of our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LZ and LW are the mainly responsible for the writing of the article. LT is mainly responsible for research design. CC is mainly responsible for data analysis. LZ and SR are responsible for the guidance of the entire research. The corresponding author is YZ and she is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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Effects of Parecoxib Sodium Application Combined with Enhanced Recovery After Surgery Nursing on Inflammatory Factors and Knee Joint Function in Elderly Patients After Total Knee Arthroplasty

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Objectives: To study the effect of parecoxib sodium (PS) application, combined with enhanced recovery after surgery (ERAS) nursing, on inflammation and knee joint function in elderly patients after total knee arthroplasty (TKA).

Methods: In this prospective cross-sectional study, we recruited 120 elderly patients treated with TKA who were randomly divided into two groups, the combine group and the control group, with 60 patients in each group. Patients in the control group received ERAS nursing and normal saline, and the patients in the combine group received ERAS nursing and PS. At different times after surgery, we compared the hemoglobin (Hb), complete white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and serum IL-1β, TNF-α, and IL-6, and recovery time for different ranges of joint motion and the knee joint function HSS (hospital for special surgery scale) score between the two groups.

Results: On the third and seventh postoperative days, the levels of Hb in the patients of the combine group were significantly lower than those in the control group ($p < 0.05$), while the levels of WBC, ESR, serum IL-1β, TNF-α, and IL-6 in the patients of the combine group were all significantly lower than those in the control group ($p < 0.05$). Compared with the patients in the control group, the recovery time for 30, 60, 90, and 120 angles of joint motion in patients of the combine group was significantly decreased ($p < 0.05$), and the HSS score of patients in the combine group was significantly higher than that in the control group on the first, third, and sixth postoperative months ($p < 0.05$).

Conclusion: Elderly TKA patients who received PS application, combined with ERAS nursing, had lower inflammation in peripheral blood 2 weeks after operation and faster postoperative recovery of knee joint function.

Keywords: parecoxib sodium, enhanced recovery after surgery, inflammation, knee joint function, total knee arthroplasty

INTRODUCTION

Total knee arthroplasty (TKA) is the main program for the treatment of severe knee joint diseases, and it can relieve knee joint pain and rebuild knee joint function through surgery (1, 2). However, 15%–20% of patients after TKA are dissatisfied with analgesia because they cannot perform functional exercise due to pain, there is delayed discharge, and they are prone to complications such as deep vein thrombosis, pulmonary embolism, infection, and postoperative ankylosis. Therefore, scientific nursing and analgesic protocols are valuable for patients receiving TKA (3, 4). In addition, severe pain after TKA makes it difficult for many patients to participate in early postoperative rehabilitation and exercise, which may lead to unsatisfactory recovery of knee joint function and greatly reduce the quality of life of the patients (5). Perioperative pain directly affects postoperative recovery and surgical outcome. Therefore, a scientifically rational model of care and analgesic administration will be valuable for TKA patients.

Enhanced recovery after surgery (ERAS) nursing is a series of perioperative optimization measures based on evidence-based medicine to reduce the body's stress response, promote postoperative recovery of patients, shorten hospital stay, reduce postoperative complications, and reduce readmission risk and the risk of death (6, 7). However, the degree of pain severely restricts the implementation of ERAS, affecting important evaluation indicators such as joint range of motion, time to start functional exercise, and average hospital stay (8). Therefore, TKA perioperative analgesia is an important option that needs to be popularized under the ERAS concept. For patients undergoing surgical procedures, there are many analgesic protocols that are currently available, including preemptive analgesia (9–11). Preemptive analgesia is the administration of a certain dose of analgesics before the transmission of pain stimuli to block nociceptive transmission and achieve the purpose of reducing postoperative pain. Preemptive analgesia protocols is the administration of a certain dose of analgesics before the transmission of pain stimuli to block nociceptive transmission and achieve the purpose of reducing postoperative pain (12, 13). PS is a specific COX-2 inhibitor that can inhibit peripheral COX-2 expression and reduce the synthesis of peripheral prostaglandins (PG), thereby exerting analgesic and anti-inflammatory effects (14, 15). At the same time, PS can also inhibit the expression of central COX-2, reduce the synthesis of central PG, significantly reduce the level of PGE2 in the cerebrospinal fluid, reduce central sensitization, and exert dual analgesic effects (14, 15).

In this prospective cross-sectional study, we aim to ascertain the effect of PS application, combined with ERAS, on inflammation and knee joint function in elderly patients after TKA.

MATERIALS AND METHODS

Patients and Ethics Statement

The present study is approved and supervised by our Hospital Ethics Committee, and it conforms to the principles of the Declaration of Helsinki. Moreover, all volunteers who participated in this study were briefed about its content, following which they signed an informed consent form.

In this prospective cross-sectional study, we enrolled 120 elderly patients treated with TKA from January 2020 to September 2021. The inclusion criteria were as follows: (1) age >60 years; (2) treated with TKA; (3) ASA stages I–III; (4) weight range from 45 to 90 kg; and (5) complete clinical data and voluntary participation in this study. The exclusion criteria were as follows: (1) coagulation dysfunction; (2) liver, kidney, or other tissue and organ dysfunction; (3) patients with immune system diseases, tumors, and chronic infectious diseases; (4) history of central and peripheral nervous system disease; (5) history of drug abuse, alcohol abuse, opioid abuse, non-steroidal anti-inflammatory drug allergy; (6) surgery within 1 year; and (7) intellectual disability or mental illness.

Parecoxib Sodium Administration

In this study, all patients who had undergone TKA treatment received ERAS nursing. However, patients in the combine group received PS administration. The protocol of PS administration was as follows: After completing the anesthesia protocol and before preparing to cut the skin, the patients in the combine group were injected with 40- mg PS intravenously. At 12, 24, 36, and 48 h after TKA treatment, these patients were again injected with 40- mg PS intravenously. Patients in the control group were intravenously injected with an equal volume of normal saline at the same time. The protocol of ERAS nursing was as follows (2 weeks): (1) Dorsiflexion training: dorsiflexion exercise 6 h after operation, dorsiflexion for 5 s, and then plantar flexion for 5 s and 100 times/h; (2) Walking on the ground: walking out of bed on the second day after operation, 1 time/2 h and 10 min/time; (3) Knee joint flexion and extension exercise: On the third day after operation, the affected limb knee joint extension exercise and flexion exercise were performed on the bed, both 1 time/2 h and 10 min/time second rate.

Hematology Indicators

Before surgery and 1, 3, 7, and 14 days after surgery, 10 ml of peripheral blood was collected from each patient to detect the levels of hemoglobin (Hb), complete white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and serum IL-1β, TNF-α, and IL-6.

Knee Joint Function

Before surgery and first, third, and sixth months after surgery, we used the hospital for special surgery scale (HSS) to evaluate the knee joint function. The HSS score includes the following 7 sub-items: pain, function, range of motion, muscle strength, flexion deformity, stability, and deduction items. Higher HSS scores indicate better knee function. At the same time, we recorded the recovery time for 30, 60, 90, and 120 angles of joint motion in patients with TKA treatment.

Statistical Analysis

SPSS 20.0 (NIH, USA) was used to analyze the data in the present study. Measurement data that conform to a normal distribution pattern are presented as (mean ± standard deviation), and the difference in the measurement data between the two groups is compared using an independent-samples *t*-test. Categorical data are presented as numbers and percentages and analyzed by Chi-squared analysis or the Fisher exact-probability test. A score of $p < 0.05$ was considered statistically significant.

TABLE 1 | Comparison of baseline data of two groups of patients (n, $\bar{x} \pm s$).

Index	Combine group ($n = 60$)	Control group ($n = 60$)	t/χ^2	p
Gender (n)				
Male	28	30	0.075	0.726
Female	32	30		
Age (years)	64.3 ± 7.9	65.2 ± 9.4	0.537	0.715
BMI (kg/m^2)	24.6 ± 1.3	24.5 ± 1.2	1.021	0.191
ASA Grade				
I + II	38	34	0.278	0.598
III	22	26		
Surgical site				
Right	26	29	1.004	0.316
Left	24	21		
Surgical time (min)	80.2 ± 10.3	79.8 ± 9.5	0.631	0.602

RESULTS

Baseline Data

We compared the baseline data including gender, age, BMI, ASA grade, surgical, and surgical time between the combine group and the control group and found no significant difference (**Table 1**).

Peripheral Blood Inflammation–Related Indicators

At first, before surgery, the levels of Hb, WBC, and ESR in the patients of the combine group showed no significant difference compared with those of the control group ($p > 0.05$). On the third and seventh postoperative days, the levels of Hb in the patients of the combine group were significantly higher than those of the control group ($p < 0.05$; **Figure 1**), while the levels of WBC and ESR in the patients of the combine group were significantly lower than those of the control group ($p < 0.05$; **Figures 2** and **3**). On the 1st and 14th postoperative days, the levels of Hb, WBC, and ESR in the patients of the combine group showed no significant difference compared with those of the control group ($p > 0.05$).

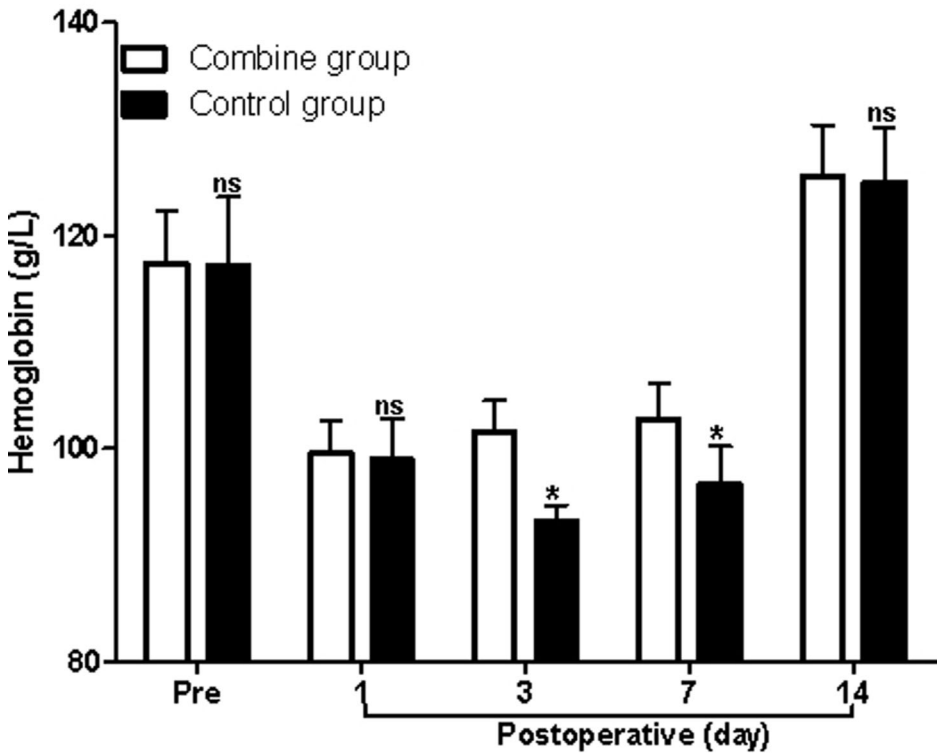

FIGURE 1 | Comparison of hemoglobin at different times in patients of two groups. Note: Compared with the combine group, $^{ns}p > 0.05$ and $^{*}p < 0.05$.

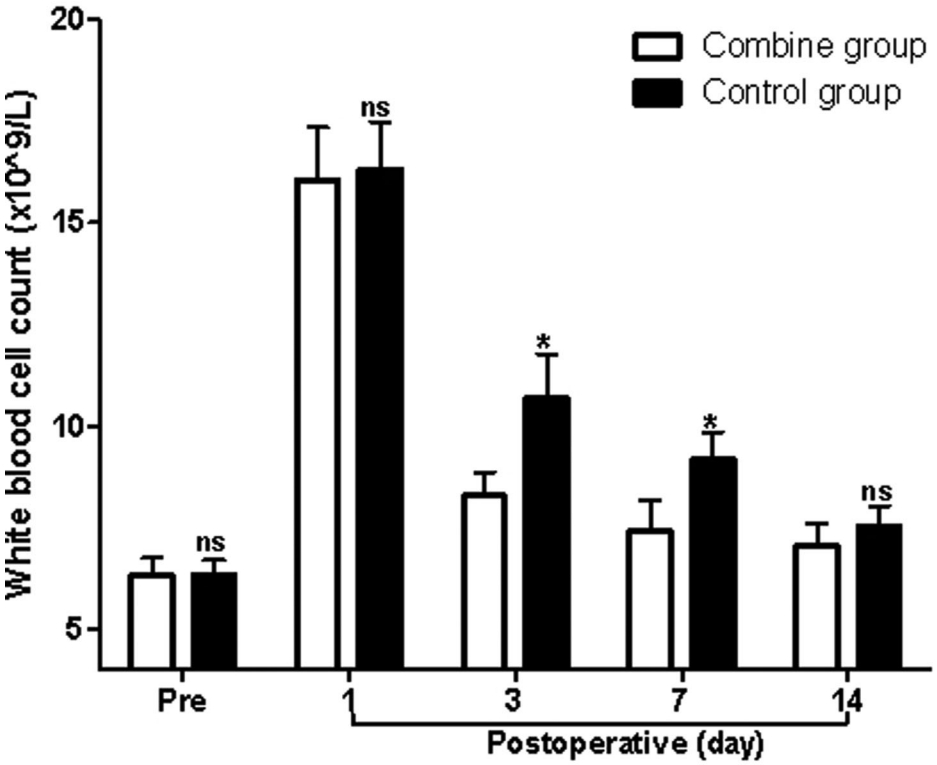

FIGURE 2 | Comparison of white blood cell count at different times in patients of two groups. Note: Compared with the combine group, $^{ns}p > 0.05$ and $^{*}p < 0.05$.

Serum Inflammatory Cytokines

At first, before surgery, the serum levels of IL-1β, TNF-α, and IL-6 in the patients of the combine group showed no significant difference compared with those of the control group ($p > 0.05$). On the third and seventh postoperative days, the serum levels of IL-1β, TNF-α, and IL-6 in the patients of the combine group were all significantly lower than those of the control group ($p > 0.05$; **Figures 4–6**), while there was no significant difference on the 1st and 14th postoperative days ($p > 0.05$).

Recovery Time for Different Ranges of Joint Motion

Compared with patients in the control group, the recovery time for 30, 60, 90, and 120 angles of joint motion in patients of the combine group was significantly decreased ($p < 0.05$; **Table 2**).

Knee Joint Function HSS Score

Before surgery, the HSS score of patients in the combine group showed no significant difference from that of patients in the control group ($p > 0.05$). On the first, third, and sixth postoperative months, the HSS score of patients in the combine group was significantly higher than that in the control group ($p < 0.05$; **Table 3**).

DISCUSSION

Degenerative knee arthritis is a disease with a high incidence among the elderly people, and the clinical features are mainly redness, swelling, pain, and snapping of the knee joint (16, 17). If patients cannot receive timely treatment, it will lead to severe joint deformity and even disability. The pathogenesis of degenerative joint disease is related to advanced age, obesity, trauma, genetic, and metabolic factors. At present, in the early stage of the disease, conservative treatment is mainly used to delay the development of the disease, while in the middle and late stages of the disease, when the knee joint function is lost due to joint pain, deformity, etc., only a part of the joint function can be restored through knee joint replacement and other methods (18). Currently, TKA is a common method for the treatment of severe knee osteoarthritis (18). However, TKA is more traumatic to patients with knee osteoarthritis, and severe inflammatory reaction occurs after surgery and releases pain-causing substances, causing postoperative pain and affecting the recovery of postoperative joint function (5). Perioperative analgesia can help reduce the inflammatory response caused by TKA, reduce tissue exudation and edema, reduce perioperative hidden and overt bleeding, promote wound healing, and accelerate the functional recovery of the affected knee joint (9–11).

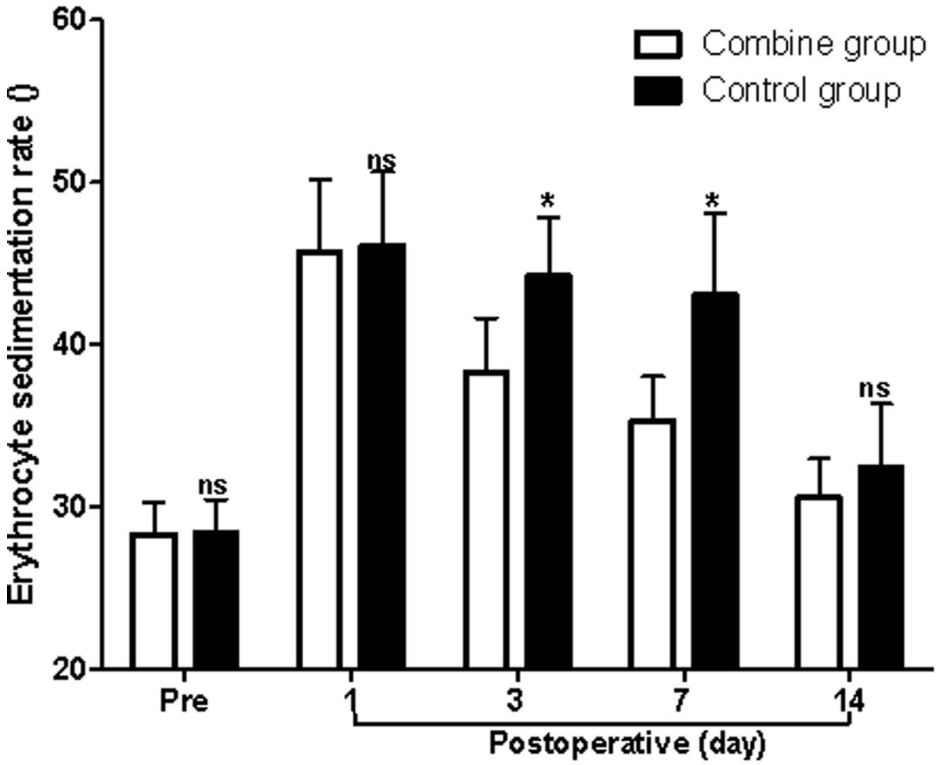

FIGURE 3 | Comparison of the erythrocyte sedimentation rate at different times in patients of two groups. Note: Compared with the combine group, $^{ns}p > 0.05$ and $^{*}p < 0.05$.

Severe inflammatory and release of pain-causing substances will occur after TKA, which are the main inducers of postoperative pain in the body (19, 20). PS is a new type of non-steroidal anti-inflammatory drug with analgesic, antipyretic, anti-inflammatory, and anti-rheumatic effects. PS is suitable for pain management of various acute and chronic inflammatory arthritis and is widely used in perioperative multimodal preemptive analgesia (14, 15). In addition, parecoxib is a prodrug of valdecoxib. On the one hand, it can reduce the synthesis of PG by inhibiting the activity of COX-2 in the peripheral and central regions, thereby reducing peripheral and central sensitization (14, 15). On the other hand, it exerts the analgesic effect by reducing the postoperative inflammatory response and shortening the duration of this response (21, 22).

In the present study, patients in the combine group received ERAS nursing and PS, while patients in the control group received ERAS nursing and normal saline. We found that the levels of Hb in the patients of the combine group were significantly higher than those of the control group, while the levels of WBC, ESR, serum IL-1β, TNF-α, and IL-6 in the patients of the combine group were all significantly lower than those of the control group on the third and seventh postoperative days, which suggested that patients in the combine group had lower postoperative inflammation in peripheral blood. Tissue damage caused by TKA can activate the complement system and immune cells, causing the body to release a variety of inflammatory factors such as IL-1β, IL-6, and TNF-α (23–26). IL-1β and IL-6 are the main pro-inflammatory factors of acute inflammatory response and play an important role in regulating body damage, infection, etc. The levels of IL-1β and IL-6 increase rapidly under stress, which is closely related to the degree of tissue damage (23–26).

The recovery time of postoperative knee joint function in patients receiving TKA is the gold standard for evaluating the efficacy of postoperative analgesia and nursing modes. In this study, we found that the recovery time for 30, 60, 90, and 120 angles of joint motion in patients of the combine group was significantly lower than that of the control group, which suggested that patients in the combine group showed a faster postoperative recovery of knee joint function. Moreover, we found that the HSS score of patients in the combine group was significantly higher than that in the control group on the first, third, and sixth postoperative months, which also that suggested patients in the combine group showed a faster postoperative recovery of knee joint function. Lesser postoperative inflammation in peripheral blood leads to lesser postoperative pain, that is, a better analgesic effect, and a better analgesic effect helps to reduce the inflammatory reaction caused by TKA and also reduce tissue exudation and edema. It can reduce the amount of hidden and dominant bleeding in the perioperative period, promote wound healing, and accelerate the functional recovery of the affected knee joint (27–29).

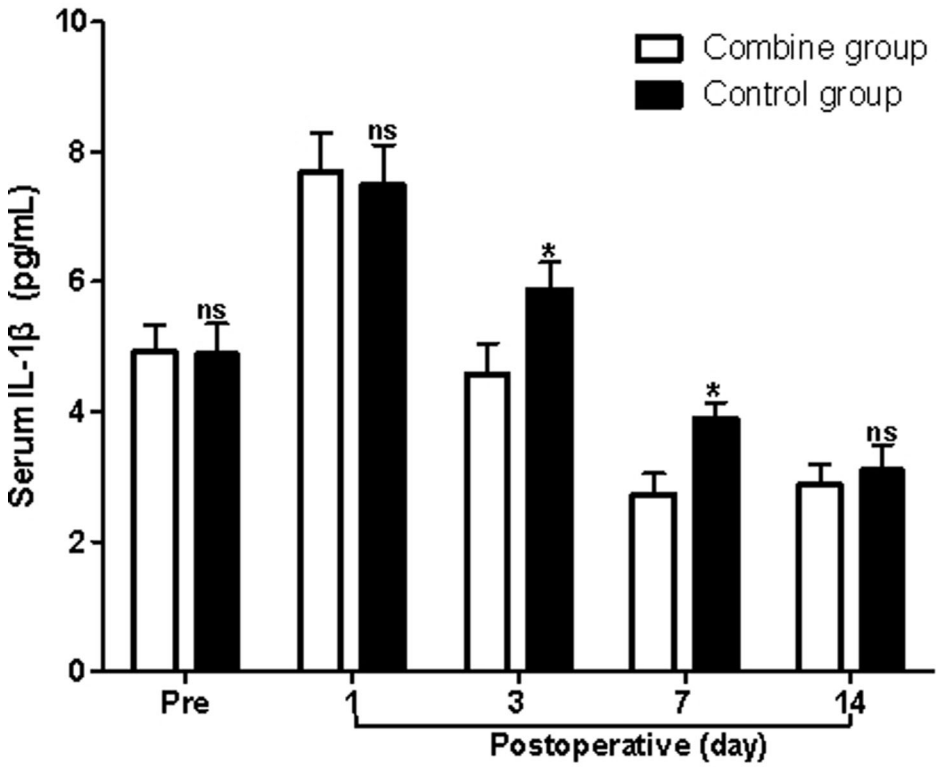

FIGURE 4 | Comparison of serum IL-1β levels at different times in patients of two groups. Note: Compared with the combine group, $^{ns}p > 0.05$ and $^{*}p < 0.05$.

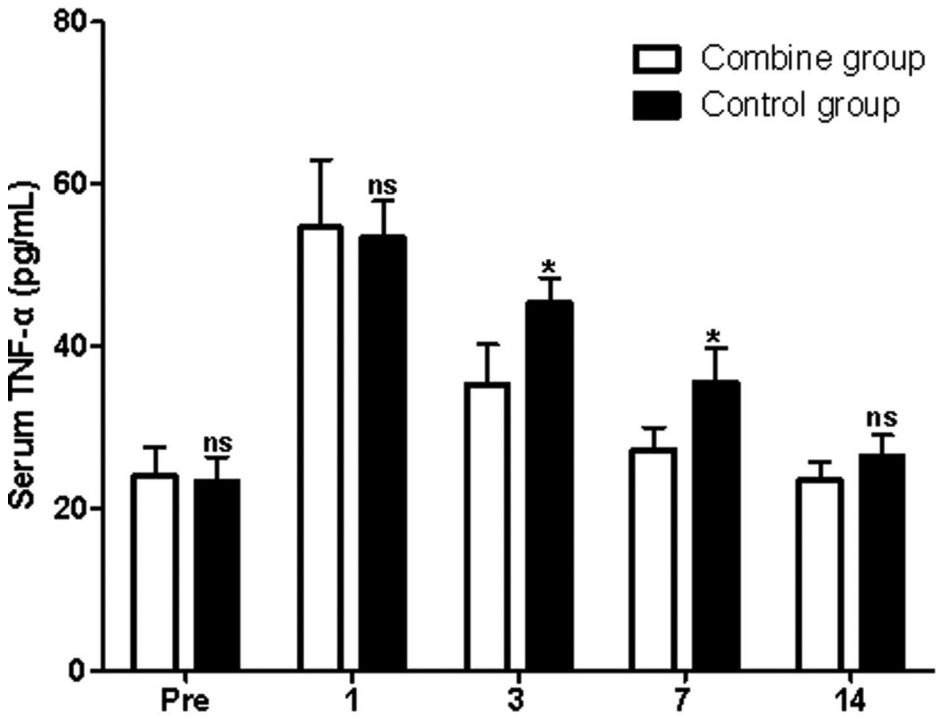

FIGURE 5 | Comparison of serum TNF-α levels at different times in patients of two groups. Note: Compared with the combine group, $^{ns}p > 0.05$ and $^{*}p < 0.05$.

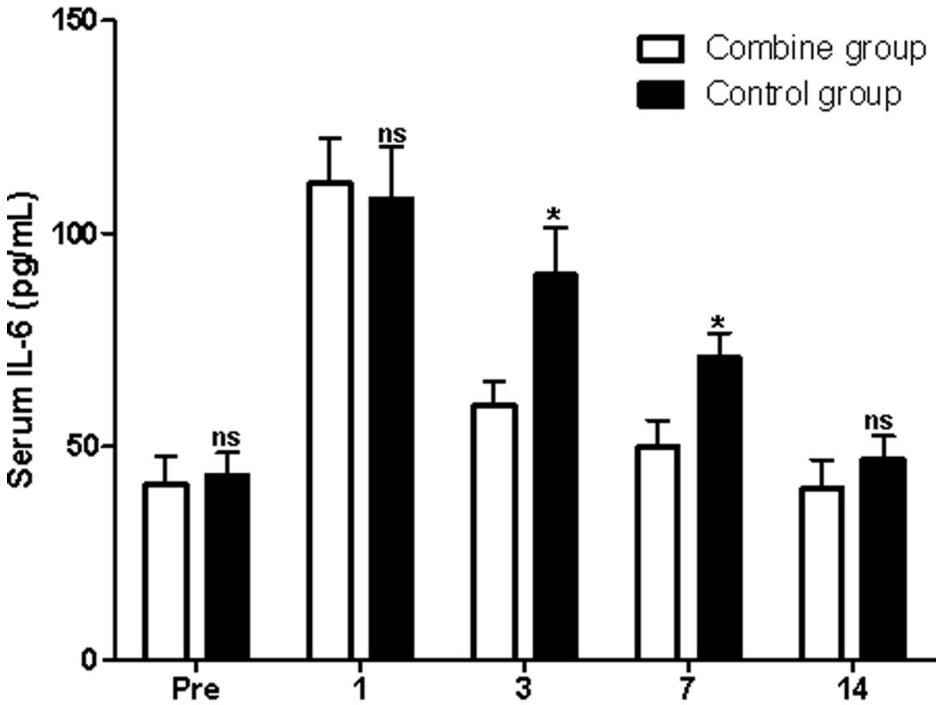

FIGURE 6 | Comparison of serum IL-6 levels at different times in patients of two groups. Note: Compared with the combine group, $^{ns}p > 0.05$ and $^{*}p < 0.05$.

TABLE 2 | Comparison of recovery time for different ranges of joint motion in patients of two groups (n, $\bar{x} \pm$ s).

Group	*n*	Range of motion (°)			
		30 (days)	60 (days)	90 (days)	120 (days)
Combine group	60	1.0 ± 0.3	6.0 ± 2.1	20.5 ± 3.8	28.2 ± 4.8
Control group	60	6.5 ± 1.8	13.7 ± 4.3	27.5 ± 4.8	40.1 ± 6.4
t		6.592	7.326	9.526	13.824
p		<0.001	<0.001	<0.001	<0.001

TABLE 3 | Comparison of the HSS score at different times in patients of two groups (n, $\bar{x} \pm$ s, scores).

Group	*n*	Preoperative	Postoperative (month)		
			1	3	6
Combine group	60	45.6 ± 9.8	65.8 ± 9.3	75.6 ± 5.8	86.5 ± 6.2
Control group	60	45.9 ± 9.6	56.2 ± 7.5	68.2 ± 5.9	77.5 ± 7.1
t		0.786	5.326	3.291	2.913
p		0.382	<0.001	0.026	0.039

CONCLUSION

Elderly TKA patients who received PS application, combined with ERAS, had lower inflammation in peripheral blood 2 weeks after operation and showed faster postoperative recovery of knee joint 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 our hospital. All subjects gave informed consent and signed the informed consent form. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LD is mainly responsible for the writing, research, and research design of the article. LT is mainly responsible for data analysis. LD is responsible for the guidance of the entire research. All authors contributed to the article and approved the submitted version.

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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.

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ORIGINAL RESEARCH
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Application Value of Gastroenterography Combined With CT in the Evaluation of Short-Term Efficacy and Prognosis in Patients With Esophageal Cancer Radiotherapy

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Purpose: To observe the application value of gastroenterography combined with CT in the evaluation of short-term efficacy and prognosis in patients with esophageal cancer radiotherapy.

Methods: From January 2013 to December 2020, the clinical data of 207 patients with esophageal cancer treated by radiotherapy in our hospital were collected retrospectively. All patients received gastroenterography and CT examination before and after radiotherapy, and the patients were followed-up for 1 year, and the evaluation value of their short-term efficacy and prognosis was observed.

Results: After radiotherapy, the length diameter, short diameter, and volume of the lymph node were lower than those before radiotherapy ($p < 0.05$), but the maximum tube wall thickness had no significant difference ($p > 0.05$). The length diameter, short diameter, and volume of the lymph node, and the maximum tube wall thickness in the good efficacy group and the good prognosis group were lower, and the objective response rate in the good prognosis group was higher ($p < 0.05$). The area under the curve (AUC) of the length diameter, short diameter, and volume of the lymph node to evaluate the short-term efficacy of patients with esophageal cancer was 0.738, 0.705, and 0.748, respectively, and the AUC to evaluate the prognosis of patients with esophageal cancer was 0.751, 0.776, and 0.791, respectively.

Conclusion: Gastroenterography combined with CT has a good application value in the evaluation of short-term efficacy and prognosis in patients with esophageal cancer radiotherapy.

Keywords: esophageal cancer, radiotherapy, gastroenterography, CT, short-term efficacy, prognosis

INTRODUCTION

The main manifestations of esophageal cancer are damage to the esophageal wall and narrowing of the esophageal cavity. Lesions will involve the submucosa, leading to muscular hyperplasia, which affects patients' esophageal diastolic function (1). In recent years, with the changes in people's lifestyles and eating habits, the number of patients with esophageal cancer is increasing. The disease has a serious impact on the life safety of patients and has become the main disease endangering human health. According to the report, in 2020, esophageal cancer ranks eighth (600,000) in the global cancer incidence, and ranks sixth (540,000) in the number of deaths. Furthermore, in 2020, esophageal cancer ranks sixth (320,000) in China's cancer incidence, and it ranks fourth (300,000) in the number of deaths (2). Therefore, early treatment of patients with esophageal cancer can effectively improve the prognosis of patients. Once the patients with esophageal cancer are diagnosed, only about 20% of patients can be treated by radical resection, and about 80% of patients need radiotherapy or other methods to relieve the disease (3). Radiotherapy is one of the commonly used methods to treat esophageal cancer. This method can significantly reduce the volume of the lesion, create favorable conditions for further treatment of patients, and is of great significance for improving the prognosis of patients (4). However, some patients still have local and regional recurrence after radiotherapy, which leads to treatment failure. If the short-term efficacy of radiotherapy in patients with esophageal cancer can be scientifically and accurately evaluated, and prognosis evaluation can be carried out, it will be beneficial to improve the quality of life of patients. At present, with the continuous development of imaging technology, more and more physicians choose evaluation tools, such as CT and X-ray gastroenterography to comprehensively evaluate the curative effect and prognosis of patients with esophageal cancer (5). However, the use of a single tool to evaluate the disease status of patients with esophageal cancer has many limitations. Therefore, we aimed to observe the application value of gastroenterography combined with CT in the evaluation of short-term efficacy and prognosis in patients with esophageal cancer radiotherapy.

MATERIALS AND METHODS

Research Object

From January 2013 to December 2020, the clinical data of 207 patients with esophageal cancer treated by radiotherapy in our hospital were collected retrospectively. Inclusion criteria: it was esophageal cancer, as confirmed by pathological puncture; received radiotherapy for the first time; there were no contraindications of radiotherapy; the patient was able to take care of themselves; and the basic information was complete. Exclusion criteria: the lesion had metastasized to a distant place; Karnofsky score $<$ 70 points; combined with other malignant tumors; there were metabolic diseases; there were blood diseases; there were autoimmune diseases; existence of mental illness; and there were important organ injuries. Among 207 patients, there were 113 men and 94 women, with an average age of (59.16 ± 3.27) years. Pathological classification: 185 cases of squamous cell carcinoma, 19 cases of adenocarcinoma, and 3 cases of small cell carcinoma; clinical staging: 28 cases in stage I, 105 cases in stage II, and 74 cases in stage III; location of lesions: 15 cases of the cervical segment (cricoid cartilage—thoracic cavity entrance), 50 cases of the upper thoracic segment (thoracic cavity entrance—tracheal bifurcation), 118 cases of a middle thoracic segment (tracheal bifurcation—the upper half of the full length of the esophagogastric junction), and 24 cases of the lower thoracic segment (lower half of the full length of the esophagogastric junction).

Research Methods

① Gastroenterography examination: medical staff instructed the patient to be in an upright position, and orally took 65 ml air barium suspension. Multi-position radiography was used to determine the lesion scope.

② Imaging examinations before radiotherapy: gastroenterography and CT examination were performed using a CT scanner [SOMATOM Definition AS (SIEMENS)]. The medical staff instructed patients to lie in the supine position and instruct patients to breathe evenly in a calm condition. The scanning layer thickness was 3 mm, and the layer spacing was set to 3 mm. The neck, upper abdomen, and chest of a patient were scanned, and the scan should reach the lower part of the kidney from the entrance of the esophagus. Medical staff reconstructs 3D images by scanning images. The location of the lesions was determined according to the results of imaging examinations, such as gastroenterography, CT, and fiberoptic esophagoscopy. Criteria for the location of lesions are: the thickness of esophageal wall $>$5 mm, the excluded diameter of tracheal lumen $>$ 10 mm, thickening of the esophageal wall, and/or local stenosis of the esophageal lumen. The dose of radiotherapy was 54–69 or 1.8–2.0 Gy/time, and patients need to be treated with radiotherapy 5 times a week.

③ Imaging examination after radiotherapy: the interval between layers was set to 6 mm. The patient's neck to the upper abdomen was scanned. According to the location of the lesion known before radiotherapy, the location of the original lesion on the CT scan image after radiotherapy can be determined. The maximum tube wall thickness was measured, and the length diameter, short diameter, and volume of lymph nodes before and after radiotherapy were determined.

④ The short-term efficacy of gastroenterography was evaluated after 3 months of radiotherapy according to the esophageal cancer practice guidelines (6). Complete response (CR): the lesion completely disappears, barium can completely pass through, the esophageal lumen has slight stenosis or no stenosis, the esophageal mucosa is thickened, and the tube wall is slightly stiff; partial response (PR): the lesion disappeared by $\geq$30%, no extra-cavity ulcer, and esophageal distortion were found, barium could pass completely, the edge of the esophagus was not smooth enough, and small niches could be observed; stable disease (SD): the lesion is not significantly reduced, the esophageal filling defect is significant, and the lumen stenosis is serious; and progressive disease (PD): obvious new lesions were observed. Objective response rate (ORR) = CR+PR/total cases $\times$ 100%.

⑤ After radiotherapy, the medical staff told the patients to follow-up regularly. They followed-up patients for 1 year, and their survival rate was recorded.

Statistical Methods

In this study, SPSS 22.0 was used for data processing. The measurement data that conform to the normal distribution were expressed by mean ± standard deviation (SD), and the comparison was made by *t*-test. The count data were expressed by percentage, and the comparison was made by the χ^2 test. The receiver operating characteristic curve (ROC) was used to analyze the evaluation value of imaging results. The value of $p < 0.05$ was statistically significant.

RESULTS

Comparison of Imaging Results Before and After Radiotherapy

After radiotherapy, the length diameter, short diameter, and volume of the lymph node were lower than those before radiotherapy ($p < 0.05$), but the maximum tube wall thickness had no significant difference ($p > 0.05$) (as shown in **Figure 1**).

Comparison of Imaging Results of Patients With Different Efficacy

Among 207 patients with esophageal cancer treated by radiotherapy, CR was 62 cases, PR was 124 cases, SD was 18

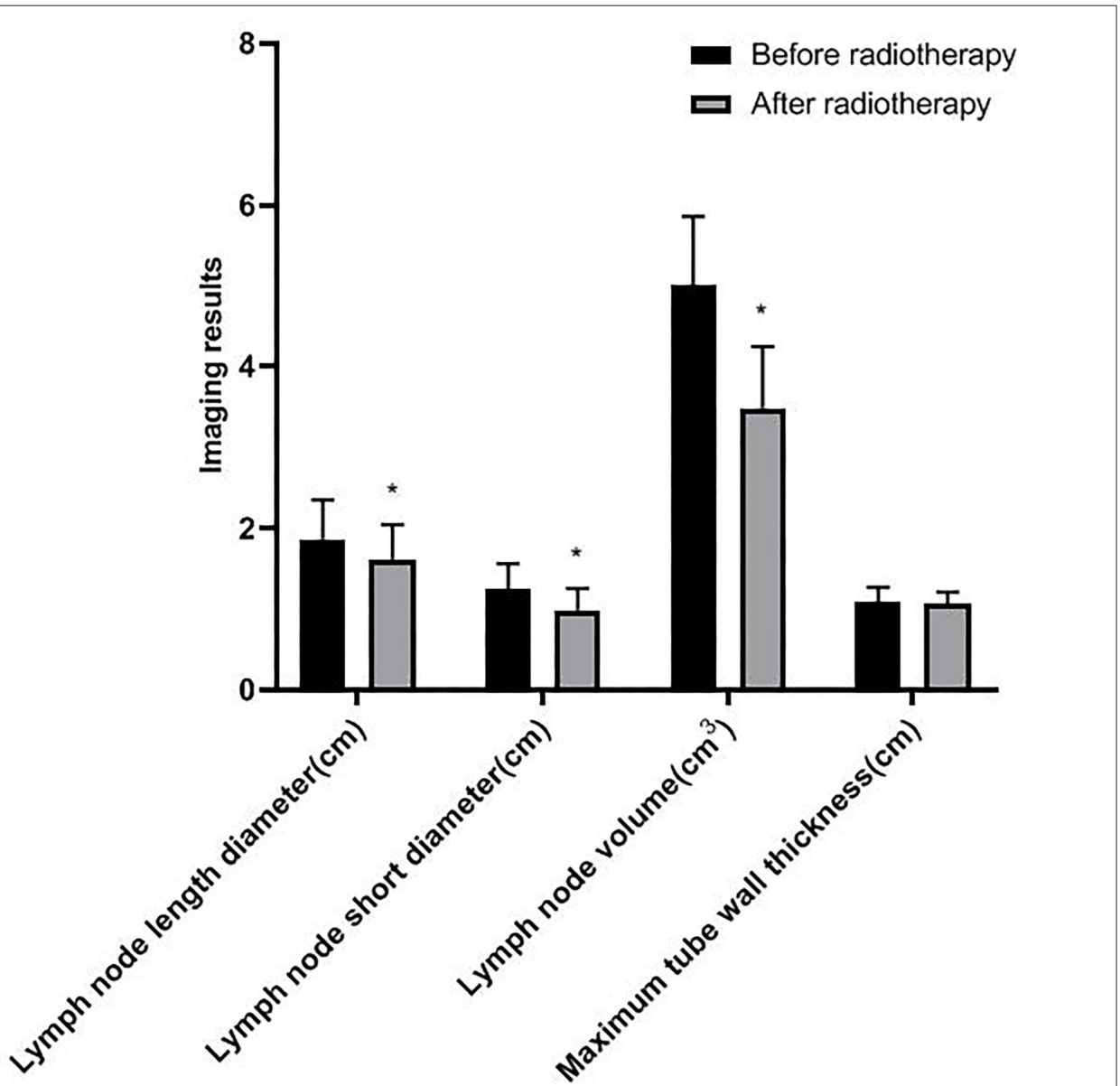

FIGURE 1 | Comparison of imaging results before and after radiotherapy. Compared with before radiotherapy, *$p < 0.05$.

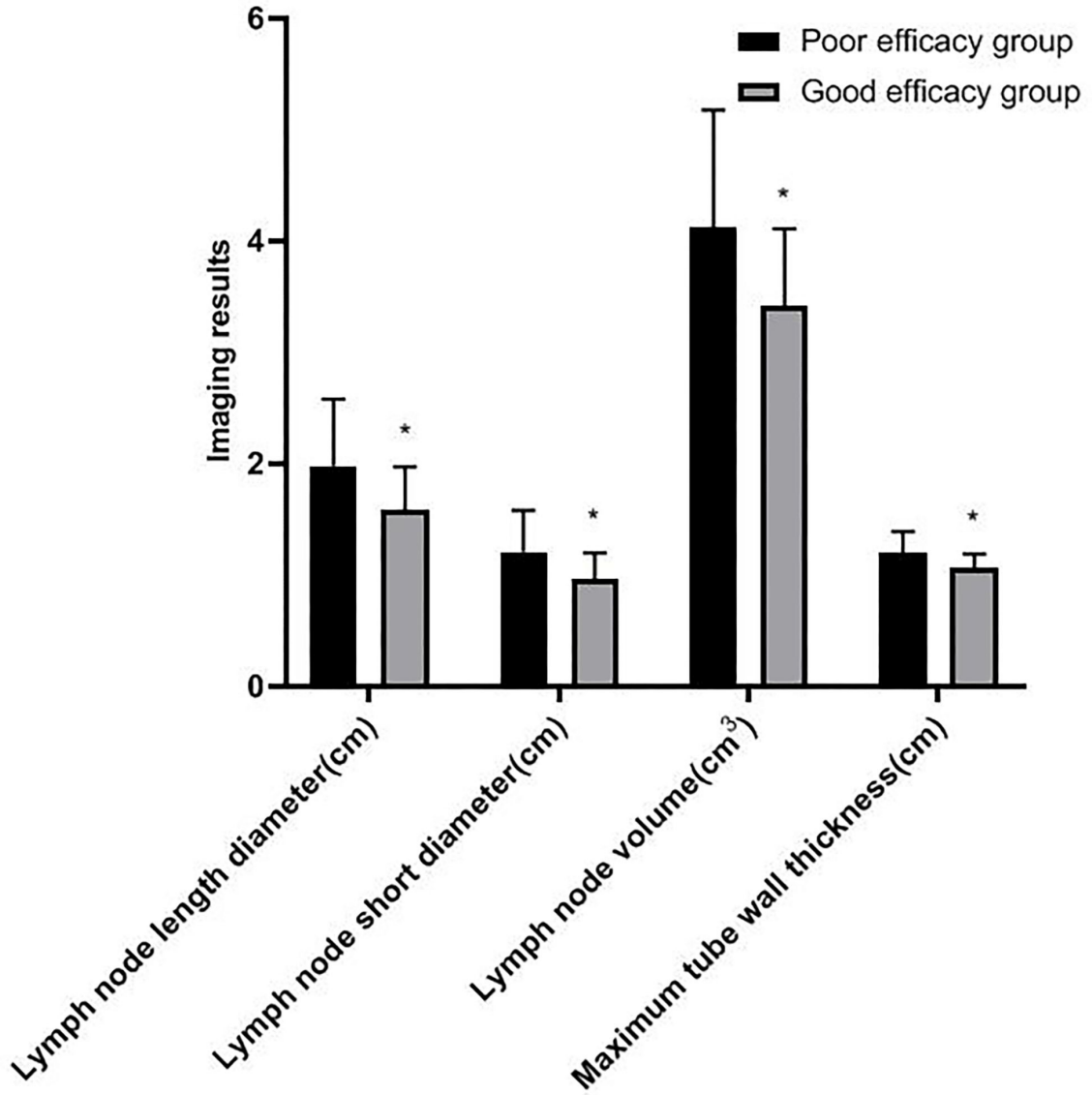

FIGURE 2 | Comparison of imaging results of patients with different efficacy. Compared with the poor efficacy group, $^{*}p < 0.05$.

cases, PD was 3 cases, and ORR was 89.85% (186/207). After radiotherapy, the patients were divided into two groups: the good efficacy group (186 cases) and the poor efficacy group (21 cases). The length diameter, short diameter, and volume of lymph nodes and the maximum tube wall thickness in the good efficacy group were lower than those in the poor efficacy group ($p < 0.05$) (as shown in **Figure 2**).

Comparison of Imaging Results of Patients With Different Prognosis

After radiotherapy, the patients were followed-up for 1 year. Among 207 patients with esophageal cancer treated by radiotherapy, 173 cases survived and 34 cases died, and the survival rate was 83.57% (173/207). Patients were divided into two groups: the good prognosis group (173 cases) and the poor prognosis group (34 cases). The length diameter, short diameter, and volume of lymph nodes and the maximum tube wall thickness in the good prognosis group were lower than those in the poor prognosis group, and the ORR of the good prognosis group (93.64%) was higher than the poor prognosis group (70.59%) ($p < 0.05$) (as shown in **Figure 3**).

Value of Imaging Results in Evaluating Short-Term Efficacy

The area under the curve (AUC) of length diameter, short diameter, and volume of the lymph node in evaluating the short-term efficacy of esophageal cancer patients was 0.738, 0.705, and 0.748, respectively ($p < 0.05$). The AUC of maximum tube

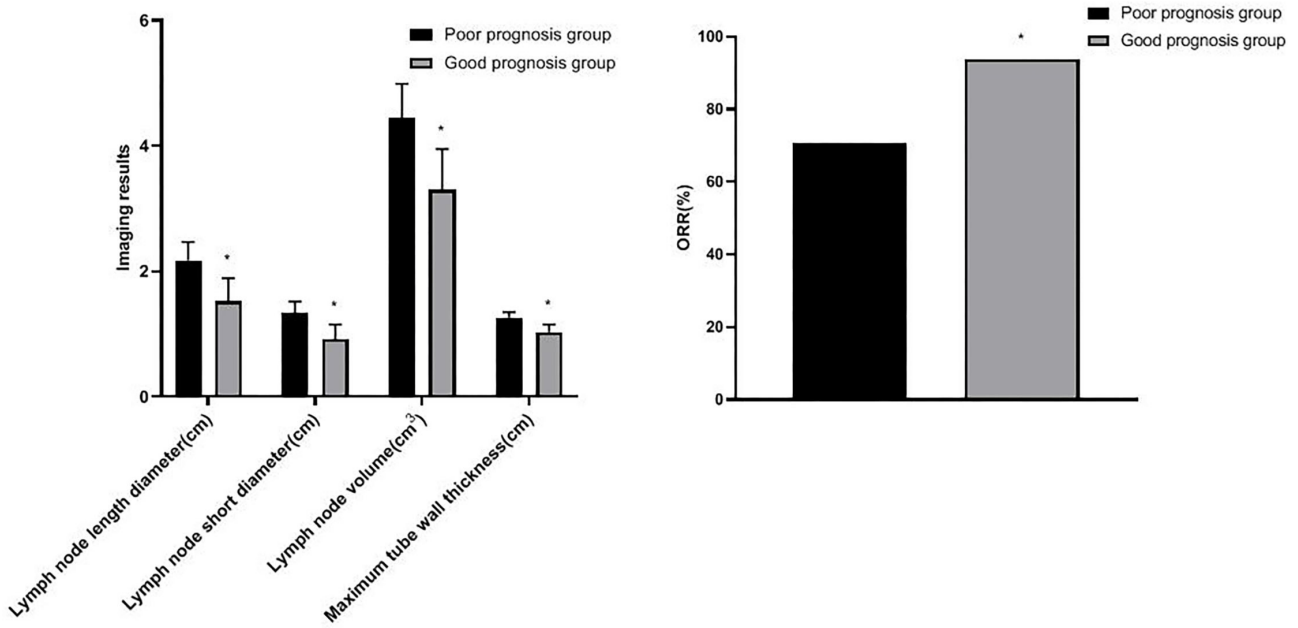

FIGURE 3 | Comparison of imaging results of patients with different prognosis. Compared with the poor prognosis group, $^*p < 0.05$.

TABLE 1 | Value of imaging results in evaluating short-term efficacy.

Index	AUC	Asymptotic 95% confidence interval		Standard error	*P*-value
		Lower limit	Upper limit		
Lymph node length diameter	0.738	0.592	0.879	0.072	0.000
Lymph node short diameter	0.705	0.561	0.849	0.074	0.002
Lymph node volume	0.748	0.603	0.894	0.074	0.000
Maximum tube wall thickness	0.622	0.459	0.784	0.083	0.068

wall thickness in evaluating the short-term efficacy of esophageal cancer patients was 0.622 ($p > 0.05$) (as shown in **Table 1** and **Figure 4**).

Value of Imaging Results in Evaluating Prognosis

The AUC of length diameter, short diameter, and volume of the lymph node in evaluating the prognosis of patients with esophageal cancer was 0.751, 0.776, and 0.791, respectively ($p < 0.05$). The AUC of maximum tube wall thickness in evaluating the prognosis of esophageal cancer patients was 0.606 ($p > 0.05$) (as shown in **Table 2** and **Figure 5**).

DISCUSSION

In recent years, China's radiotherapy technology and equipment have made rapid development. From ordinary external irradiation to current three-dimensional conformal or intensity-modulated radiotherapy, it has become the main treatment of esophageal cancer. After radiotherapy, the local control rate and long-term survival rate of patients with esophageal cancer were improved compared with before radiotherapy (7, 8). However, it is still clinically necessary to accurately evaluate the short-term curative effect and prognosis of patients with esophageal cancer after radiotherapy, which has a positive role in improving the quality of life of patients.

Gastroenterography is a traditional examination method of digestive tract diseases, which is mainly used to observe digestive tract diseases, such as inflammation, ulcers, and tumors (9). The inspection principle of gastroenterography is: after the patient has taken a contrast agent, the reaction of the barium agent under the X-ray can be used to see the outline of the digestive tract and reveal the location of the disease (10). This examination is usually used for patients who cannot tolerate or cannot undergo gastrointestinal endoscopy. It has the advantages of relative safety, no side effects, and simple operation (11). Gastroenterography is widely used in clinical diagnosis and treatment. It is the most commonly used imaging examination method for esophageal cancer, and it is also the simplest examination method to evaluate the efficacy of radiotherapy. This examination method is highly sensitive to small lesions, mainly by observing mucosal folds to determine the location

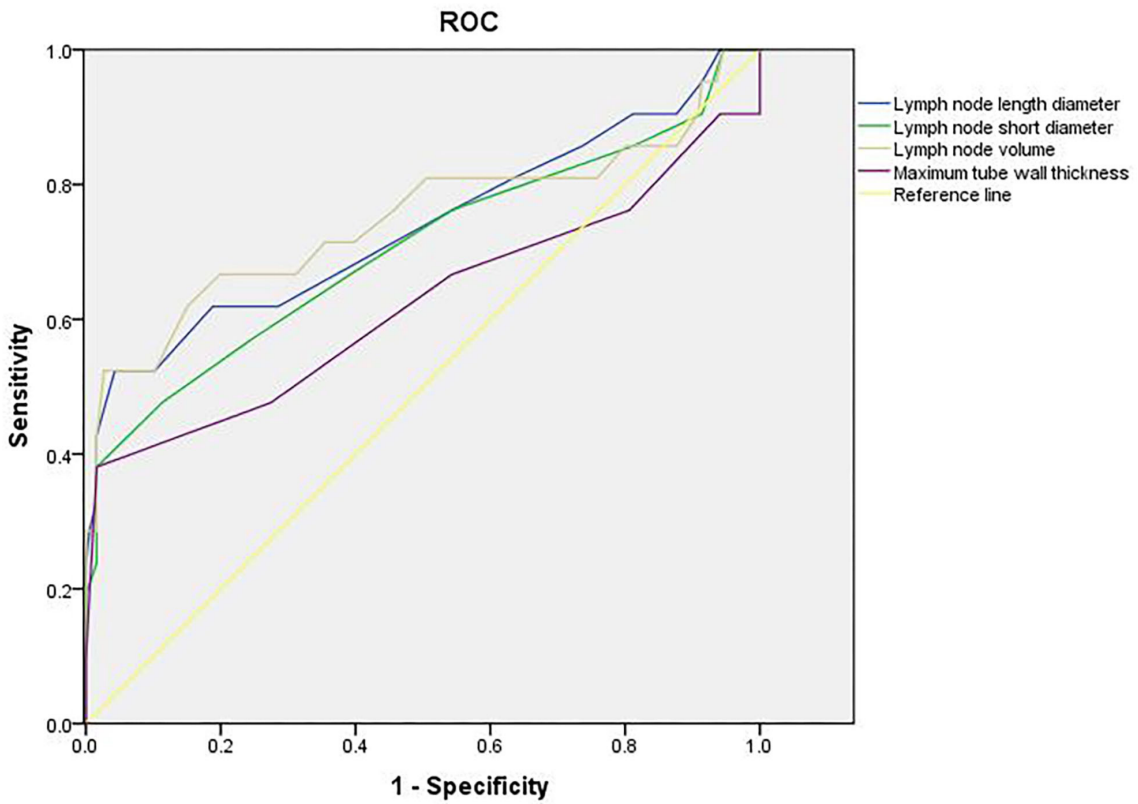

FIGURE 4 | Value of imaging results in evaluating short-term efficacy.

TABLE 2 | Value of imaging results in evaluating prognosis.

Index	AUC	Asymptotic 95% confidence interval		Standard error	*P*-value
		Lower limit	Upper limit		
Lymph node length diameter	0.751	0.639	0.862	0.057	0.000
Lymph node short diameter	0.776	0.660	0.893	0.059	0.000
Lymph node volume	0.791	0.692	0.891	0.051	0.000
Maximum tube wall thickness	0.606	0.468	0.743	0.070	0.052

of esophageal lesions, to know the information on lesion size, growth form, and so on, and to reflect the changes in the esophageal cancer cavity (12, 13). However, gastroenterography can only evaluate the local remission of the primary tumor of esophageal cancer, and cannot effectively reflect the lymph node metastasis. Besides, there are some limitations in the evaluation of the wall thickness changes of esophageal cancer, and it cannot predict the prognosis more systematically (14).

At present, there are more and more studies on the combination of various imaging technologies for evaluating the curative effect and prognosis of tumors. As a technology characterized by displaying organ function and metabolic state, CT can not only observe the thickness of the esophageal wall and the interface at the wall before and after radiotherapy, but also determine the extent and degree of extra-esophageal cavity invasion, and the lymph node metastasis and distant metastasis can also be identified (15). CT is of great value in evaluating the extension of esophageal cancer. The esophagus lacks a serosa layer, and drainage lymph is unusually rich, so it is easy to directly invade adjacent organs and metastasis. There is a layer of fat around the esophagus, so CT can clearly show the relationship between the shape of the esophagus and the adjacent mediastinal organs below the esophagus (16, 17). CT scan directly measure the wall thickness, which is characterized by high resolution and simple operation. It can make up for the deficiency that gastroenterography can only observe local lesions in the esophageal cavity, and has higher accuracy in the evaluation of the short-term curative effect of radiotherapy, which is conducive to guiding clinical treatment (18). Gastroenterography combined with CT for comprehensive evaluation can complement each

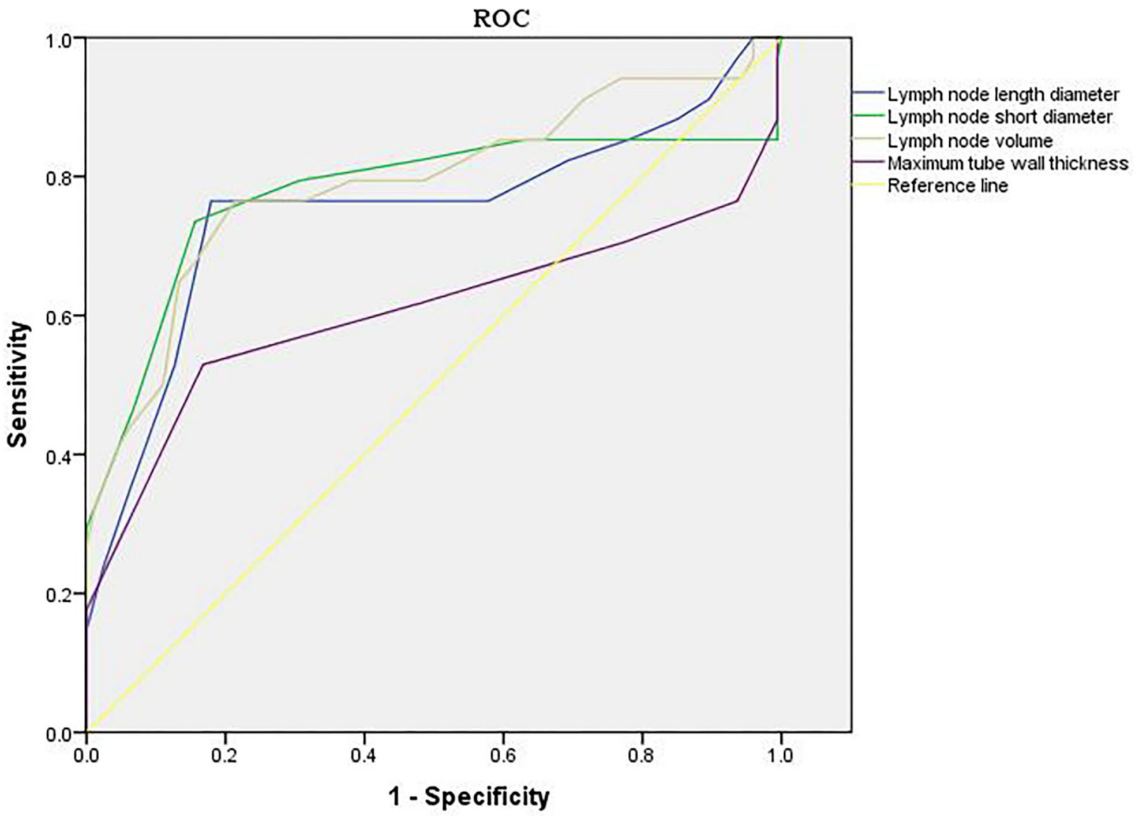

FIGURE 5 | Value of imaging results in evaluating prognosis.

other's advantages and play a synergistic role in the evaluation of curative effect and prognosis of esophageal cancer.

Zhou's team found that the maximum diameter of metastatic lymph nodes may be an effective biomarker to predict the prognosis of patients who received radiotherapy after esophagectomy (19). Wu's team believed that the AUC for the minimum diameter of lymph nodes and the maximum diameter of lymph nodes for diagnosing lymph node metastasis were 0.679 and 0.666, respectively. CT can effectively evaluate lymph node metastasis in patients with thoracic esophageal cancer (20). In this study, after radiotherapy, the length diameter, short diameter, and volume of lymph nodes were lower than those before radiotherapy. The length diameter, short diameter, and volume of the lymph node in the good efficacy group and good prognosis group were lower, and the ORR in the good prognosis group was higher. The results showed that after radiotherapy, the smaller the length diameter, short diameter, and volume of lymph node, the more significant the short-term efficacy and the better the prognosis. The change of length diameter, short diameter, and volume of the lymph node is an important indicator to evaluate the risk of lymph node metastasis, and has a great influence on the therapeutic effect and prognosis.

Generally speaking, the tumor target area of radiotherapy for esophageal cancer is mainly based on the thickness of the esophageal wall (21). In this study, there was no significant difference in the maximum tube wall thickness before and after radiotherapy. The possible reasons are as follows: after radiotherapy, there are many changes in the inner mucosa of patients with esophageal cancer, such as edema, infiltration of inflammatory cells, congestion, erosion, and proliferation of connective tissue, granulation tissue, and collagen tissue in some places, which make it difficult for the thickness of the esophageal wall of patients to return to normal in a short time. Although some tumor cells were killed after radiotherapy, there was little change in the maximum tube wall thickness (22–24). Wu's team found that in patients with esophageal cancer undergoing radiotherapy and chemotherapy, the percentage of maximum wall thickness reduction was independently associated with pathological complete response ($p = 0.027$), and could predict the recurrence of the disease (25). Wongwaiyut's team found that the survival of patients with esophageal cancer with a maximum wall thickness of <10 mm and ≥ 10 mm was different, and the larger the maximum wall thickness, the worse the prognosis of patients (26). We found that the maximum tube wall thickness was lower in the good efficacy group and good prognosis group, but its value in evaluating the short-term efficacy and prognosis of patients with esophageal cancer was not high, and there was no significant difference. This indicated that the maximum tube wall thickness of patients with esophageal cancer is not related to short-term efficacy and prognosis, which may be due to the

smaller maximum tube wall thickness of patients included in this study. In addition, the ROC curve of this study also found that the AUC of the length diameter, short diameter, and volume of the lymph node to evaluate the short-term efficacy of patients with esophageal cancer was 0.738, 0.705, and 0.748, respectively, and the AUC to evaluate the prognosis of patients with esophageal cancer was 0.751, 0.776, and 0.791, respectively. The results further showed that lymph nodes are closely related to the short-term efficacy and prognosis of patients with esophageal cancer. Gastroenterography combined with CT has a good application value in the evaluation of short-term efficacy and prognosis in patients with esophageal cancer radiotherapy. Conventional CT has higher requirements on the filling degree of the esophageal cavity. If the filling of the esophagus is not good, the display effect of CT will be affected to a certain extent. Medical personnel should pay attention to this during the detection process.

CONCLUSION

To sum up, gastroenterography combined with CT has a good application value in the evaluation of short-term efficacy and prognosis in patients with esophageal cancer radiotherapy. There are still some deficiencies in this study. We only evaluated the 1-year survival rate of the patients, and the evaluation effect of gastroenterography combined with CT on the long-term prognosis of patients with esophageal cancer radiotherapy needs to be discussed in subsequent studies.

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 Ethics Committee of our hospital. All subjects gave informed consent and signed the informed consent form. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LX is the executor and writer of the paper. LE is responsible for searching data and data analysis. DG is ensuring that the descriptions are accurate and agreed by all authors. ZW is responsible for research design. All the authors contributed to this article.

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ORIGINAL RESEARCH
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Comparative Clinical Study of Percutaneous Epididymal Sperm Aspiration and Testicular Biopsy in the Outcome of ICSI-Assisted Fertility Treatment in Patients with Obstructive Azoospermia

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Objective: To compare and contrast the effects of percutaneous epididymal sperm aspiration (PESA) and testicular sperm aspiration (TESA) on the outcome of intracytoplasmic sperm injection (ICSI)-assisted fertility treatment in patients with obstructive azoospermia.

Methods: Patients with obstructive azoospermia with an age distribution of 20–36 years admitted to the male department of the Reproductive Center of the Second Affiliated Hospital of South China University (Hengyang Nanhua Xing Hui Reproductive Health Hospital) from December 2018 to December 2020 were used in this study. One group was set up as the PESA group to perform PESA, and the other group was set up as the TESA group to perform percutaneous testicular biopsy for sperm extraction. Patients who were unsuccessful in PESA continued to undergo TESA, and if sperm were retrieved, they were classified as the TESA group. General information on male patients and their partners was collected and compared in patients from different sperm source groups. Embryo development (normal fertilization rate, high-quality embryo rate, and high-quality blastocyst rate) and pregnancy outcome (clinical pregnancy rate, miscarriage rate, and ectopic pregnancy rate) were compared between the two groups.

Results: Finally, there were 26 patients in the PESA group and 31 patients in the TESA group. There were no significant differences in terms of age, years of infertility, testosterone level, (FSH) follicle-stimulating hormone level, and testicular volume between the male patients in the PESA and TESA groups of two different sperm sources, and no significant differences were found in the general conditions of the female patients in terms of age, number of eggs obtained, number of sinus follicles, basal FSH value, and basal E2 value ($p > 0.05$). The rate of high-quality blastocysts in the TESA group was significantly higher than that in the PESA group ($p < 0.05$); the differences in clinical

normal fertilization rate, high-quality embryo rate, clinical pregnancy rate, miscarriage rate, and ectopic pregnancy rate between the two groups were not statistically significant ($p > 0.05$).

Conclusion: ICSI with different sources of sperm in patients with male factor infertility alone, which had no significant effect on embryo development, embryo implantation rate, clinical pregnancy rate, and miscarriage rate, resulting in better clinical outcomes.

Keywords: obstructive azoospermia, percutaneous epididymal sperm aspiration, testicular sperm aspiration, ICSI for fertility, pregnancy outcome

INTRODUCTION

Male infertility is a complex clinical syndrome that accounts for 40%–50% of fertility abnormalities and is the result of multiple diseases or factors, among which azoospermia is one of the common causes of male infertility (1, 2). Men with three consecutive and intermittent sperm retrievals, with not a single sperm found under the microscope after routine semen examination and centrifugal sedimentation, are called azoospermia, which accounts for about 15%–20% of male infertility patients (3). The causes of azoospermia are summarized into two main types: one is spermatogenic dysfunction of the testes themselves such as genetic abnormalities and endocrine disorders resulting in testicular spermatogenic dysfunction, thus preventing sperm production leading to male infertility, called primary azoospermia or non-obstructive azoospermia. The second is obstructive azoospermia, in which the spermatozoa occur normally in the testes of such patients and cannot be excreted normally due to an obstruction of the vas deferens, including the intratesticular, epididymal, vas deferens and ejaculatory duct openings, due to urogenital tract infection, congenital anomalies, or trauma (4, 5).

Intracytoplasmic sperm injection (ICSI), an assisted fertilization technique in which sperm is injected directly into the oocyte plasma, is currently the mainstay of treatment for male infertility (6). This technique fertilizes sperm by injecting them directly into the oocyte plasma of the oocyte through microinsemination techniques, using sperm from the epididymis or testes in addition to naturally ejaculated sperm (7). There are various methods of obtaining sperm from the testes for the diagnosis of azoospermia, such as microsurgical epididymal sperm aspiration (8), percutaneous epididymal sperm aspiration (PESA) (9), testicular biopsy sperm aspiration (TESA) (10), and testicular fine needle aspiration (11) (TFNA), among which PESA and TESA have the advantages of less trauma, lower cost, and better results. The practice of using PESA or TESA to obtain sperm when using self-seminal ICSI for assisted reproduction varies among assisted reproduction facilities, and the fertility outcomes after sperm acquisition for ICSI-assisted fertility treatment reported in the relevant literature (12–14) are also controversial. Therefore, this study provides a comprehensive analysis of the treatment outcomes of PESA- and TESA-obtained sperm applied to patients with obstructive azoospermia undergoing ICSI-assisted fertility, with the aim of further clarifying the priority levels of the two sperm retrieval procedures.

MATERIALS AND METHODS

Subjects

Patients with obstructive azoospermia admitted to the male department of the Reproductive Center of the Second Affiliated Hospital of South China University (Hengyang Nanhua Xing Hui Reproductive Health Specialist Hospital) were included in this study. The diagnostic criteria were as follows: (i) There should be two sperm retrievals, and no sperm should have been found under the microscope after routine semen examination and centrifugal sedimentation; (ii) Bilateral testes should be of normal size and bilateral epididymis should be in normal position; (iii) Sex hormones such as follicle-stimulating hormone (FSH) and Inhibin B (INHB) should be in the normal range; (iv) No abnormality should be seen during peripheral blood karyotype analysis and the azoospermia factor (AZF) gene test; (v) Ultrasound should show grid-like changes in the epididymal duct. The inclusion criteria were also follows: (i) Those who agreed and cooperated with this study; (ii) Those whose spouses had no abnormalities or whose infertility factors were only tubal factors. The exclusion criteria were as follows: (i) Chromosomal abnormalities in either the patient or the spouse; (ii) Acute uterus, endometriosis, or hydrosalpinx in the patient's spouse; (iii) Poor ovarian response with <3 eggs obtained.

General Data Collection

Clinical data related to infertility were recorded for each case, including the age of the couple, the number of years of infertility, and the collection of information on the patient's infertility-related tests. Among them, the definition of infertility was based on the WHO (15)-recommended criteria. According to this definition, male infertility is a result of a couple who have lived together for more than 1 year without using any contraceptive measures and the female partner is infertile due to the male partner.

Case Grouping

Patients with obstructive azoospermia admitted from the period December 2018 to December 2020 with an age distribution of 20–36 years according to the inclusion criteria were divided into two groups according to the randomized control

principle. One group was set up as a PESA group to perform percutaneous epididymal puncture for sperm extraction, and the other group was set up as a TESA group to perform percutaneous testicular biopsy for sperm extraction. Patients who had unsuccessful PESA were continued with TESA, and if sperm was retrieved, they were classified as the TESA group. All enrolled cases were confirmed by temporary sperm retrieval at the time of ICSI on the day of egg retrieval by the female partner and one preoperative sperm retrieval. Finally, there were 26 patients in the PESA group and 31 patients in the TESA group.

Superovulation Protocol

Different protocols were used for superovulation according to the patients' own hormone levels and sinus follicles. Human chorionic gonadotropin (HCG) of 5,000–10,000 IU (Manufacturer: Ningbo Renjian Pharmaceutical Group Co., Ltd, Lot No.: 130117, Specification: 1,000 IU) was injected intramuscularly when ≥1 dominant follicle reached a size of 18 mm in diameter or ≥2 dominant follicles reached 16 mm in diameter. The eggs were retrieved by ultrasound-guided transvaginal posterior vault puncture after 34–36 h. After 2–4 h of incubation, the eggs were degranulated using hyaluronidase, and MII eggs were selected for ICSI.

Epididymal puncture for sperm retrieval: During the operation, the towel was routinely disinfected and the surgeon wore sterile gloves, 2% lidocaine was used for local infiltration anesthesia at the puncture site, and after satisfaction, a scalp needle was used to enter vertically from the puncture site. A 10- ml syringe was repeatedly aspirated until a pale yellow fluid was seen and sent to the laboratory, and a sufficient number of PR spermatozoa were visible on microscopic examination to signal the end of the operation.

Testicular Biopsy for Sperm Extraction

The routine operation and anesthesia were the same as before. The surgeon held the testis with the left hand, and the right hand held the vas separator forceps to enter the skin vertically from the puncture point. Slightly forcefully, the white membrane was punctured, until there was a sense of breakthrough, and the vas separator forceps was opened and the tissue clamped inside the testis, until the varicocele was pulled out and sent to the laboratory. The microscopic examination showed a sufficient number of NP spermatozoa to signal the end of the operation. The obtained sperm was inseminated by an embryologist with ICSI.

Fertilization, Cleavage, and Embryo Transfer

Three days after egg retrieval, fresh cleavage embryos were selected for transfer into the uterus or fresh blastocysts were transferred after blastocyst culture, depending on the actual situation of the partner. Frozen oocytes or blastocysts would be transferred as needed. Luteal support was routinely performed, and after 3 to 4 weeks, ultrasound was used to check for a successful pregnancy. The pregnancy outcome was then counted at follow-up.

OBSERVATION INDICES

Laboratory Indices

(i) Normal fertilization rate: The ratio of the number of 2PN oocytes cleaved in each group 72 h after insemination to the number of eggs to be inseminated by ICSI in this group. (ii) High-quality embryo rate: The ratio of embryos with 7–9 cells of grade II or higher to 2PN oocytes at 72 h of insemination. (iii) High-quality blastocyst rate: The ratio of blastocysts rated as 3BB or above to 2PN oocyte cleavage embryos source blastocysts.

Pregnancy Outcome

(i) Clinical pregnancy rate: the ratio of the number of successful pregnancies to the number of embryos transferred. A positive HCG was measured 14 days after transfer and was considered a biochemical pregnancy. A clinical pregnancy was defined as a gestational sac and fetal heartbeat on ultrasound monitoring 35 days after transfer, which included intrauterine and ectopic pregnancies 3–4 weeks after transfer. (ii) Spontaneous abortion rate: the ratio of the number of abortions to the number of pregnancies in each group, and pregnancy loss occurring within 28 weeks of gestation was considered as spontaneous abortion. (iii) Ectopic pregnancy rate: the ratio of ectopic pregnancies to the number of pregnancies in each group. Ectopic pregnancy was defined as an ectopic gestational sac and/or cardiac pulsation visible by ultrasound and confirmed by postoperative pathology.

STATISTICAL METHODS

SPSS 20.0 software was applied for statistical analysis, and continuous variables were tested by an independent sample *t*-test or nonparametric test according to their distribution. The rates were compared by using the χ^2 test, and $p < 0.05$ was considered statistically significant.

RESULTS

Comparison of the General Conditions of Male Patients in Two Different Sperm Source Groups

There was no significant difference ($p > 0.05$) in the comparison of the general conditions of male patients in the PESA and TESA groups in terms of age (A), years of infertility (B), testosterone level (C), FSH level (D), and testicular volume (E) between the two different sperm groups (**Figure 1**).

Comparison of General Conditions of Female Patients in Two Different Sperm Groups

There were no significant differences in the general conditions of female patients in the PESA and TESA groups between the two different sources of sperm groups in terms of age (A), number of eggs obtained (B), number of sinus follicles (C), basal FSH values (D), and basal E2 values (E) ($p > 0.05$) (**Figure 2**).

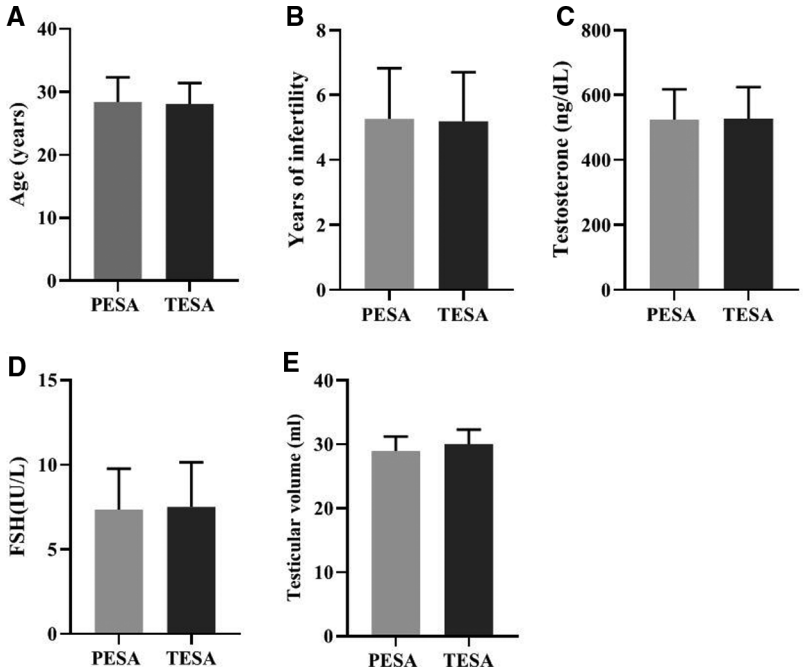

FIGURE 1 | Comparison of the general conditions of male patients in the two different sperm source groups [Mean, Standard deviation (Mean, SD)].

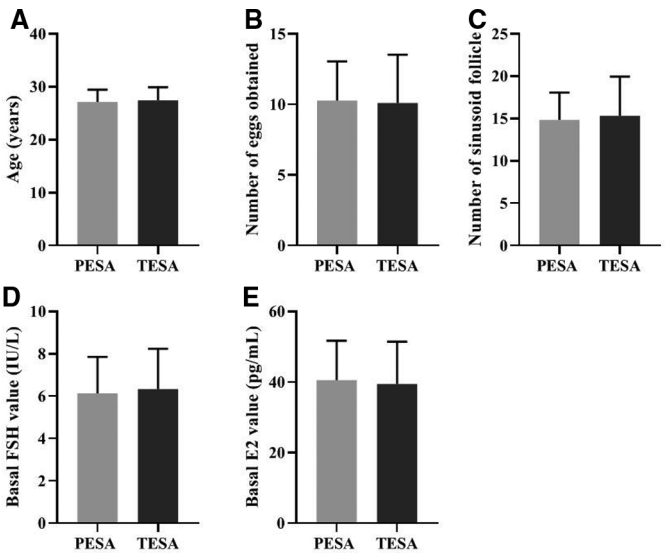

FIGURE 2 | Comparison of the general conditions of female patients in two different sperm groups (Mean, SD).

Comparison of Laboratory Parameters in Patients with Two Different Sources of Sperm Groups

Twenty-six patients underwent PESA and 31 patients underwent TESA, and the frozen embryos were transferred first to blastocysts and then to cleaved embryos. Results: A total of 293 eggs were inseminated by ICSI in the PESA group and 197 2PN fertilized eggs were formed, with a normal fertilization rate of 67.24%; 89 high-quality cleaved embryos, with a high-quality embryo rate of 45.18%; 79 high-quality blastocysts were formed out of 110 blastocysts of 2PN origin with a high-quality blastocyst rate of 71.82%. A total of 378 eggs were fertilized by ICSI in the TESA group, and 278 2PN fertilized eggs were formed, with a normal fertilization rate of

73.54%; 129 high-quality oocytes were formed, with a high-quality embryo rate of 46.40%; 142 high-quality blastocysts were formed among 172 blastocysts of 2PN origin, with a high-quality blastocyst rate of 82.56%. The analysis showed that the rate of high-quality blastocysts in the TESA group was significantly higher than that in the PESA group ($p < 0.05$); the differences in the rates of normal fertilization and high-quality embryos between the two groups were not statistically significant ($p > 0.05$) (**Table 1**).

Comparison of Pregnancy Outcomes in Patients with Two Different Sources of Sperm Groups

The PESA group had 18 transferred fresh cleaved embryos, 6 fresh blastocysts, 5 transferred frozen cleaved embryos, and 69 frozen blastocysts, for a total of 98 embryos, with 63 clinical pregnancies (64.29%), 11 spontaneous abortions (17.46%), and 2 ectopic pregnancies (3.17%). There were 14 fresh cleaved embryos and 13 fresh blastocysts, 4 frozen cleaved embryos, and 77 frozen blastocysts, totaling 108 embryos, 63 clinical pregnancies (58.33%), 9 miscarriages (14.29%), and 1 ectopic pregnancy (1.59%). The differences in the clinical pregnancy rate, spontaneous miscarriage rate, and ectopic pregnancy rate between the two groups were not statistically significant ($p > 0.05$) (**Table 2**).

Observation of Pathological Results

Patient Zheng, who underwent bilateral percutaneous testicular biopsy for sperm extraction in our hospital on 21 April 2019, had bilateral testicular tissue biopsies taken intraoperatively. The microscopic morphology was that spermatogonia at different stages of development were visible in the wall of the seminiferous tubules, and the ratio was basically normal, but the overall number was reduced and the seminiferous epithelium was thinned (**Figure 3**).

TABLE 1 | Comparison of the laboratory indices of patients in two different sources of sperm groups (*n*, %).

Information	PESA group	TESA group	χ^2 value	*p*-value
Normal fertilization rate	67.24% (197/293)	73.54% (278/378)	3.178	0.075
High-quality embryo rate	45.18% (89/197)	46.40% (129/278)	0.070	0.792
High-quality blastocyst rate	71.82% (79/110)	82.56% (142/172)	4.565	0.033

TABLE 2 | Comparison of pregnancy outcomes in patients from two different sperm source groups (*n*, %).

Information	PESA group	TESA group	χ^2 value	*p*-value
Clinical pregnancy rate	64.29% (63/98)	58.33% (63/108)	0.766	0.381
Spontaneous abortion rate	17.46% (11/63)	14.29% (9/63)	0.238	0.626
Ectopic pregnancy rate	3.17% (2/63)	1.59% (1/63)	0.342	0.559

DISCUSSION

In recent years, the incidence of male infertility has been increasing year after year due to many influences such as the natural and social environment and the general decline of male fertility. The conventional IVF-ET technique offers hope for infertility caused by female factors; however, it has no therapeutic effect on severe male factor and some unexplained infertility (16, 17). The ICSI technique is currently the most effective conception assistance method for the treatment of patients with severe male factor infertility due to its ability to inject a single sperm directly into the mature oocyte and to achieve fertilization, pregnancy, and ultimately their own genetic offspring with only a few sperm (18). Severe oligospermia and weak and malformed spermatozoa are the main indications for ICSI, and with the development of male surgical techniques, patients with obstructive or testicular failure non-obstructive azoospermia can also obtain their own offspring by obtaining sperm in the epididymis or testes for ICSI treatment through percutaneous epididymal sperm aspiration and testicular sperm aspiration (19, 20). The question whether different sperm sources affect the outcome of ICSI treatment has gradually attracted the attention of many scholars, but there is some variation in the findings reported by domestic and international scholars.

Some studies (21) reported no significant differences in the fertilization rate, oogenesis rate, and clinical pregnancy rate between the sperm of different PESA/TESA sources. Some studies (22) also concluded that there was no significant difference in the clinical pregnancy rate between PESA and TESA, while some studies showed that the fertilization rate of sperm from epididymal sources was significantly higher than that of TESA, and the difference in the abortion rate was not significant. The results of Dozortsev et al. (23) concluded that the fertilization rate of PESA from different sperm sources was significantly higher than that of TESA, but the clinical pregnancy rate was significantly lower and the miscarriage rate was higher than that of TESA. High-quality blastocysts are usually able to achieve higher pregnancy and implantation rates, which are important indicators of the developmental potential of transferred embryos *in vivo* (24). With regard to the effect of sperm from different surgical sources on pregnancy outcomes in assisted reproduction, some authors (25, 26) have concluded that there is no significant difference in the effect of testicular and epididymal sperm on clinical pregnancy rates and miscarriage rates. The results of this study showed that the rate of high-quality blastocysts in the TESA group was 82.56%, which was significantly higher than that in the PESA group (71.82%).The higher rate of high-quality blastocysts in the TESA group may be due to the fact that the sperm obtained by the TESA procedure were local fresh sperm from the testicular tissue, while the patients in the PESA group may have had a poor sperm storage microenvironment due to long vasal obstruction, resulting in

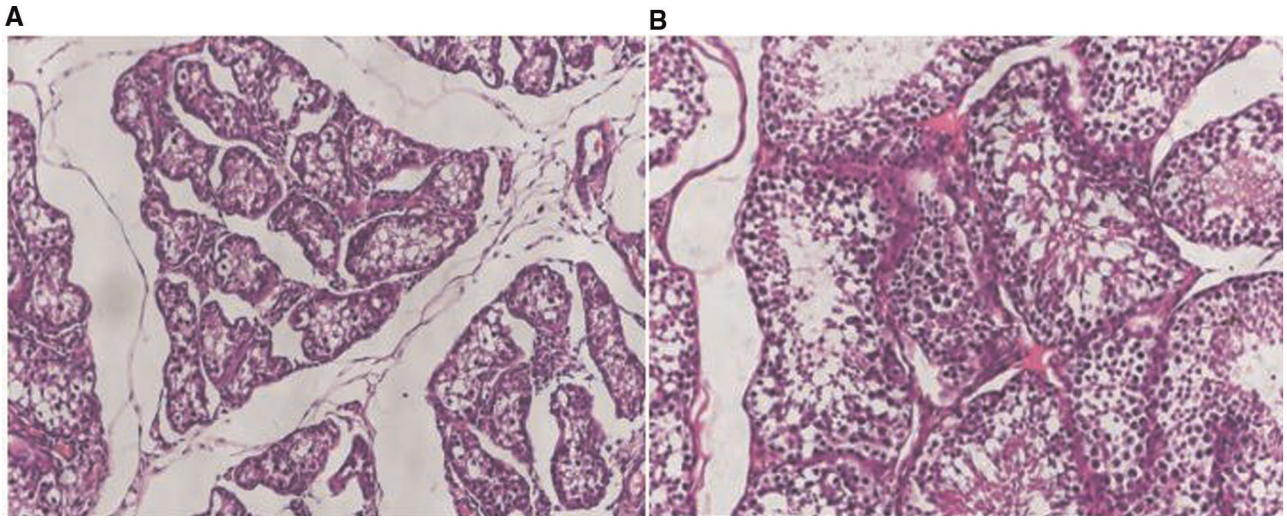

FIGURE 3 | Observation of pathological results. (**A**) HE staining of testicular tissue from a patient with obstructive azoospermia (×20); (**B**) HE staining of testicular tissue from a patient with obstructive azoospermia (×100).

more sperm DNA fragmentation, which may eventually cause the nucleus of fertilized eggs to develop asynchronously, manifesting as lower-quality blastocysts.

The results of most domestic and international studies (27, 28) showed no statistical difference in the fertilization rate, high-quality embryo rate, miscarriage rate, and ectopic pregnancy rate between TESA and PESA surgical sperm sources. The results of this study also showed no effect of TESA and PESA sperm on the fertilization rate, quality embryo rate, clinical pregnancy rate, early miscarriage rate, and ectopic pregnancy rate in ICSI outcomes. Although early blastocyst quality was slightly worse in the PESA group than in the TESA group, after *in vitro* culture and selection of the highest-quality embryos for transfer, there was no difference in the final pregnancy outcome, and neither epididymal nor testicular sperm had any effect on clinical pregnancy rates. The possible reasons are as follows: the sperm obtained by TESE for ICSI were all morphologically good and motile sperm after laboratory culture treatment, the infertility in both groups was due to purely male factors, both patients had normal fertility and their endometrium had the normal ability to allow embryo implantation, and the quality of oocytes and endocrine conditions were better in the patients' spouses, who were both under 38 years of age. This shows that there is no significant effect on ICSI pregnancy outcome as long as a certain number of good-quality transferable embryos can be obtained, regardless of whether the patient obtained the sperm from epididymal or testicular puncture (29, 30).

In conclusion, patients with pure male factor infertility can achieve satisfactory clinical pregnancy outcomes either with sperm obtained by the PESA procedure or by applying ICSI with TESA surgical approach sperm. Current studies are mostly limited to the effects of different sperm sources on early embryo quality and pregnancy outcomes after ICSI, and there is a lack of studies on the long-term prognosis of their offspring, still necessitating comprehensive and large samples for long-term follow-up.

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

Informed consent was obtained from the patient or the patient's family for this trial. This trial was approved by our medical ethics committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LL was mainly responsible for writing the article; the research was completed by HL and JX; the data analysis of the article was done by ML. LL was responsible for guiding the entire research. The corresponding author is LW, and he was responsible for ensuring that the descriptions in the article were accurate and agreed upon by all authors. All authors contributed to the article and approved the submitted version.

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Correlation of Blood Lipid and Serum Inflammatory Factor Levels With Hypertensive Disorder Complicating Pregnancy

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Purpose: To explore the changes of blood lipid and serum inflammatory factors in pregnant women with hypertensive disorder complicating pregnancy (HDP) and the relationship with disease development.

Methods: 107 pregnant women with HDP who had regular prenatal examination in our hospital from July 2018 to July 2021 were selected as the research objects. According to the severity of the disease, they were divided into gestational hypertension group, mild preeclampsia group and severe preeclampsia group. 30 healthy pregnant women who underwent prenatal examination in the same period were selected as the healthy group. Serum total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), lipoprotein-associated phospholipaseA2 (Lp-PLA2), C- reactive protein (CRP), interleukin -6 (IL-6), tumor necrosis factor-α (TNF-α) were measured. Receiver operating characteristic curve (ROC) was used to analyze the predictive value of blood lipid and serum inflammatory factors in pregnant women with HDP.

Results: The levels of serum TC, TG and LDL-C increased with the progression of HDP, the level of serum HDL-C decreased with the progression of HDP ($P < 0.05$). The levels of serum Lp-PLA2, CRP, IL-6 and TNF-α increased with the progression of HDP ($P < 0.05$). The AUC of serum TC, TG, HDL-C and LDL-C levels for predicting HDP were 0.759, 0.854, 0.770 and 0.785, respectively. The AUC of serum Lp-PLA2, CRP, IL-6 and TNF-α levels for predicting HDP were 0.873, 0.991, 0.966 and 0.999, respectively.

Conclusion: The levels of blood lipid and serum inflammatory factor are closely related to HDP, which has certain value in predicting the occurrence and development of HDP.

Keywords: hypertensive disorder complicating pregnancy, blood lipid, inflammatory factors, preeclampsia, predictive value

INTRODUCTION

Hypertensive disorder complicating pregnancy (HDP) is the main cause of adverse maternal and infant outcomes, with an incidence of 5%–12%, and usually occurring after the 20th week of pregnancy (1). The main typical manifestations of HDP are hypertension, edema and proteinuria, but most pregnant women with mild HDP lack obvious clinical manifestations. Severe HDP can cause coma, convulsion, organ failure and other symptoms, and even lead to complications such as placental abruption, intrauterine fetal death and cerebrovascular events (2, 3). The pathogenesis and etiology of HDP have not been completely clear, and it is generally believed to be related to maternal, placental, fetal and other pathogenic factors (4). According to the severity of the disease, HDP can be divided into gestational hypertension, preeclampsia, eclampsia, pregnancy complicated with chronic hypertension and chronic hypertension complicated with preeclampsia. In HDP, gestational hypertension and preeclampsia are more likely to occur, which may induce maternal and infant death. Therefore, finding effective indicators for early prediction of the occurrence and development of HDP has attracted more and more attention. Studies have shown that the levels of blood lipids and serum inflammatory factors in pregnant women with HDP are often abnormally expressed (5). The purpose of this study is to observe the expression of blood lipid and serum inflammatory factors in pregnant women with HDP with different conditions, in order to carry out early intervention for pregnant women with HDP.

MATERIALS AND METHODS

Research Object

107 pregnant women with HDP who had regular prenatal examination in our hospital from July 2018 to July 2021 were selected as the research objects. According to the severity of the disease (6), they were divided into gestational hypertension group (42 cases: There was no history of hypertension, and blood pressure began to rise to systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation), mild preeclampsia group (36 cases: The systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, and the 24 h proteinuria ≥0.3 g were measured more than twice) and severe preeclampsia group (29 cases: The systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥110 mmHg, and 24 h proteinuria ≥2.0 g or serum creatinine ≥1.2 mg/dL). 30 healthy pregnant women who underwent prenatal examination in the same period were selected as the healthy group. Inclusion criteria: Age ≥20 years old; Gestational week ≥20 weeks; Natural conception; Clear consciousness. Exclusion criteria: With essential hypertension; Multiple pregnancy; Non-assisted reproductive technology conception; The patients have taken drugs that affect lipid metabolism and inflammatory response; Combined diabetes; Complicated with heart disease; There is a history of alcoholism (Drinking more than 14 units of alcohol per week on average, 1 unit = 360 mL beer) and smoking (Smoking more than 1 cigarette per day).

Research Methods

All pregnant women were taken 5 mL of venous blood in the morning fasting state. After anticoagulation and centrifugation, the serum was separated and stored at −70°C for testing. Researchers should do a good job in quality control, require the samples to be tested under the same conditions, and avoid the influence of interference factors on the test results. ① Blood lipid: Serum total cholesterol (TC) and triglyceride (TG) were measured by phosphoglycerol oxidase method, and high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were measured by direct method. ② Serum inflammatory factors: Serum lipoprotein-associated phospholipaseA2 (Lp-PLA2) was measured by enzymatic kinetic method, serum C-reactive protein (CRP) was measured by latex enhanced transmission turbidimetry, and serum interleukin -6(IL-6) and tumor necrosis factor-α (TNF-α) were measured by enzyme-linked immunosorbent assay.

Statistical Methods

SPSS 22.0 was used to analyze the data. Counting data was expressed by ratio, compared by χ^2 test. Measurement data was expressed by mean ± standard deviation, compared by variance analysis. The predicted value was expressed by the ROC area under curve (AUC). The evaluation range of AUC: 0.5–0.7 indicates low predictive value, 0.7–0.9 indicates medium predictive value, ≥0.9 indicates high predictive value. $P < 0.05$ was statistically significant.

RESULTS

Comparison of General Data in Each Group

There was no significant difference in age, gestational week, pregnancy times, pre-pregnancy body mass index and parity among the groups ($P > 0.05$) (**Table 1**).

Comparison of Blood Lipid Levels in Each Group

Compared with healthy group, the levels of serum TC, TG, LDL-C in gestational hypertension group, mild preeclampsia group and severe preeclampsia group all increased, while the level of serum HDL-C decreased. The levels of serum TC, TG and LDL-C increased with the progression of HDP, the level of serum HDL-C decreased with the progression of HDP ($P < 0.05$) (**Figure 1**).

Comparison of Serum Inflammatory Factors in Each Group

Compared with healthy group, the levels of serum Lp-PLA2, CRP, IL-6 and TNF-α in gestational hypertension group, mild preeclampsia group and severe preeclampsia group all

TABLE 1 | Comparison of general data in each group (n, %, $\bar{x} \pm s$).

Group	Number of cases	Age (years)	Gestational week (week)	Pregnancy times (times)	Pre-pregnancy body mass index (kg/m^2)	Parity	
						Primipara	Multipara
Healthy group	30	28.48 ± 2.17	24.85 ± 1.24	2.83 ± 0.54	25.26 ± 2.71	21(70.00%)	9(30.00%)
Gestational hypertension group	42	28.29 ± 2.25	25.21 ± 1.06	2.79 ± 0.61	24.98 ± 2.63	29(69.05%)	13(30.95%)
Mild preeclampsia group	36	29.06 ± 2.13	24.92 ± 1.35	2.65 ± 0.60	25.18 ± 2.59	26(72.22%)	10(27.78%)
Severe preeclampsia group	29	28.43 ± 2.24	25.27 ± 1.13	2.72 ± 0.58	24.87 ± 2.61	17(58.62%)	12(41.38%)
F/χ^2 value		0.877	0.989	0.624	0.145	1.540	
P-value		0.454	0.400	0.600	0.932	0.673	

increased. The levels of serum Lp-PLA2, CRP, IL-6 and TNF-α increased with the progression of HDP ($P < 0.05$) (**Figure 2**).

Predictive Value of Blood Lipid Level in Pregnant Women With HDP

The AUC of serum TC, TG, HDL-C and LDL-C levels for predicting HDP were 0.759, 0.854, 0.770 and 0.785, respectively (**Table 2** and **Figure 3**).

Predictive Value of Serum Inflammatory Factors in Pregnant Women With HDP

The AUC of serum Lp-PLA2, CRP, IL-6 and TNF-α levels for predicting HDP were 0.873, 0.991, 0.966 and 0.999, respectively ($P < 0.05$) (**Table 3** and **Figure 4**).

DISCUSSION

At present, clinically, it is generally believed that the occurrence of HDP is related to heredity, immunity, nutritional deficiency, inflammatory reaction, vascular endothelial damage and other factors, and its occurrence and development are affected by environmental and psychological factors (7). The progress of HDP is closely related to the life and health of mother and infant, and the disease has gradually received attention in the field of pregnancy complications. Therefore, it is clinically necessary to judge the severity of HDP by monitoring serum indicators, and then improve the maternal and infant outcomes.

In this study, the levels of serum TC, TG and LDL-C increased with the progression of HDP, while the level of serum HDL-C decreased with the progression of HDP. This indicated that dyslipidemia may increase the risk of HDP, and it is closely related to the development of HDP. TC is the precursor of bile acids, steroid hormones and other substances, which is closely related to atherosclerosis and cardiovascular diseases. The main function of TG is to supply and store energy, and it can also fix and protect internal organs. LDL-C is a risk factor for vascular endothelial injury, and it can cause atherosclerosis. HDL-C is a vascular protective factor, which can remove lipids from blood vessels. In pregnant women with HDP, with the aggravation of the disease, the levels of TC, TG, LDL-C with vascular destruction increased, while the level of HDL-C with vascular protection decreased (8). High levels of TC and TG will lead to the decrease of prostacyclin synthesis in endothelial cells, resulting in imbalance between thromboxane A2 and prostacyclin, and the spasm of blood vessels, which will lead to the occurrence of preeclampsia (9). LDL-C is easily oxidized, and participates in the formation of atherosclerotic plaque, damages smooth muscle cells and endothelial cells, increases the permeability of vascular endothelial cells, reduces arterial lumen and increases peripheral resistance, which leads to the increase of blood pressure (10). The decrease of HDL-C may weaken the protective mechanism against atherosclerosis, inhibit the anti-lipid accumulation, leading to an increase in blood lipid peroxide, which directly damages the vascular endothelial cells, which will aggravate the severity of preeclampsia (11). In addition, estrogen, as a substance that reduces the lipase activity of liver endothelial cells, plays an inhibitory role in the absorption of HDL-C by the liver. Compared with normal pregnant women, pregnant women with HDP have less estrogen secretion and lower HDL-C release, which leads to compensatory responses and increases in serum TC, TG and LDL-C levels, further affects vascular endothelial cell functions and aggravates atherosclerosis (12). Elevated blood pressure can promote the formation of acute atherosclerosis, which in turn can promote the contraction of blood vessels, resulting in thickening and hardening of blood vessel walls, slow blood flow, obstruction of blood supply and oxygen supply to placenta, resulting in further increase of blood pressure, forming a vicious circle (13). The disorder of lipid metabolism in pregnant women with HDP can aggravate atherosclerosis, enhance oxidative stress, increase the production of peroxide products and toxic substances, and then damage vascular endothelial cells (14). At the same time, abnormal blood lipid levels can reduce the synthesis of nitric oxide, resulting in vasoconstriction and relaxation disorders, showing systemic arteriolar spasm and abnormally high blood pressure, which provides conditions for the disease progression of HDP (15).

We also found that the levels of serum Lp-PLA2, CRP, IL-6 and TNF-α were positively correlated with the severity of HDP. Lp-PLA2 can promote the release of inflammatory mediators,

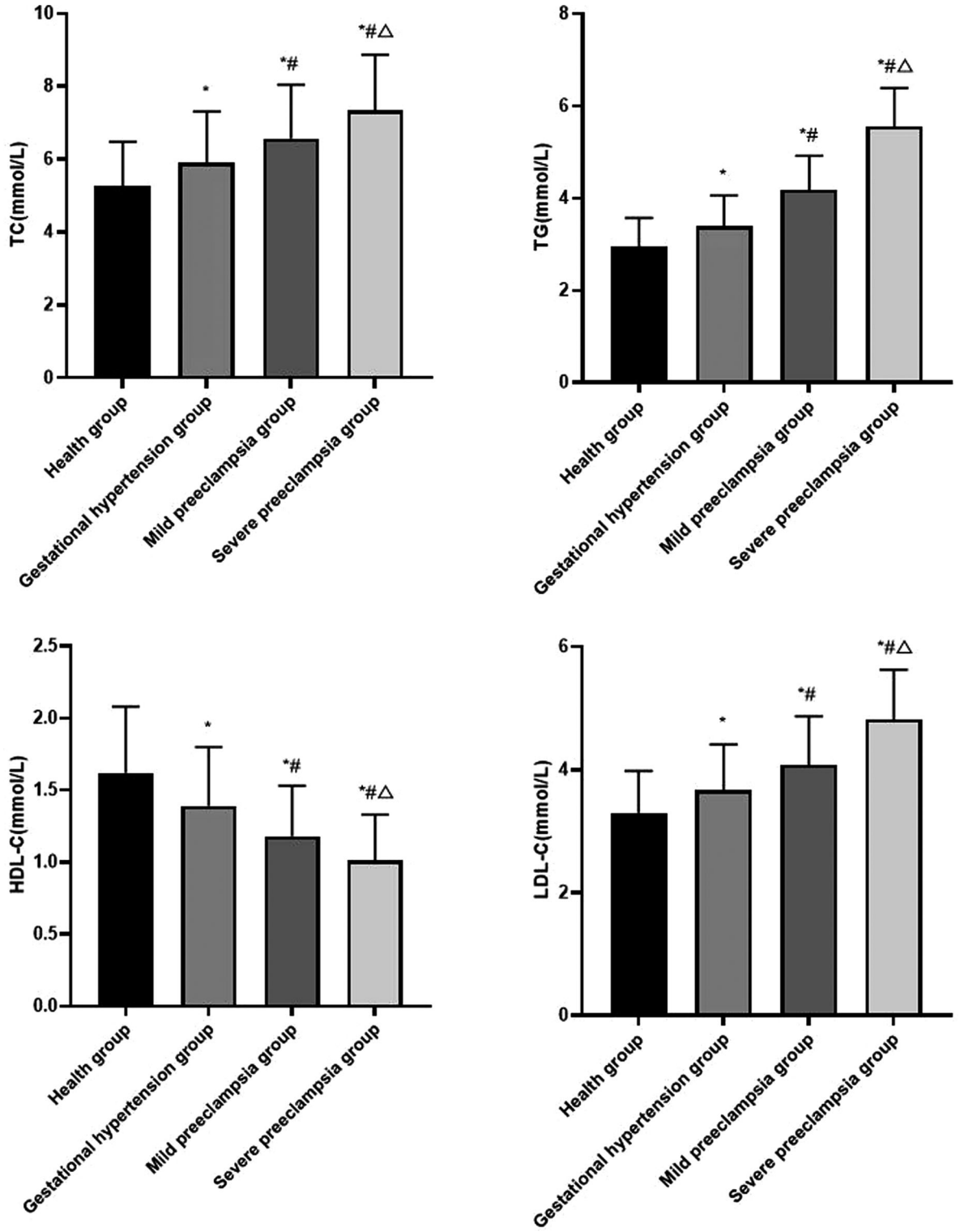

FIGURE 1 | Comparison of blood lipid levels in each group Compared with healthy group, $^{*}P < 0.05$; Compared with gestational hypertension group, $\#P < 0.05$; Compared with mild preeclampsia group, $\triangle P < 0.05$.

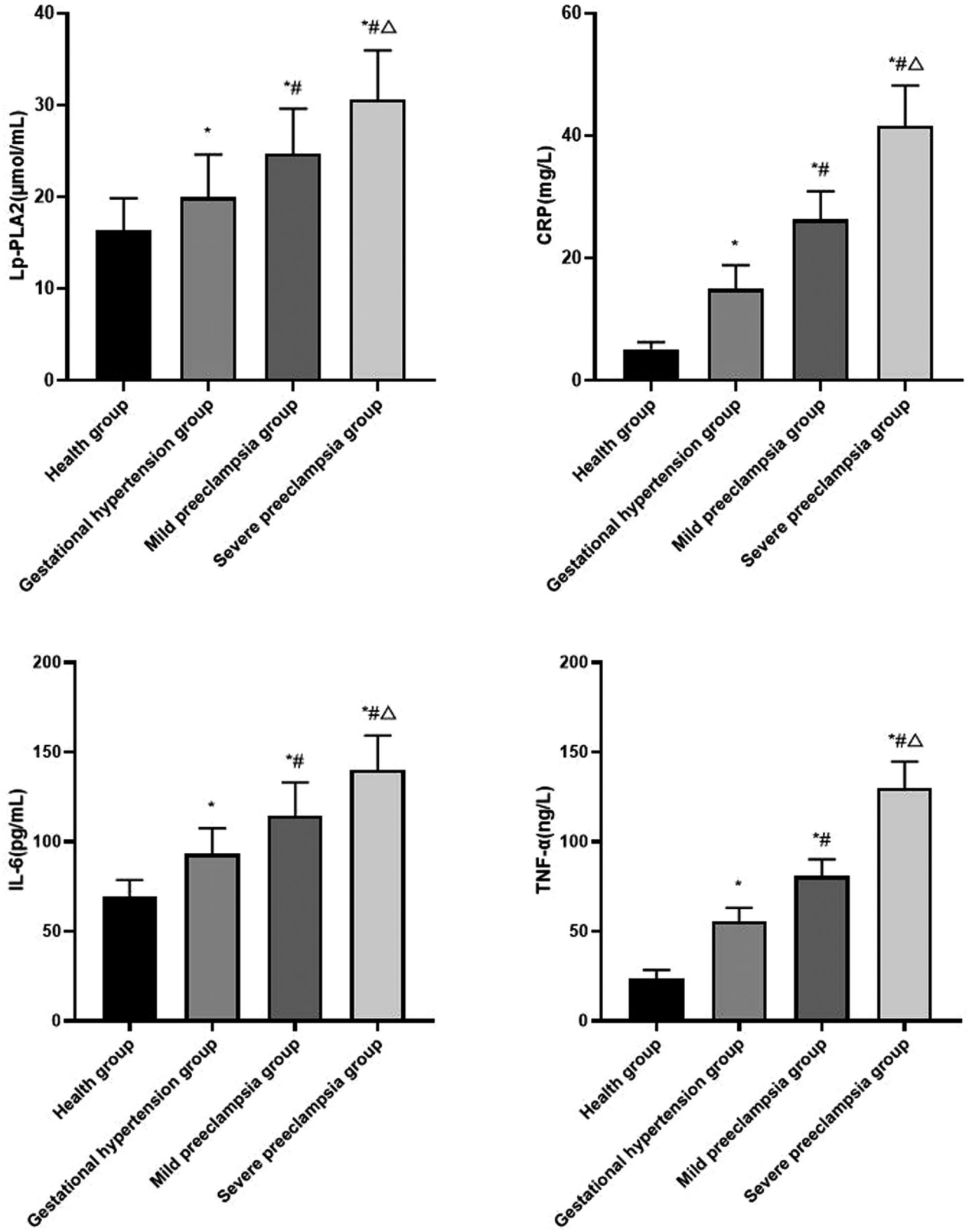

FIGURE 2 | Comparison of serum inflammatory factors in each group Compared with healthy group, $^{*}P < 0.05$; Compared with gestational hypertension group, $^{\#}P < 0.05$; Compared with mild preeclampsia group, $\triangle P < 0.05$.

TABLE 2 | Predictive value of blood lipid level in pregnant women with HDP.

Index	AUC	95% CI		Std. Error	*P*-value	Youden index
		Lower limit	Upper limit			
TC	0.759	0.666	0.853	0.047	<0.0001	0.507
TG	0.854	0.786	0.923	0.035	<0.0001	0.648
HDL-C	0.770	0.675	0.864	0.048	<0.0001	0.410
LDL-C	0.785	0.698	0.872	0.044	<0.0001	0.563

TABLE 3 | Predictive value of serum inflammatory factors in pregnant women with HDP.

Index	AUC	95% CI		Std. Error	*P*-value	Youden index
		Lower limit	Upper limit			
Lp-PLA2	0.873	0.811	0.935	0.031	<0.0001	0.713
CRP	0.991	0.973	1.000	0.009	<0.0001	0.990
IL-6	0.966	0.937	0.996	0.014	<0.0001	0.862
TNF-α	0.999	0.998	1.000	0.001	<0.0001	0.991

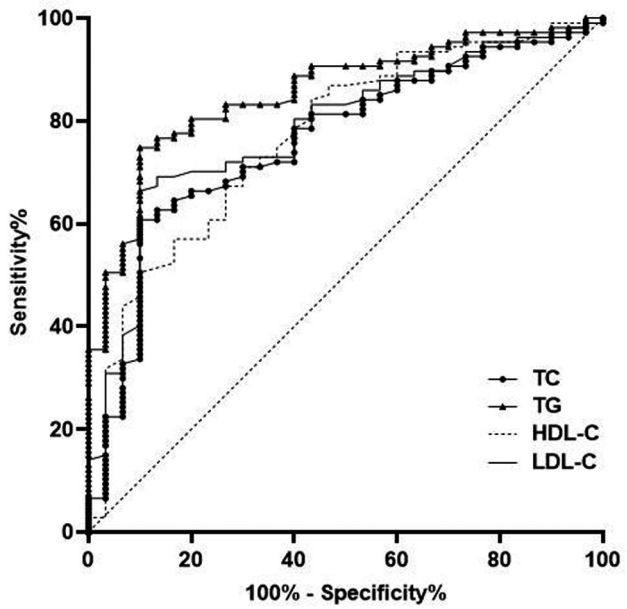

FIGURE 3 | Predictive value of blood lipid level in pregnant women with HDP.

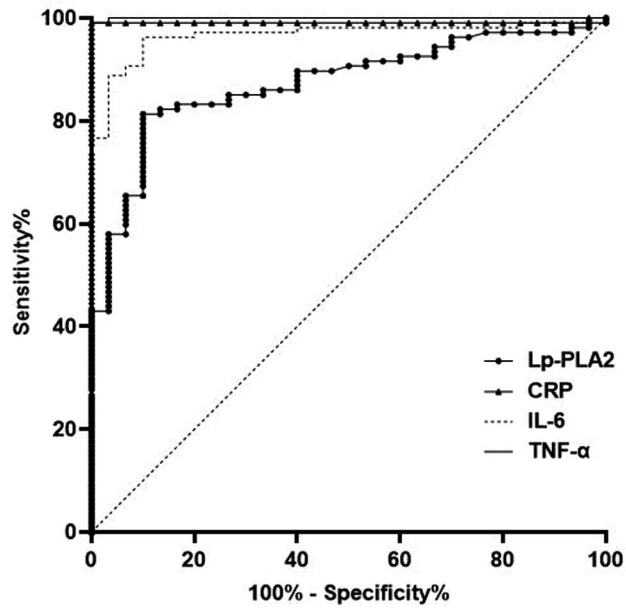

FIGURE 4 | Predictive value of serum inflammatory factors in pregnant women with HDP.

activate inflammatory response and damage vascular endothelial cells, which is an independent risk factor for preeclampsia. The possible mechanisms of Lp-PLA2 inducing HDP are as follows: ① Lp-PLA2 can combine apolipoprotein B with low density lipoprotein, causing lipid metabolism disorder, and then leading to atherosclerosis of uterine and placental arteries, resulting in decreased placental function, leading to the occurrence of HDP. ② Lp-PLA2 can hydrolysis and oxidation of lecithin, and produce strong pro-inflammatory mediators such as free fatty acids and lysolecithin. By activating cytokines and adhesion factors, vascular endothelial cells become dysfunctional, thereby increasing blood pressure. ③ Lp-PLA2 promotes the release of inflammatory mediators, collagen deposition and fibroblast proliferation in inflammatory reaction sites, and platelet aggregation, which plays an anti-inflammatory and anti-atherosclerosis role and promotes the progress of HDP (16–18). As a marker of inflammatory reaction in the body, CRP can activate platelet activity, inhibit platelet activating factor, promote platelet release of arachidonic acid and platelet aggregation, and inhibit the binding of platelet activating factor and neutrophils, which plays a role in regulating inflammatory reaction (19). CRP can not only aggravates the inflammatory reaction, but also reduces the sensitivity of tissue cells to insulin, and play a certain role in lipid metabolism disorder (20). There is inflammation in artery wall of pregnant women with HDP, and there are many trophoblast cells in blood from placenta, which can combine with antibodies in maternal blood to form immune complexes. CRP can combine with immune complex, activate the complement system of the body, produce a large amount of terminal reaction protein deposition, resulting in vascular endothelial cell damage, increase the production of vasoconstrictor substances, and then cause contraction and spasm of small blood vessels in the whole body, and increase blood pressure (21). The body of pregnant women with HDP is in a state of oxidative stress,

which can promote neutrophil infiltration, release of a variety of proteases, inhibit vascular endothelial function, and lead to the increase of IL-6 and TNF-α levels (22). IL-6 can maintain chronic inflammation and promote the cascade amplification of inflammation. At the same time, IL-6 can interact with a variety of cytokines and induce with TNF-α, IL-1 and other inflammatory factors in the body (23). High levels of IL-6 can damage vascular endothelial cells, increase vascular permeability, interfere with vasoconstriction and relaxation, and lead to an increase in blood pressure, eventually leads to a series of clinical manifestations of preeclampsia (24). The increase of TNF-α can directly damage the vascular endothelium by releasing oxygen free radicals, causing systemic arteriole spasm, resulting in lumen stenosis and increased peripheral resistance, thereby exacerbating the progression of HDP (25). In pregnant women with HDP, TNF-α can promote the formation of neovascularization and thrombosis, inhibit the activities of lipolytic acid and lipoprotein lipic acids, which makes it difficult for lipids to dissolve, and then deposits on the wall of blood vessels, resulting in an increase in blood pressure (26).

In addition, ROC was used for further analysis in this study. The results showed that the AUC of serum TC, TG, HDL-C and LDL-C levels for predicting HDP were 0.759, 0.854, 0.770 and 0.785, respectively. The AUC of serum Lp-PLA2, CRP, IL-6 and TNF-α levels for predicting HDP were 0.873, 0.991, 0.966 and 0.999, respectively. This results further confirmed that the levels of blood lipid and serum inflammatory factor are closely related to HDP, which has certain value in predicting the occurrence and development of HDP. This is helpful to judge the occurrence of HDP and evaluate the status of HDP.

CONCLUSION

To sum up, the levels of blood lipid and serum inflammatory factor are closely related to HDP, which has certain value in predicting the occurrence and development of HDP. We believe that dietary control and lifestyle changes can control blood lipids and reduce inflammation, and drug treatment can be used when necessary, which is conducive to improving the pathological changes of HDP. The sample size of this study is small, and a large number of clinical samples are still needed to provide further theoretical basis in the future, and it is also necessary to further explore the specific pathogenesis of HDP.

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 This study was approved by the ethics committee of our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WC is the mainly responsible for the writing of the article. YG is mainly responsible for research design. XY is mainly responsible for data analysis. DZ is responsible for the guidance of the entire research. The corresponding author is WC and she is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Obstetric Risk Factors and Serological Characteristics of Early-Onset Neonates Bacterial Infections

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Purpose: To analyze the obstetric high-risk factors and serological characteristics of early-onset neonatal bacterial infections (EONBI).

Methods: 119 neonates with early-onset bacterial infection who were admitted to the neonatal ward of our hospital from October 2020 to December 2021 were recorded as the study group, and 100 neonates without bacterial infection who were admitted during the same period were used as the reference group. Comparative analysis of obstetric high-risk factors and serological characteristics of EONBI.

Results: There was no statistical difference between the two groups in terms of gender and age at admission ($P > 0.05$). The gestational age and birth weight of newborns in the study group were lower than those in the reference group ($P < 0.001$). Comparing the maternal factors of EONBI between the two groups, there was no statistical difference in age, number of obstetric inspections, whether to use antibiotics, and mode of delivery ($P > 0.05$). Univariate analysis showed that preterm birth, unexplained asphyxia, fecal contamination of amniotic fluid, maternal infection during pregnancy, and premature rupture of membranes ≥18 h were significantly associated with EONBI ($P < 0.05$); while there was no significant difference between the two groups in the comparison between diabetic mother and child and maternal fever at delivery ($P > 0.05$). Multifactorial analysis showed that preterm birth, fecal contamination of amniotic fluid, maternal infection during pregnancy, and premature rupture of membranes ≥18 h had a good multivariate dependence on EONBI ($P < 0.05$), while there was no significant association with unexplained asphyxia, diabetic mother and child, and maternal fever at delivery ($P > 0.05$). The incidence of neonatal temperature >37.9°C was higher in the study group than in the reference group ($P < 0.05$), and there were no statistical differences in the comparison of other clinical manifestations ($P > 0.05$). The CRP level of neonates in the study group (47.33 ± 4.14) mg/L was higher than that of the reference group (4.84 ± 1.03) mg/L ($P < 0.001$). The WBC level of neonates in the study group (5.64 ± 1.18) 10^9/L was higher than that of the reference group (0.28 ± 0.04) 10^9/L ($P < 0.001$). The PCT level of neonates in the study group (5.41 ± 0.85) μg/L was higher than that of the reference group (0.24 ± 0.07) μg/L ($P < 0.001$).

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Conclusion: EONBI is closely associated with several obstetric high-risk factors, including preterm birth, fecal contamination of amniotic fluid, maternal infection during pregnancy, and premature rupture of membranes ≥18 h; EONBI has no specific symptoms and signs, but serum CRP, WBC, and PCT levels are significantly higher than those of newborns without co-infection with bacteria.

Keywords: neonatal, early-onset bacterial infections, obstetrics, high-risk factors, serological features

INTRODUCTION

Newborn infants are immunocompromised and have low resistance, so bacteria can easily invade the body from the skin mucosa, umbilical cord stump, respiratory and digestive tracts causing bacterial infections in newborns, which are common types of inflammatory infections in the first 72 h of life (1, 2). Generally, the first symptom of bacterial infection in newborns is fever (3). Coughing and coughing up sputum may occur in the case of respiratory tract infections caused by bacterial infections (4). In case of bacterial infection of the intestinal tract, abdominal pain and diarrhea may be present (5). If bacterial infection such as bacteremia and sepsis occurs, it is a more serious situation, and effective antibiotic treatment is required in time.

Currently, no global assessment data on the incidence of bacterial infections in newborns are available for each country. According to incomplete statistics at home and abroad, the incidence of early-onset neonatal bacterial infections (EONBI) can range from 1% to 10% throughout live births, and once a neonate develops a systemic infection, the chance of causing its death can be 20% to 40%, and even if the child survives, 10% to 30% of the children can still be left with varying degrees of sequelae later in life (6, 7). Alerting newborns to danger signs and early identification of bacterial infections from other pathogens in a simple bedside laboratory test is of great importance to control the severity of bacterial infections in newborns and reduce neonatal mortality.

According to previous reports, in the early stages of bacterial infection, children often present with some signs, symptoms or changes in laboratory tests of inflammatory response, and these children are often accompanied by the presence of high-risk factors predisposing the newborn to bacterial infection (8). However, the clinical manifestations after infection in children are mostly not obvious, and laboratory findings are often not specific, making early diagnosis of early-onset bacterial infections in neonates relatively difficult (9). Based on the above, it is necessary to properly assess whether bacterial infections occur in the early neonatal period and to study the relationship between the occurrence of early infections and obstetric high-risk factors. This study analyzes the obstetric high-risk factors and serological characteristics of EONBI, with a view to and provides a favorable reference for its early diagnosis and timely and effective control treatment. The details are as follows.

MATERIALS AND METHODS

Research Object

The subjects of this experiment were neonates with ≥1 of the following obstetric high-risk factors who were admitted to the neonatal ward of our hospital from October 2020 to December 2021: preterm birth, unexplained asphyxia, diabetic mother and child, fecal contamination of amniotic fluid, maternal fever at delivery (≥38°C), maternal infection during pregnancy (including third trimester vaginitis, chorioamnionitis), premature rupture of membranes ≥18 h. All children were admitted to the hospital at an age of ≤3 days and had no other obstetric high-risk factors or complications outside the scope of the above study, and no congenital anomalies.

Grouping and Inclusion/Exclusion Criteria

The children were divided into the study group ($n = 119$) with co-infection and the reference group ($n = 100$) without co-infection according to whether they were co-infected with bacteria or not. Inclusion criteria for the study group: ① With ≥1 obstetric high-risk factor; ② At least one of the following main conditions was met: blood culture or sputum culture or peripheral secretion culture (+); one or more clinical signs of infection (e.g., the child showed signs of systemic bacterial infection such as fever, low response, reduced milk intake); ③ If the above primary condition was (−), then at least one of the following secondary conditions was satisfied: elevated C-reactive protein (CRP) >8 mg/L; increased white blood cell (WBC) $>25 \times 10^9$/L or decreased $<5 \times 10^9$/L; decreased platelets $<100 \times 10^9$/L. Exclusion criteria for the study group: Excluding sepsis, pneumonia, necrotizing small bowel colitis, urinary tract infection, meningitis, enteritis and impetigo and other diseases with clear etiology and site of infection, excluding infection by other pathogenic microorganisms such as viruses, mycobacteria and protozoa. Inclusion criteria for the reference group: children with obstetric high-risk factors but no clinical manifestations of infection, negative laboratory indicators, and clinical exclusion of infection.

Observation Items

Baseline information was collected upon admission of the child, including gender, age at admission, gestational age, and birth weight. Maternal factors that might be present in EONBI were collected, including age, number of obstetric inspections, whether to use antibiotics, and mode of delivery, etc. The

obstetric high-risk factors present in the two groups of newborns were counted, and the relationship between EONBI and obstetric high-risk factors was analyzed by univariate and multiple logistic regression. Both groups of neonates were observed for clinical manifestations and examined for CRP, blood routine and blood culture before the administration of antibiotics. If there were clinical manifestations, sputum culture, umbilical or ocular secretion culture or chest X-ray were added according to the condition of the child. Comparison of CRP, WBC, and calcitoninogen (PCT) levels prior to antibiotic administration in both groups to assess their serological characteristics. The assay was performed by collecting 5 mL of fasting elbow vein blood, centrifuging it at 2,000 r/min for 10 min, and finally storing the separated plasma in a refrigerator at −20°C. 7,600 Hitachi automatic biochemical analyzer (Beijing Tailin Oriental Trading Co., Ltd.) and immunoturbidimetry were used to detect CRP and PCT levels, AU5800 automatic blood analyzer [Beckman Coulter Trading (China) Co., Ltd.] and supporting reagents were used to detect WBC levels.

Treatment Methods

The neonates in both groups were monitored continuously for 72 h, and they were given antibiotics of the third generation or more of cephalosporin immediately after infection for 1–3 weeks. Those who ruled out infection were given lower antibiotics or no antibiotics, paying attention to intensive care of local infection.

Statistical Methods

SPSS 22.0 software was applied for statistical analysis, and the measurement data were expressed as mean ± standard deviation, and paired t-test and ANOVA were performed. The statistical data were expressed as ratios, and the χ^2 test was performed. In order to exclude the influence of confounding factors on the results of the study, with EONBI as the dependent variable, the relationship between EONBI and 7 obstetric high-risk factors was analyzed by multivariate Logistic regression. $P < 0.05$ was considered statistically significant.

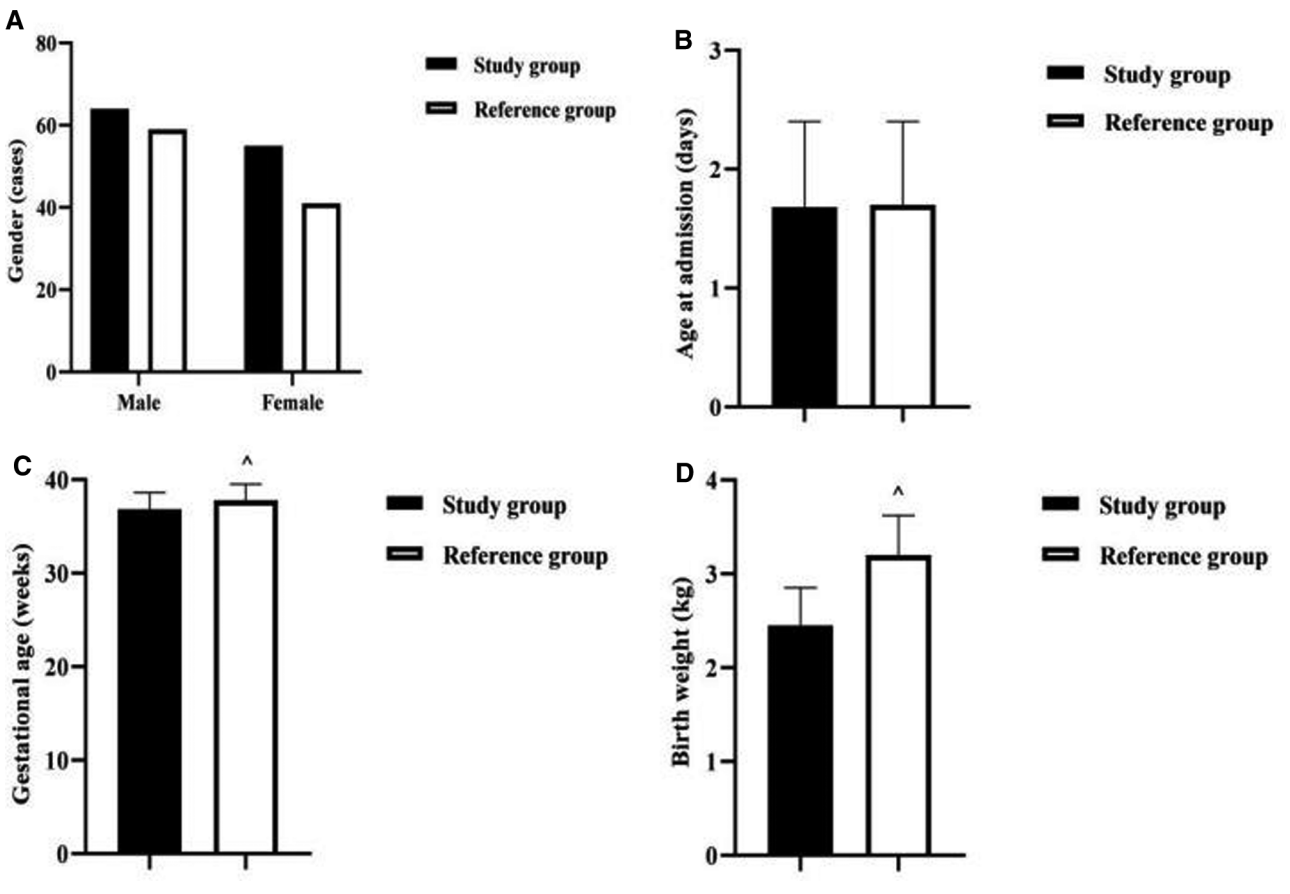

FIGURE 1 | Comparison of baseline information between the two groups of newborns. Note: (**A**) Comparison of neonatal gender between the two groups. (**B**) Comparison of neonatal age at admission between the two groups. (**C**) Comparison of neonatal gestational age between the two groups. (**D**) Comparison of neonatal birth weight between the two groups. Comparison with the study group $^{\wedge}P < 0.001$.

RESULTS

Comparison of Baseline Information Between the Two Groups of Newborns

There was no statistical difference between the two groups in terms of gender and age at admission ($P > 0.05$). The gestational age and birth weight of newborns in the study group were lower than those in the reference group ($P < 0.001$) (**Figure 1**).

Analysis of the Maternal Factors of EONBI

Comparing the maternal factors of EONBI between the two groups, there was no statistical difference in age, number of obstetric inspections, whether to use antibiotics, and mode of delivery ($P > 0.05$) (**Figure 2**).

Univariate Analysis of EONBI and Obstetric High-Risk Factors

Univariate analysis showed that preterm birth, unexplained asphyxia, fecal contamination of amniotic fluid, maternal infection during pregnancy, and premature rupture of membranes ≥18 h were significantly associated with EONBI ($P < 0.05$); while there was no significant difference between the two groups in the comparison between diabetic mother and child and maternal fever at delivery ($P > 0.05$) (**Table 1**).

TABLE 1 | Univariate analysis of EONBI and obstetric high-risk factors.

High-risk factors	Study group (*n* = 119)		Reference group (*n* = 100)		χ^2	*P*
	n	%	*n*	%		
Preterm birth	85	71.43	31	31.00	35.651	<0.001
Unexplained asphyxia	71	59.66	15	15.00	45.452	<0.001
Diabetic mother and child	19	15.97	11	11.00	1.134	0.287
Fecal contamination of amniotic fluid	86	72.27	35	35.00	30.526	<0.001
Maternal fever at delivery	33	27.73	35	35.00	1.341	0.247
Maternal infection during pregnancy	42	35.29	11	11.00	17.483	<0.001
Premature rupture of membranes r18 h	104	87.39	43	43.00	48.530	<0.001

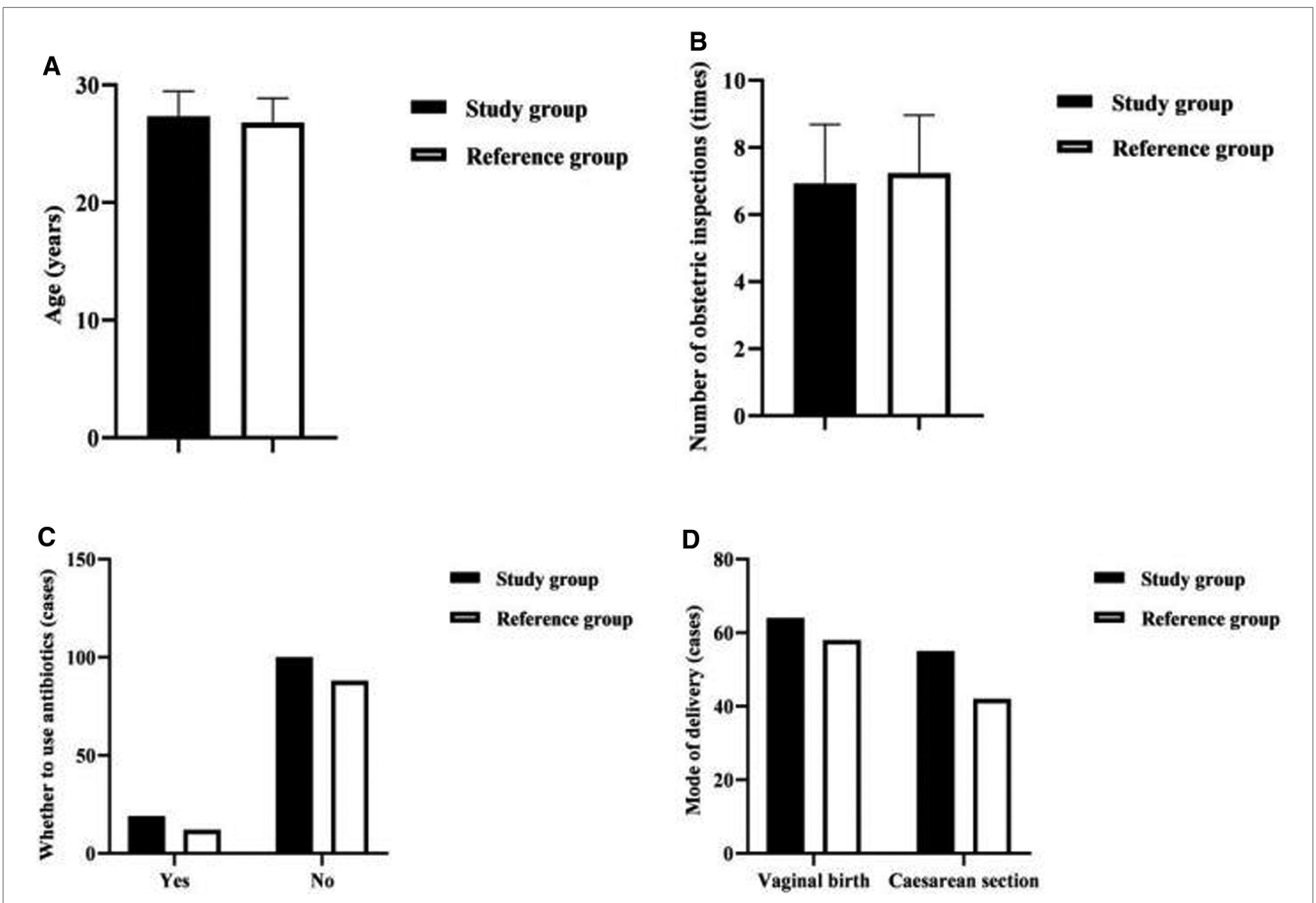

FIGURE 2 | Analysis of the maternal factors of EONBI. Note: (**A**) Comparison of maternal age in both groups (years). (**B**) Comparison of the number of obstetric inspections in both groups (times). (**C**) Comparison of whether to use antibiotics in both groups (cases). (**D**) Comparison of the mode of delivery in both groups (cases).

Multifactorial Analysis of EONBI and Obstetric High-Risk Factors

Multifactorial analysis showed that preterm birth, fecal contamination of amniotic fluid, maternal infection during pregnancy, and premature rupture of membranes ≥18 h had a good multivariate dependence on EONBI ($P < 0.05$), while there was no significant association with unexplained asphyxia, diabetic mother and child, and maternal fever at delivery ($P > 0.05$) (**Table 2**).

Analysis of Clinical Manifestations in Two Groups of Newborns

The incidence of neonatal temperature >37.9°C was higher in the study group than in the reference group ($P < 0.05$), and there were no statistical differences in the comparison of other clinical manifestations ($P > 0.05$) (**Table 3**).

Analysis of Serological Characteristics of Two Groups of Newborns

The CRP level of neonates in the study group (47.33 ± 4.14) mg/L was higher than that of the reference group (4.84 ± 1.03) mg/L ($P < 0.001$). The WBC level of neonates in the study group (5.64 ± 1.18) 10^9/L was higher than that of the reference group (0.28 ± 0.04) 10^9/L ($P < 0.001$). The PCT level of neonates in the study group (5.41 ± 0.85) μg/L was higher than that of the reference group (0.24 ± 0.07) μg/L ($P < 0.001$) (**Figure 3**).

DISCUSSION

The clinical symptoms of early neonatal bacterial infections are atypical. At present, the diagnostic criteria for neonatal bacterial infection at home and abroad are mostly based on the clinical manifestations of severe infection or even sepsis. There is a lack of scientificity and consistency in the early judgment of infection, and there are often two drawbacks: One is the failure to detect bacterial infections in newborns in a timely manner, leading to the spread of infection; the other is the use of antibiotic treatment for all newborns with obstetric high-risk factors, leading to the misuse of antibiotics (10). As seen above, it is extremely important to clarify the obstetric high-risk factors of EONBI and its infection status for the smooth implementation of the next treatment.

The results of this paper showed that preterm birth, unexplained asphyxia, fecal contamination of amniotic fluid, maternal infection during pregnancy, and premature rupture of membranes ≥18 h were significantly associated with EONBI. Preterm delivery has been reported as a high risk factor significantly associated with EONBI and 64% of fecal contamination of amniotic fluid is associated with chorioamnionitis (11). The present study confirmed this finding, analyzing the reasons for this, premature infants have immature immune systems and all systems, and are more likely to acquire infections via the above-mentioned routes or through the skin and respiratory tract. In neonatal asphyxia, humoral and cellular immune functions are impaired, and the number of invasive operations during treatment predisposes to bacterial invasion, resulting in early bacterial infections (12).

TABLE 3 | Analysis of clinical manifestations in two groups of newborns.

Clinical manifestations	Study group ($n = 119$)		Reference group ($n = 100$)		χ^2	P
	n	%	n	%		
Body temperature <36°C	5	4.20	3	3.00	0.223	0.637
Body temperature >37.9°C	18	15.13	4	4.00	7.444	0.006
Breathing >60 breaths/min	1	0.84	1	1.00	0.015	0.902
Heart rate <100 or >160 Beats/min	10	8.40	9	9.00	0.024	0.876
Primitive reflections Weaken or disappear	1	0.84	2	2.00	0.541	0.462
Poor feeding	15	12.61	8	8.00	1.226	0.268
Breast rejection	2	1.68	1	1.00	0.186	0.666
Bloating	1	0.84	1	1.00	0.015	0.902
Vomiting	7	5.88	9	9.00	0.780	0.377
Breathing difficulties	1	0.84	1	1.00	0.015	0.902
Poor response	10	8.40	6	6.00	0.464	0.496
No or less crying	3	2.52	1	1.00	0.701	0.402
Irritable and irritable	7	5.88	4	4.00	0.404	0.525
Pale gray face	8	6.72	9	9.00	0.394	0.530

TABLE 2 | Multifactorial analysis of EONBI and obstetric high-risk factors.

High-risk factors	β	SE	Wald	P	OR	95% CI	
						Lower limit	Upper limit
Preterm birth	0.247	0.036	6.309	0.012	1.280	1.193	1.374
Unexplained asphyxia	1.450	0.770	3.681	0.055	4.263	0.943	19.283
Diabetic mother and child	1.745	1.253	0.281	0.596	5.726	0.491	66.745
Fecal contamination of amniotic fluid	3.141	1.385	11.449	0.001	23.127	1.532	349.184
Maternal fever at delivery	1.823	1.788	0.137	0.712	6.190	0.186	205.918
Maternal infection during pregnancy	4.265	1.023	19.625	<0.001	71.165	9.582	528.520
Premature rupture of membranes ≥18 h	2.520	1.122	7.864	0.005	12.429	1.378	112.070

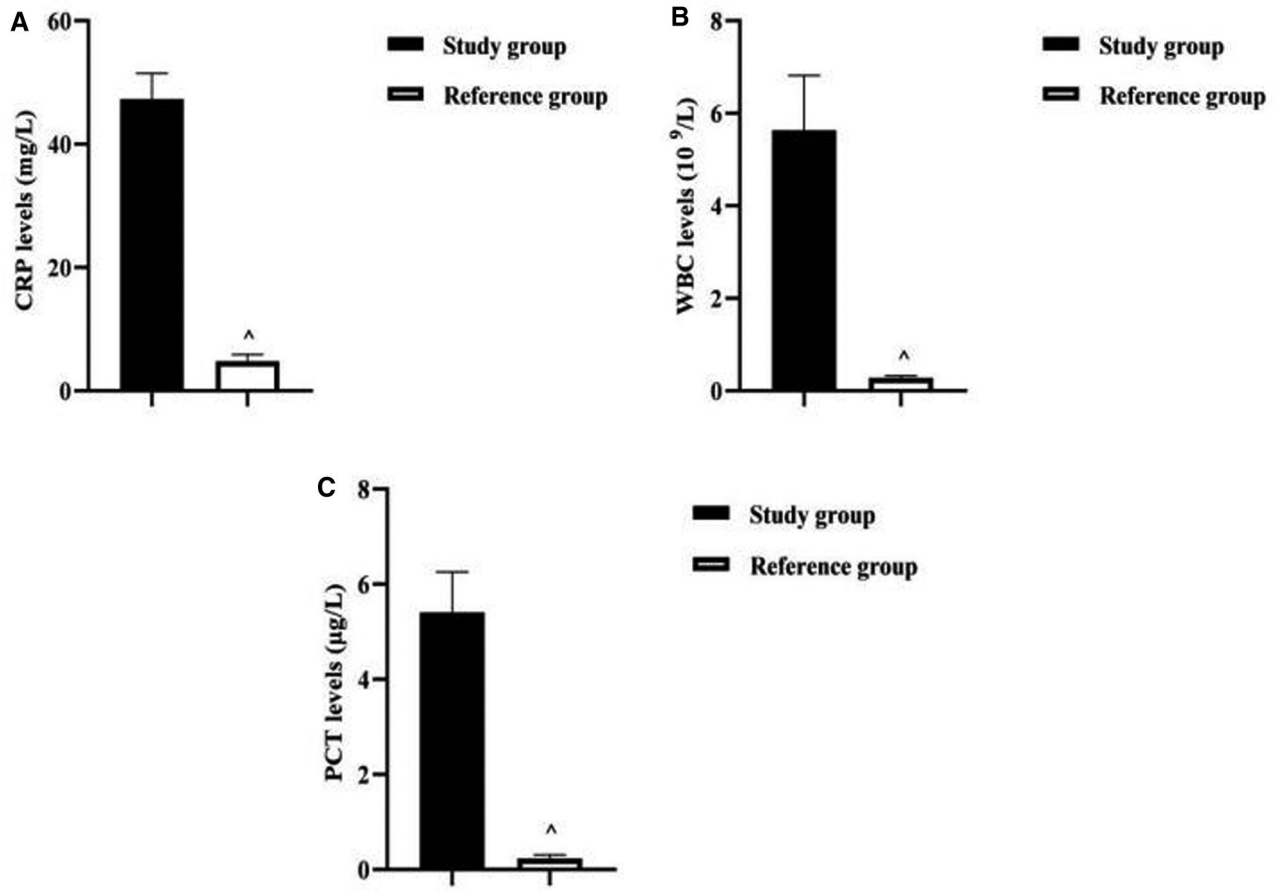

FIGURE 3 | Analysis of serological characteristics of two groups of newborns. Note: (**A**) Comparison of CRP levels between two groups of neonates. (**B**) Comparison of WBC levels between two groups of neonates. (**C**) Comparison of PCT levels between two groups of neonates. Comparison with the study group ^$P < 0.001$.

And EONBI mostly originates from intrauterine and is closely related to fecal contamination of amniotic fluid, maternal infection during pregnancy, premature rupture of membranes, etc. The infection routes include maternal hematogenous spread, ascending infection, retrograde fallopian tube implantation, invasive operation, etc. (13, 14). The most common of these are episodic infections, such as those caused by the upward movement of bacteria in the birth canal after premature rupture of membranes, and when bacteria spread to the amniotic cavity and grow in the amniotic fluid, the fetus can also become ill by inhaling contaminated amniotic fluid before and during delivery (15, 16).

The multifactorial analysis in this paper shows that preterm birth, fecal contamination of amniotic fluid, maternal infection during pregnancy, and premature rupture of membranes ≥18 h had a good multivariate dependence on EONBI, and the most significant risk factor for EONBI is maternal infection during pregnancy. This further confirms that genital tract infection during maternal pregnancy is an important factor in triggering intrauterine infection (17). During intrauterine infection, bacteria and their products stimulate the mRNA expression of cytokines such as IL-1β, IL-6, IL-8, and TNF-α in the amniotic membrane and trophoblast cells, which induce preterm labor and lead to EONBI (18). In this study, the OR value of maternal infection during pregnancy was 71.165, which suggested that the risk of EONBI in the presence of this high-risk factor was 71.165 times higher than that in the absence of this high-risk factor. Unexplained asphyxia was not significantly associated with EONBI after controlling for confounders. This may be because the rapid development of aseptic technique and medical devices in recent years has led to a decrease in infections acquired through resuscitation.

In recent years, there has been a significant increase in the prevalence of gestational diabetes, which has been reported to be as high as 5.8% to 25.1% (19). As the placenta is rich in blood supply, the number of villi increases, the villi gap narrows accordingly, and cells proliferate, making the circulatory barrier between mother and fetus widen and the small metaplastic arteries narrow, while the potential microangiopathy in pregnant women with diabetes can

aggravate the obstruction of small arteries on the fetal side of the villi stem, leading to chronic intrauterine hypoxia, acidosis, and secondary infection in the fetus (20). However, the present results after controlling for confounders showed no significant association between diabetic mother and child and EONBI. This may be related to the popularization of gestational diabetes screening in my country and the vigorous intervention of gestational diabetes in recent years. The present results also showed that maternal fever at delivery was also not significantly associated with EONBI. This may be related to the higher priority given to it by obstetricians and therefore earlier intervention. It is also possible that the sample size in this study was limited and further studies with larger sample sizes are needed to understand more precisely the relationship between the two. In this result, the gestational age and birth weight of newborns in the study group were lower than those in the reference group. This may be due to the fact that 71.43% of the newborns in the study group were preterm, much higher than the 31.00% in the reference group, so the children were under gestational age and most of them had a birth weight of no more than 2.5 kg. In this paper, the incidence of neonatal temperature >37.9°C was higher in the study group than in the reference group, and there were no statistical differences in the comparison of other clinical manifestations. This further confirms that the clinical signs and symptoms of EONBI are atypical and that the first symptom of bacterial infection in newborns is fever.

Previously, the clinical diagnosis of neonatal infectious diseases was based on the detection of peripheral blood WBC counts, and the results of WBC detection were affected by various factors, and some neonates had poor WBC count bases, and the detected WBC levels were still in the normal range even though bacterial infections had occurred in the body, so WBC could only be used as a routine reference index for the diagnosis of infectious diseases (21, 22). CRP, synthesized by inflammatory factors stimulating hepatocytes, is an acute phase response protein that triggers immunomodulation, phagocytosis, formation of immune complexes, and activation of the complement system, and has been clinically used as a nonspecific marker of the systemic inflammatory response (23). When inflammatory reaction or tissue damage occurs in the organism, CRP levels can rise abruptly within hours or 1–2 days, and its level is positively correlated with the degree of infection in the organism, so it is often used as an early diagnostic indicator of bacterial infection (24). Besides, in recent years, PCT has been considered as an ideal serological marker for the diagnosis of bacteriological infections, which is considered to have not only high specificity and sensitivity, but also can compensate for the lack of lag in bacterial culture, thus facilitating the accurate and rapid diagnosis and treatment of diseases (25). The levels of CRP, WBC, and PCT in the newborns of this result study group were higher than those of the reference group. This suggests that health care providers can use this serological characteristics as an important reference indicator to identify the presence of bacterial infection in newborns.

CONCLUSION

EONBI is closely associated with several obstetric high-risk factors, including preterm birth, fecal contamination of amniotic fluid, maternal infection during pregnancy, and premature rupture of membranes ≥18 h; EONBI has no specific symptoms and signs, but serum CRP, WBC, and PCT levels are significantly higher than those of newborns without co-infection with bacteria.

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 This study was approved by the ethics committee of our hospital (21459-0-01). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The first author is YW, she is the executor and writer of the paper. The second author is QC, he is responsible for searching data and data analysis. The third author is SX, she is responsible for research design. SC is the corresponding author, she is ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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Study on the Correlation Between CT Features and Vascular Tumor Thrombus Together With Nerve Invasion in Surgically Resected Lung Adenocarcinoma

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Background: We aimed to analyze the relationship between pulmonary adenocarcinoma patients with vascular tumor thrombus and nerve invasion and different CT features.

Methods: The preoperative CT scanning data of 86 patients with lung adenocarcinoma who underwent surgical resection in our hospital from January 2020 to January 2022 were analyzed in the form of retrospective analysis. The CT images of all patients were observed, and the relationship between them and vascular tumor thrombus and nerve invasion of lung adenocarcinoma was analyzed. At the same time, the sensitivity, specificity, and accuracy of enhanced CT and plain CT were compared to evaluate the diagnostic efficacy of both.

Results: The results showed that the vascular tumor thrombus of lung adenocarcinoma was mainly related to the solid components and lobulated and calcified tumors in CT images, and the nerve invasion of lung adenocarcinoma was mainly related to the tumors with bronchial inflation sign in CT images ($P < 0.05$). The sensitivity, specificity, and accuracy of enhanced CT in the diagnosis of vascular tumor thrombus were 78.26%, 96.83%, and 91.86%, respectively, and the sensitivity, specificity, and accuracy in the diagnosis of nerve invasion were 75.00%, 98.72%, and 96.51%, respectively. The sensitivity, specificity, and accuracy of plain CT in the diagnosis of vascular tumor thrombus were 43.48%, 92.06%, and 79.07%, respectively, and the sensitivity, specificity, and accuracy in the diagnosis of nerve invasion were 25.00%, 94.87%, and 88.37%, respectively. The contrast showed that the sensitivity and accuracy of enhanced CT were higher than those of plain CT ($P < 0.05$), but the difference of specificity was not obvious ($P > 0.05$).

Conclusions: Solid components and lobulated and calcified tumors in CT signs are closely related to vascular tumor thrombus of lung adenocarcinoma, while patients with bronchial inflation sign are related to nerve invasion.

Keywords: lung adenocarcinoma, vascular carcinoma thrombus, nerve invasion, surgical excision, CT features

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INTRODUCTION

Lung cancer is a common malignant tumor in clinical practice. Its incidence rate and mortality rate rank first in China. According to the relevant survey, the incidence rate of lung cancer is increasing year by year in China. The incidence rate in male population is the highest, and lung adenocarcinoma is the most common, accounting for 45.5% (1) of all lung cancer patients. Surgical resection is an effective way to treat lung adenocarcinoma, but the survival and recurrence of patients are still difficult to guarantee. It has been reported that the survival time and disease recurrence of patients with lung adenocarcinoma after the operation are mainly affected by vascular tumor thrombus, and vascular tumor thrombus and nerve invasion are also important risk factors for lymph node metastasis of lung adenocarcinoma (2). At present, the clinical diagnosis of vascular cancer thrombus and nerve invasion is mostly confirmed by postoperative pathology, but it is the lack of predictability that is easy to cause patients to miss the best operation opportunity. Therefore, it is very important to find a more effective diagnosis method. Chest CT is a routine method for clinical screening of lung lesions. In recent years, with the continuous improvement and optimization of CT technology, the information presented by this image is much rich and accurate. Therefore, it is possible to predict vascular tumor thrombus and nerve invasion of lung adenocarcinoma by preoperative enhanced CT (3). This paper mainly studies the correlation between different CT features and vascular tumor thrombus and nerve invasion of lung adenocarcinoma to clarify the value of CT scanning in the prognosis of patients.

PATIENTS AND METHODS

Patients

A total of 86 patients with lung adenocarcinoma who underwent surgical resection in our hospital from January 2020 to January 2022 were selected, and their clinical data were analyzed retrospectively. All patients underwent CT scanning before operation and were confirmed by pathological results after operation. There were 45 males and 31 females; the lower limit of age was 35 years, the upper limit was 85 years, and the average age was 55.38 ± 8.72 years; the lesions were located in the right lung in 44 cases and in the left lung in 44 cases; and there were 71 cases of invasive type and 15 cases of microinvasive type. This study was approved by the ethics committee of the 900 Hospital of the Joint Logistics Team. Signed written informed consent was obtained from all participants before the study.

Inclusion and Exclusion Criteria

Inclusion criteria (4) are as follows: (1) lung adenocarcinoma confirmed by postoperative histopathological examination; (2) the chest was examined by enhanced CT before operation, and there were complete image data; (3) patients did not receive any antitumor drugs before operation; and (4) there were no other malignant tumors. Exclusion criteria are as follows: (1) patients with contrast medium allergy and unable to complete CT scan; (2) combined with other malignant tumors and treated with antitumor therapy; (3) the quality of enhanced CT image is too poor for accurate analysis; and (4) the CT image was more than 1 month away from the operation time.

METHODS

The chest CT scanning equipment was Ge VCT 64 row, Lianying uct780 64 row, Ge Discovery HD 750, and ingenuity flex16 row. The tube voltage of the scanning instrument was set to 120 kv, the rotating speed was 0.7 s per revolution, the matrix was 512×512, and the layer thickness was set to 5 mm. During the scan, the patient laid on his back on the bed and was asked to hold his breath and lift his hands above his head. After completing the plain CT scan, the enhanced scan was started with a delay of 30s. During the enhanced scan, the patient was injected with 80 ml of contrast agent iohexol (350 mg/ml) through a high-pressure syringe. The injection site was in the vein of the elbow, and 3 ml was injected every second. After scanning, the CT images of all patients were reconstructed into images with a layer thickness of 1.25 mm and uploaded to the imaging workstation to analyze the lesions.

Image Analysis

CT images were discussed and analyzed by two experienced radiologists, mainly analyzing multiple CT signs such as boundary, composition, lobulation sign, bronchial inflation sign, pleural thickening, calcification, pleural depression sign, vascular bundle sign, vacuole, peripheral emphysema, and pleural effusion.

Statistical Analysis

Statistical Product and Service Solutions (SPSS) 22.0 (IBM, Armonk, NY, USA) was applied for statistical analysis. Each categorical variable was expressed as enumeration data [n(%)] and passed the χ^2 value test. When the results were compared, $P < 0.05$ indicated a significant difference.

RESULTS

Postoperative Pathology and CT Diagnosis Results

After histopathological examination of 86 patients with lung adenocarcinoma, 23 (26.74%) were positive for vascular tumor thrombus and 63 (73.26%) were negative and 8 (9.30%) were positive for nerve invasion and 78 (90.70%) were negative. Enhanced CT scan showed that 20 cases (23.26%) were positive for vascular tumor thrombus and 66 cases (76.74%) were negative and 7 cases (8.14%) were positive for nerve invasion and 79 cases (91.86%) were negative. CT scan showed that 15 cases (17.44%) were positive for vascular tumor thrombus and 71 (82.56%) were negative and 6 (6.98%) were positive for nerve invasion and 80 (93.02%) were negative.

Relationship Between Different CT Features of Lung Adenocarcinoma and Vascular Tumor Thrombus

Lung adenocarcinoma patients with solid components and lobulated and calcified tumors were all significantly correlated with vascular tumor thrombus ($P < 0.05$), while other signs had no significant correlation ($P > 0.05$) (**Table 1**).

Relationship Between Different CT Signs and Nerve Invasion in Patients With Lung Adenocarcinoma

After analysis, it was found that the nerve invasion of surgically resected lung adenocarcinoma was mainly related to tumors with air bronchi signs ($P < 0.05$), and there was no significant difference with other signs and no correlation ($P > 0.05$) (**Table 2**).

Comparison of Contrast-Enhanced CT and Plain CT in the Diagnosis of Vascular Tumor Thrombus in Lung Adenocarcinoma

Compared with plain CT, enhanced CT scanning sensitivity and accuracy were significantly higher ($P < 0.05$), and there was no difference in specificity between the two scanning methods ($P > 0.05$) (**Tables 3** and **4**).

Comparison of Contrast-Enhanced CT and Plain CT in the Diagnosis of Nerve Invasion in Lung Adenocarcinoma

Compared with plain CT, the sensitivity and accuracy of enhanced CT were significantly higher ($P < 0.05$), but there was no significant difference in specificity between the two ($P > 0.05$) (**Tables 5** and **6**).

TABLE 1 | Relationship between different CT features of lung adenocarcinoma and vascular tumor thrombus [*n* (%)].

CT signs	Positive (*N* = 23)	Negative (*N* = 63)	χ^2	*P*
Clear boundaries	14(60.87)	47(74.60)	1.541	0.214
Solid ingredient	20(86.96)	40(63.49)	4.398	0.036
Lobulated sign	19(82.61)	37(58.73)	4.449	0.040
Glitches	17(73.91)	43(68.25)	0.256	0.613
Vascular bundle sign	20(96.96)	49(77.78)	0.895	0.344
Air bronchus sign	16(69.57)	42(66.67)	0.064	0.800
Vacuoles	10(43.48)	23(36.51)	0.346	0.556
Adjacent pleura thickening	18(78.26)	45(71.43)	0.401	0.526
Pleural indentation sign	21(91.30)	46(73.02)	3.274	0.070
With calcification	6(26.09)	5(7.94)	4.976	0.026
Pleural effusion	0(0.00)	4(6.35)	1.532	0.216
Peripheral emphysema	5(21.74)	7(11.11)	1,585	0.208
Multiple enlarged lymph nodes	4(17.39)	6(9.52)	1.015	0.314
Calcified lymph nodes	5(21.74)	9(14.29)	0.687	0.407

TABLE 2 | Relationship between different CT signs and nerve invasion in patients with lung adenocarcinoma [*n* (%)].

CT signs	Positive (*N* = 8)	Negative (*N* = 78)	χ^2	*P*
Clear boundaries	6(75.00)	70(89.74)	1.535	0.215
Solid ingredient	8(100.00)	68(87.18)	1.161	0.281
Lobulated sign	7(87.50)	54(69.23)	1.175	0.278
Glitches	8(100.00)	71(91.03)	0.782	0.377
Vascular bundle sign	6(75.00)	67(85.90)	0.672	0.413
Air bronchus sign	8(100.00)	0(66.67)	86.000	<0.001
Vacuoles	3(37.50)	24(30.77)	0.153	0.696
Adjacent pleura thickening	8(100.00)	65(83.33)	1.571	0.210
Pleural indentation sign	7(87.50)	66(84.62)	0.047	0.828
With calcification	2(25.00)	8(10.26)	1.535	0.215
Pleural effusion	0(0.00)	9(11.54)	1.031	0.310
Peripheral emphysema	1(12.50)	5(6.41)	0.415	0.520
Multiple enlarged lymph nodes	0(0.00)	3(3.85)	0.319	0.572
Calcified lymph nodes	4(50.00)	20(25.64)	2.140	0.144

TABLE 3 | Comparison of contrast-enhanced CT and plain CT in the diagnosis of vascular tumor thrombus in lung adenocarcinoma [*n* (%)].

Item		Postoperative pathology		Total
		Positive	Negative	
Enhanced CT	Positive	18	2	20
	Negative	5	61	66
Total		23	63	86
Plain CT	Positive	10	5	15
	Negative	13	58	71
Total		23	63	86

TABLE 4 | Comparison of contrast-enhanced CT and plain CT in the diagnosis of vascular tumor thrombus in lung adenocarcinoma [*n* (%)].

Item	Sensitivity	Specificity	Accuracy
Enhanced CT	78.26%(18/23)	96.83%(61/63)	91.86%(79/86)
Plain CT	43.48%(10/23)	92.06%(58/63)	79.07%(68/86)
χ^2	5.841	1.361	5.663
P	0.016	0.243	0.017

TABLE 5 | Comparison of the results of contrast-enhanced and non-enhanced CT in the diagnosis of nerve invasion in lung adenocarcinoma [*n* (%)].

Item		Postoperative pathology		Total
		Positive	Negative	
Enhanced CT	Positive	6	1	7
	Negative	2	77	79
Total		8	78	86
Plain CT	Positive	2	4	6
	Negative	6	74	80
Total		8	78	86

TABLE 6 | Comparison of the results of contrast-enhanced and non-enhanced CT in the diagnosis of nerve invasion in lung adenocarcinoma [*n* (%)].

Item	Sensitivity	Specificity	Accuracy
Enhanced CT	75.00%(6/8)	98.72%(77/78)	96.51%(83/86)
Plain CT	25.00%(2/8)	94.87%(74/78)	88.37%(76/86)
χ^2	4.000	1.860	4.077
P	0.045	0.173	0.043

DISCUSSION

Lung adenocarcinoma is highly malignant and can pose a serious threat to the life safety of patients. Although the clinical resection can temporarily save the lives of patients, the problem of postoperative survival and recurrence still puzzles the medical community. Studies have found that vascular tumor thrombus and nerve invasion are independent risk factors leading to lymph node metastasis of lung adenocarcinoma and affecting patients' recurrence (5, 6). Vascular tumor thrombus refers to the long-term effect of various reasons, which makes tumor cells invade blood vessels or lymphatic vessels and finally leads to the formation of tumor thrombus. Vascular tumor thrombus is a typical sign of tumor cells invading the vascular system and a pioneer condition for inducing lymph node metastasis (7, 8). Therefore, it is necessary to strengthen preoperative diagnosis, which is of great significance to reduce postoperative recurrence and prolong the survival of patients.

CT is currently a commonly used imaging method for clinical diagnosis of various diseases, with high sensitivity and specificity. Using it in the preoperative examination of lung adenocarcinoma can determine the deterioration by analyzing the changes of various signs (9–11). However, the research on the relationship between CT features and vascular tumor thrombus and nerve invasion of lung adenocarcinoma is still rare in the medical community. Therefore, based on the above shortcomings, this paper uses CT scanning for patients with pulmonary adenocarcinoma before operation. The results show that patients with vascular tumor thrombus are mainly closely related to CT features such as solid nodule, lobulation, and calcification, while there is a certain correlation between nerve invasion of pulmonary adenocarcinoma and patients with bronchial inflation sign ($P < 0.05$). This result is basically consistent with a previous study (12). In its report, the analysis of preoperative chest CT images of patients with surgically resected lung adenocarcinoma found that patients with vascular tumor thrombus were mostly accompanied by solid nodules, lobulated nodules, and calcified nodules, while patients with nerve invasion were mostly biased toward bronchial inflation sign tumors. This shows that CT signs were indeed related to vascular tumor thrombus and nerve invasion of lung adenocarcinoma. Preoperative enhanced CT scanning can effectively predict the condition and prognosis of patients (13, 14).

Usually, the malignant degree of solid nodules is higher than that of pure ground glass nodules and mixed ground glass nodules, and the proportion of solid components will increase significantly with the deepening of tumor infiltration. Therefore, patients with lung adenocarcinoma with solid nodules are more likely to have vascular tumor thrombus and have a high postoperative recurrence rate and poor prognosis (15). Lobulated lung adenocarcinoma is more common in solid nodules, which may be related to the great difference of tumor cell differentiation. Malignant tumors are very prone to calcification, but even after calcification, they are still likely to continue to grow, spread, and metastasize. Therefore, this sign has a certain value in predicting the prognosis of patients (16, 17). However, due to the small number of positive cases of calcification in this paper, it has little reference significance. Accompanied by bronchial inflation sign, it is usually considered as alveolar inflammatory exudation, but it does not cause significant damage to the bronchus. In the background of consolidation, the bronchial sign with air usually appears in independent nodules. This sign should be highly vigilant against malignant tumors (18).

To further understand the predictive value of different ways of CT scanning (enhanced CT and plain CT) for vascular tumor thrombus and nerve invasion of lung adenocarcinoma, the diagnostic efficacy of the two was compared. The results showed that the diagnostic sensitivity and accuracy of enhanced CT were significantly higher than those of plain CT ($P < 0.05$), but there was no significant difference in the diagnostic specificity between the two. The results suggested that enhanced CT is more valuable in the diagnosis of vascular tumor thrombus and nerve invasion of lung adenocarcinoma than plain CT, which can guide the clinical development of effective diagnosis and treatment plan. The application of spiral CT effectively improves the diagnostic accuracy, and the reconstructed CT image can observe the lesion characteristics from multiple angles and objectively analyze the lesion characteristics to improve the diagnostic accuracy and guide the clinical rational treatment of diseases (7, 19).

It is worth noting that there are still some deficiencies in this paper, such as small sample size and little reference significance of some conclusions. The pathological type was single, and no clear pathological distinction was made; The clinical stage of lung adenocarcinoma was not clear, so it still needed to be strengthened and improved in future research.

CONCLUSION

The tumors with solid components and lobulation and calcification in CT features are closely related to the vascular tumor thrombus of lung adenocarcinoma, and the tumors with bronchial inflation sign are related to the nerve invasion of lung adenocarcinoma. Therefore, it is necessary to strengthen the prediction and diagnosis of patients with lung adenocarcinoma before 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/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the 900 Hospital of the Joint Logistics Team. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

YS and DC designed the study and performed the experiments; DL and SX collected the data; DL, SX, and HX analyzed the data; and YS and DC prepared the manuscript. All authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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The Relationship Between Systemic Immune Inflammatory Index and Prognosis of Patients With Non-Small Cell Lung Cancer: A Meta-Analysis and Systematic Review

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Background: The relationship between systemic immune inflammation index (SII) and the prognosis of cancer has always been a subject of intense interest. However, the prognostic value of SII in non-small cell lung cancer (NSCLC) patients remains a controversial topic.

Objective: To evaluate the effect of SII index on prognosis of NSCLC.

Methods: We conducted a comprehensive search of PubMed, EMBASE, and the Cochrane Library databases to determine correlation between SII index, clinicopathological features, overall survival (OS), and progression-free survival (PFS). Odds ratio (ORs) and 95% confidence interval (CIs) were used to assess the connection between SII and clinicopathological parameters, and HRs and 95% CIs were used to assess the connection between SII and survival.

Results: Seventeen studies with 8,877 cases were included in the analysis. Compared with NSCLC patients with low SII level, patients with NSCLC with high SII level had a poor OS (HR = 1.75, 95% CI, 1.50–2.00; $P < 0.001$) and had a poor PFS (HR = 1.61, 95% CI, 1.25–1.96; $P < 0.001$). In addition, patients with higher pathological stage (II–III) had higher SII levels (OR = 2.32, 95% CI, 2.06–2.62; $P < 0.001$).

Conclusions: The SII index is a promising prognostic biomarker for NSCLC and may help clinicians choose appropriate NSCLC treatments.

Keywords: systemic immune inflammatory index, non-small cell lung cancer, prognosis, meta-analysis, systematic review

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INTRODUCTION

Lung cancer has a high incidence and mortality, and non-small cell lung cancer (NSCLC) accounts for about 80% of the total incidence of lung cancer (1). The incidence of NSCLC has risen steadily over the past few decades, but the mortality rate of NSCLC appears to be decreasing, possibly due to the tremendous advances in NSCLC treatment (2, 3). The treatment of NSCLC includes surgery,

radiotherapy, chemotherapy, targeted therapy, and immunotherapy (4). Nonetheless, the efficacy of these therapies in NSCLC patients remains dissatisfactory due to the lack of resultful indicators that can be utilized to predict the disease course and the widespread chemoresistance of NSCLC (5). Hence, it is necessary for researchers to identify exact biomarkers and potential therapeutic targets for NSCLC to improve survival.

In recent years, some indicators reflecting the inflammatory state of the body have been confirmed to be related to the prognosis of various malignant tumors (6). Systemic immune inflammation index (SII) is one of the new inflammatory indexes based on peripheral blood platelet count, neutrophils, and lymphocytes. SII = platelet count × neutrophils/lymphocytes. Studies have confirmed that SII can impersonally reflect the balance between inflammatory response and immune response in tumor patients (7). SII has achieved good results in predicting the prognosis of colorectal cancer, cervical cancer, pancreatic cancer and other malignant tumors (8–10). Furthermore, multiple meta-analyses have shown that SII predicts poor prognosis in a variety of malignancies (11, 12). Nevertheless, studies on SII levels in NSCLC are limited, and the prognostic value of SII levels in NSCLC is still a controversial issue. To solve this problem, we conducted a meta-analysis to synthetically assess the value of SII as a prognostic marker and determine the correlation between SII levels and pathological characteristics of NSCLC patients.

MATERIALS AND METHODS

This meta-analysis was based on preferred reporting items for systematic reviews and meta-analysis (PRISMA) (13). This study was based on previously published research data, ethical approval is not necessary.

Literature Search

We performed a comprehensive literature search of published studies using databases such as PubMed, EMBASE, and Cochrane. Studies published before January 2022 were collected. The following keywords were used in the search box: ("Systemic immune inflammation index" OR "SII" OR "neutrophil × platelets/lymphocyte" OR "platelet count × NLR") AND ("non small cell lung cancer" OR "NSCLC"). In order to find relevant literature, we also checked the references of relevant articles.

Inclusion and Exclusion Criteria

Studies that met the following conditions were considered eligible: (1) The relationship between SII index and survival of NSCLC patients was provided. (2) The critical value of preprocessing SII was provided. (3) The study offered enough data to extract the hazard ratio (HR) and 95% confidence interval (CI) for OS. Articles were excluded if they were reviews or meta-analyses, did not involve non-small cell lung cancer, or only involved animal experiments. If duplicate articles exist, only complete or up-to-date articles were included in this analysis.

Data Extraction and Quality Assessment

All relevant data will be extracted by two data collectors, and if the two collectors were unsure of the data, one researcher wound decided how to extract the data. First author, country, number of cases, patient age, SII index, clinicopathological parameters, HR, and 95% CI were extracted from each study. Quality assessment of each study was performed independently by two data collectors using the Newcastle-Ottawa Scale (NOS), and the quality score was averaged between the two data collectors. The highest NOS score was 9, and studies with a score greater than 6 were considered high quality (14).

Statistical Methods

HRs and their 95% CIs were used to assess the correlation between SII and survival, and Odds ratio (ORs) and their 95% confidence interval (CIs) were used to determine the correlation between SII and clinicopathological parameters. Heterogeneity between studies was assessed using the chi-square test and I^2. Statistics $P < 0.1$ or $I^2 > 50\%$ indicated significant heterogeneity between studies and a random effects model (REM) was selected for analysis; otherwise, a fixed effects model (FEM) was selected for analysis. Egger's test was selected for assess potential publication bias. Review Manager 5.3 (Revman the Cochrane Collaboration) and STATA 16.0 (Stata Corporation) software were selected for Meta-analysis. $P < 0.05$ means the difference is obviously significant. P values and 95% CI were two-sided tests.

RESULTS

Search Results and Study Characteristics

In this study, we collected 100 total potentially relevant articles according to the search methods previously determined. After reviewing the titles and abstracts of these articles, we excluded 67 duplicate or irrelevant studies. After a detailed review of 33 articles, we determined that 17 trials accord with inclusion criteria and were therefore included in the meta-analysis (as shown in **Figure 1**).

The information of the 17 studies (15–33) are shown in **Table 1**. Of the 17 studies, the sample size was a minimum of 42 and a maximum of 3,984. 8,877 total patients participated in the study. A total of 17 studies eligible for analysis were retrospective. Four of the studies were from the United States and Japan, and the rest were from China. Nine studies were conducted with patients with advanced stage, and the remaining studies were conducted with patients with early and advanced stage. HRs and 95% CIs were extracted directly from all original articles. The quality of the studies assessed by NOS was all ≥6. Therefore, the study was of high quality.

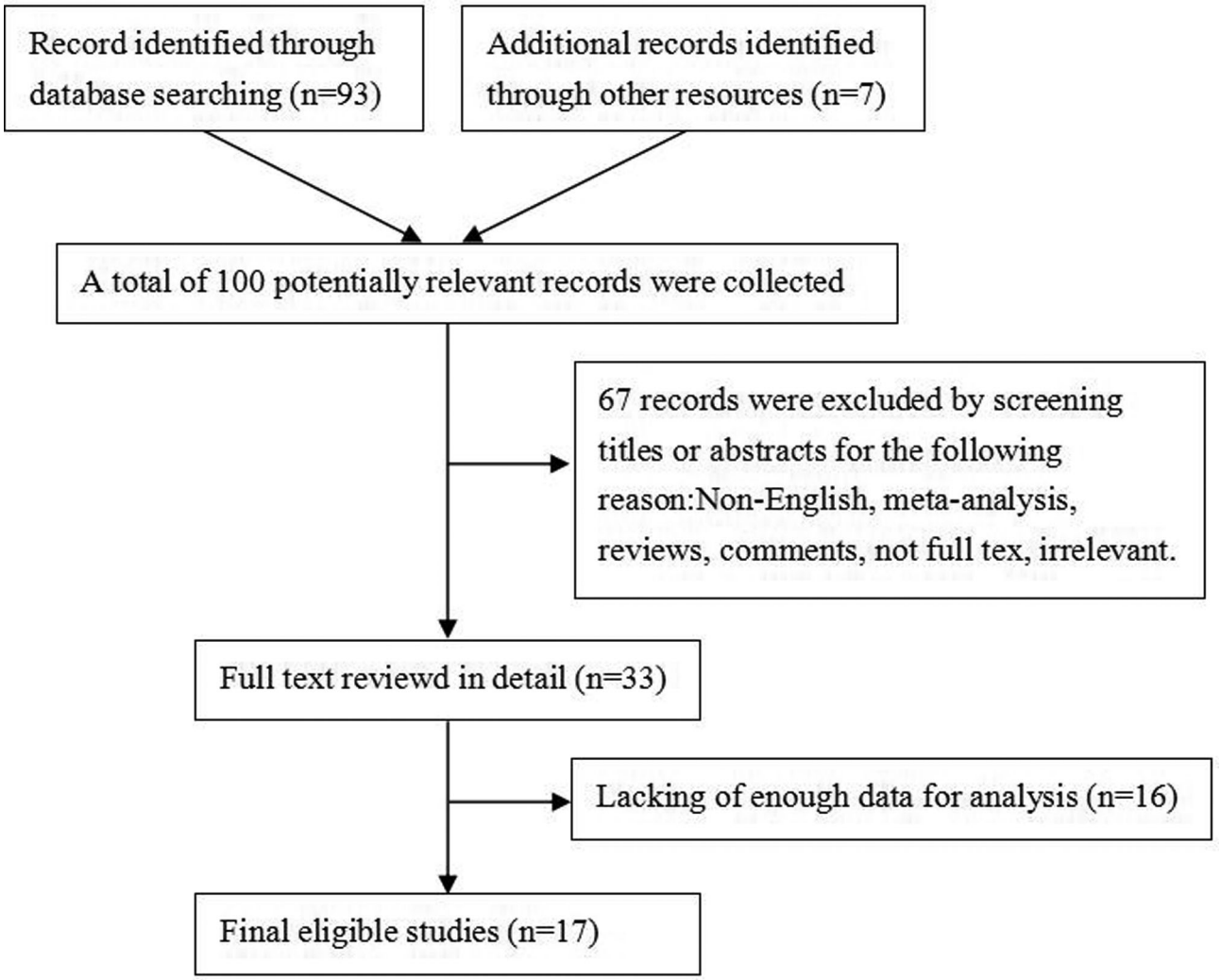

FIGURE 1 | Literature screening process.

Relationship Between SII Levels and OS

We analyzed the relationship between SII levels and overall survival (OS) in NSCLC. 8,752 total cases were included in 16 studies. The meta-analysis (as shown in **Figure 2**) demonstrated that NSCLC patients with high-level SII had a poor OS contrast to NSCLC patients with low-level SII (HR = 1.75, 95% CI, 1.50–2.00; $P < 0.001$). There was heterogeneity in the results ($I^2 = 51.32\%$, $P < 0.001$), hence, a REM was used for analysis.

Correlation of SII Levels With PFS

We analyzed the relationship between SII levels and progression-free survival (PFS) in NSCLC. Eight studies included a total of 5,496 patients. The meta-analysis (as shown in **Figure 3**) demonstrated that NSCLC patients with high-level SII had a poor PFS contrast to NSCLC patients with low-level SII (HR = 1.61, 95% CI, 1.25–1.96; $P < 0.001$). There was heterogeneity in the results ($I^2 = 70.15\%$, $P = 0.01$), hence, a REM was used for analysis.

Relationship Between SII Levels and Clinicopathological Features

In this study, we analyzed the relationship between high levels of SII and pathological stage and pathological type. The meta-analysis demonstrated that patients with higher pathological stage (II–III) had higher SII levels (OR = 2.32, 95% CI, 2.06–2.62; $P < 0.0001$). However, no obvious correlation between SII levels and pathological types (OR = 0.86, 95% CI, 0.55–1.36, $P = 0.53$), as shown in **Figure 4**.

Sensitivity Analysis

Sensitivity analysis, which involves deleting one study at a time to assess the stability of the results. After removing the literature, none of the individual studies obviously affected the whole

TABLE 1 | Characteristics of included studies.

First author/ year	Country	Total	male ratio	Age Median (range)	Survival type	Cut off value ($\times 10^9$/L)	Cut off selection	Group size	Tumor stage	NOS
Berardi R 2019	USA	311	216(69%)	68(25–86)	PFS,OS	1,270	median	High 179 /low 132	III–IV	7
Chen X 2022	China	94	55 (58.5%)	48(18–76)	PFS,OS	842	median	high 47 /low 47	IIIB–IV	6
Deng C 2019	China	203	89 (43.8%)	59(28–79)	PFS,OS	1,066.935	ROC curve analyses	high 63 /low 140	–	7
Fu F 2021	China	3,984	2,139 (53.7%)	60 (53–66)	PFS,OS	479	R package survminer	high 1,643 /low 2,341	I–III	7
Gao Y 2018	China	410	267 (65.12%)	–	OS	395.4	ROC curve analyses	high 270 /low 140	T1–T4	7
Guo D 2018	China	140	95 (67.9%)	62(33–83)	PFS,OS	521	ROC curve analyses	high 72 /low 68	IIIB – IV	7
Guo W	China	569	425 (74.7%)	60(27–80)	OS	419.6	ROC curve analyses	high 307 /low 262	I–III	7
Hong X 2015	China	919	635 (69.1%)	56(16–84)	OS	1,600	ROC curve analyses	high 127 /low 792	I–IV	7
Ju Q 2021	China	102	41 (40.2%)	59.50(30–80)	PFS,OS	841.03	ROC curve analyses	NA	III–IV	6
Keit E 2021	USA	125	64 (51.2%)	67(45–86)	PFS,OS	1,266	ROC curve analyses	high 55 /low 70	III	7
Li A 2020	China	252	145(57.5%)	58 (24–84)	OS	630.85	ROC curve analyses	high 154 /low 98	Brain metastasis	7
Li X 2020	China	345	255(73.9%)	64 (25–93)	OS	555.59	ROC curve analyses	high 196 /low 149	IIIB – IV	7
Takeda T 2021	Japan	42	22(52.4%)	67(29–85)	PFS	1,000	ROC curve analyses	high 15 /low 27	I–III	7
Tong YS 2017	China	332	206 (62%)	61(34–70)	OS	660	ROC curve analyses	high 149 /low 183	IIIA – IIIB	7
Watanabe K 2021	Japan	387	233(60.2%)	71(19–86)	RFS	715	ROC curve analyses	high 97 /low 290	IA–IIA	7
Yan X 2020	China	538	343 (63.8%)	60 (24–82)	DFS,OS	402.37	ROC curve analyses	high 339 /low 199	I–IIIA	7
Zhang Y 2021	China	124	56(45.2%)	60 (38–73)	PFS,OS	480	ROC curve analyses	high 66 /low 58	I–III	7

population, Indicating that the results of the current meta-analysis were credible.

Publication Bias

Egger's test indicated that the included studies exhibited publication bias affecting the hazard ratio for OS, with a *P* value of 0.0001, as shown in **Figure 5**.

DISCUSSION

A large number of studies have reported the relationship between inflammation and tumor and found that inflammation is one of the factors promoting the occurrence and development of tumor (34). For example, neutrophils, lymphocytes, and platelets play important roles in tumor progression. These indicators can promote tumor cell proliferation, invasion, and distant metastasis (35). For the past few years, some systemic inflammatory cell-based biomarkers, such as platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), have been shown to correlate with many The prognosis of this type of cancer is relevant (36). Nevertheless, these indicators are based on two inflammatory indices, and SII is a novel biomarker based on three indices (platelet, neutrophil, lymphocyte count) that comprehensively reflects the host immune and inflammatory status. SII is a relatively objective index and has good prognostic reliability (8–10).

As far as we know, a meta-analysis of the effect of SII index on survival in patients with NSCLC has not been reported. In this context, a comprehensive literature search was conducted and incorporated into 17 total studies with 8,877 cases. From the results of the meta-analysis, we found a obvious correlation between the SII index and the prognosis of NSCLC patients. The OS and PFS of patients with high SII levels were shorter than those with low SII levels, suggesting that SII index may be a promising prognostic factor for NSCLC patients. Berardi et al. (15), Deng et al. (17), Hong et al. (22),

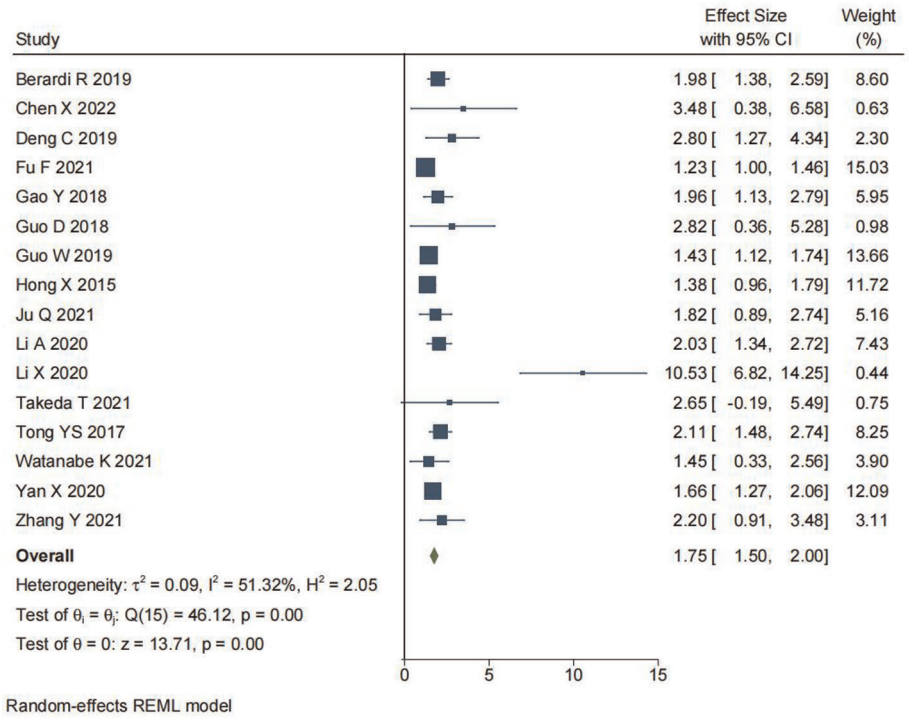

FIGURE 2 | Forest plot depicting the relationship between SII levels and OS in NSCLC.

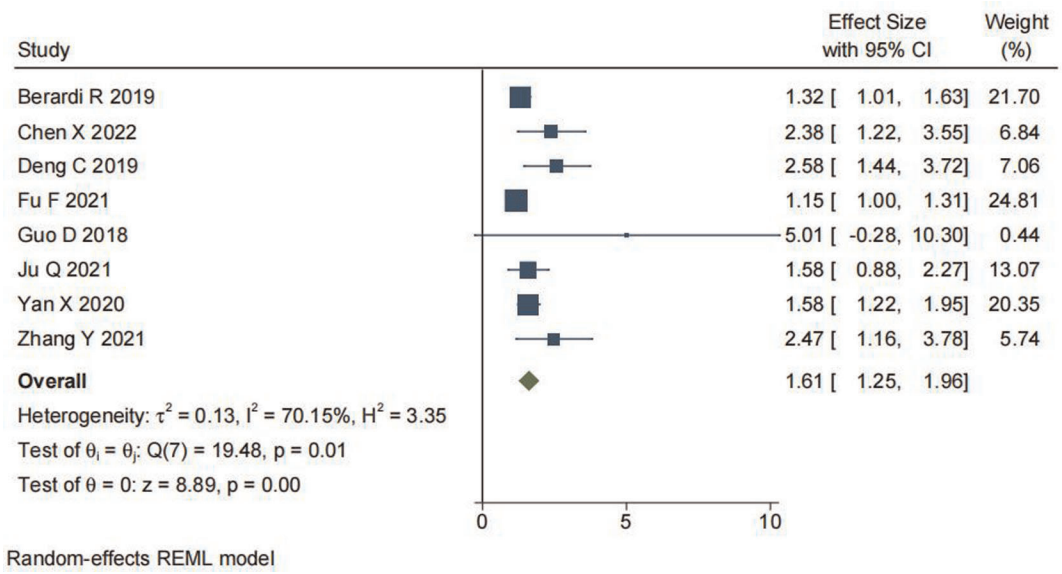

FIGURE 3 | Forest plot depicting the relationship between SII levels and PFS in NSCLC.

Li et al. (26), Tong et al. (29), Yucel et al. (32) and other results demonstrated that the median OS of patients with high SII level was obviously lower than that of patients with low SII level. In addition, this meta-analysis also observed that the SII index of NSCLC patients with higher pathological stages (II–III) was significantly higher than that of stage I patients, suggesting that SII index may be a risk factor for disease development in patients with NSCLC.

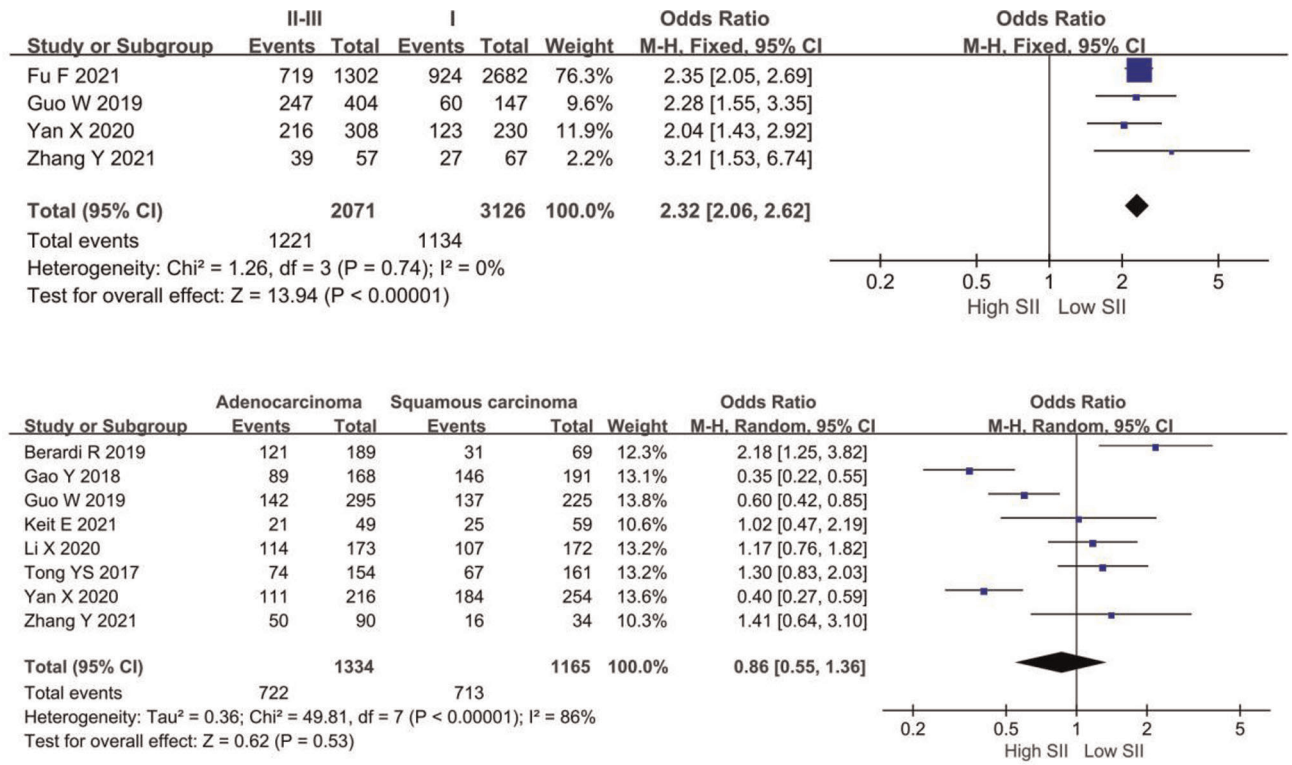

FIGURE 4 | Forest plot depicting the relationship between SII levels and clinicopathological characteristics of NSCLC patients.

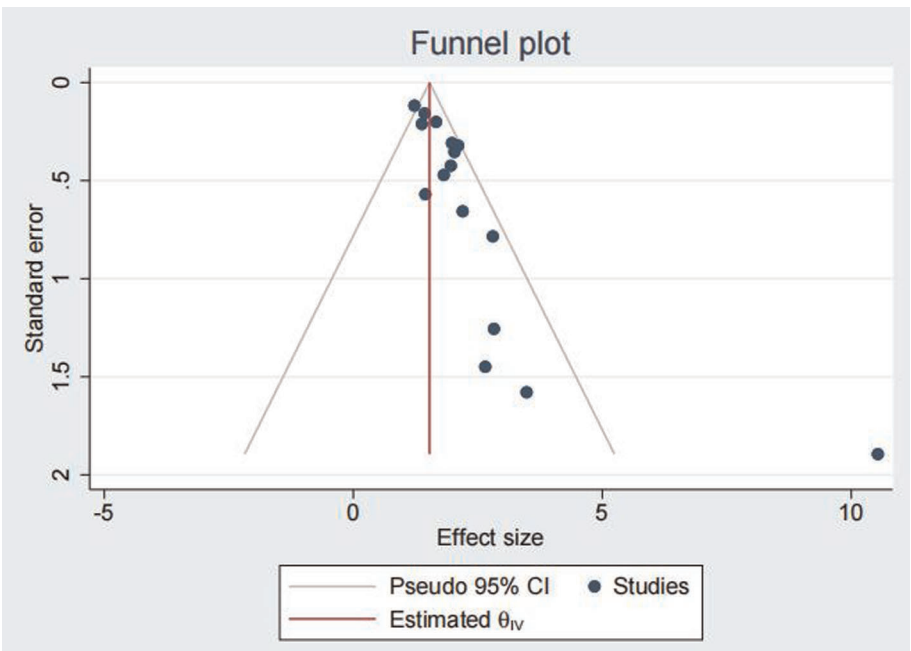

FIGURE 5 | Funnel plot, publication bias assessment.

We tried to do a comprehensive analysis, but there are still limitations to this study. First, treatment strategies not analyzed in this research may have influenced the results. Second, the included studies were limited to articles published in English and mostly from China, which may lead to publication bias. Third, the cutoff values used to determine high levels of SII also inconsistent. Finally, the sample size of the studies included in the analysis may have contributed to heterogeneity. However, this meta-analysis has proved an correlation between high levels of SII and clinicopathological factors in NSCLC. The results of this study may improve the prognosis of NSCLC. However, despite the robustness of our findings, caution is required in interpreting the validity of SII in NSCLC prognosis.

In conclusion, this meta-analysis identified pretreatment or preoperative SII index as a prognostic factor for OS and PFS in NSCLC patients. SII index may be an effective survival indicator of NSCLC. Larger multicenter studies are needed in the future to further verify the clinical application value of the SII index.

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.

AUTHOR CONTRIBUTIONS

WH is the mainly responsible for the writing, the research is completed by JW and data analysis of the article is completed by MJ. JL is responsible for the guidance of the entire research. The corresponding author is WH and he is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Early Predictive Value of NT-proBNP Combined With Echocardiography in Anthracyclines Induced Cardiotoxicity

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Objective: Determine the predictive value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) combined with echocardiography in the diagnosis of anthracyclines-induced chronic cardiotoxicity.

Methods: A total of 80 female breast cancer patients from January 2019 to October 2021 were included in our hospital. Twenty-six patients with cardiotoxicity were divided into the cardiac impairment group, and the 54 patients without cardiotoxicity were classified into the normal control group. NT-proBNP levels and cardiac echocardiography were measured before the start of the chemotherapy cycle, in cycle 3 of the chemotherapy, and after the chemotherapy cycle in all patients.

Results: After three cycles of chemotherapy and chemotherapy, the levels of NT-proBNP in patients of the two groups were significantly higher than those before chemotherapy ($P < 0.05$). The levels of NT-proBNP in the cardiac injury group after three cycles of chemotherapy and chemotherapy were higher than those in the normal control group at the same time point ($P < 0.05$). The LVEF of patients in the cardiac impairment group after chemotherapy was lower than that before chemotherapy, and the LVEF after chemotherapy was lower than that in the normal control group ($P < 0.05$). NT-proBNP had a negative correlation with LVEF ($r = -0.549$, $P < 0.001$). The AUC of NT-proBNP in combination with LVEF for predicting cardiotoxicity in our patient was 0.898(95%CI:0.829–0.966).

Conclusion: NT-proBNP combined with echocardiography has clinical significance in the detection of anthracyclines-induced cardiotoxicity, and it can detect early myocardial injury induced by anthracyclines, with early prediction value. It is important to protect heart function and judge prognosis.

Keywords: cardiac toxicity, anthracyclines, N-terminal B-type natriuretic peptide, cardiac ultrasound, early predictive value

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INTRODUCTION

Breast cancer is the most common malignant tumor among women in the world, and anthracycline, doxorubicin and other drugs are the most commonly used chemotherapy drugs after breast cancer surgical (1). anthracyclines drugs are widely used in the treatment of hematological malignancies and solid tumors, effectively reducing the mortality rate of malignant tumors and prolonging the overall survival period (2). anthracyclines, as a classic first-line chemotherapy drug, has dose-related cardiotoxicity. Most patients treated with anthracycline showed early or late cardiac insufficiency, and the main manifestations of ECG were arrhythmia, ST segment changes or conduction block (3, 4). At the same time, due to the limitation of anthracycline's cardiotoxicity, its cumulative dose in patients is greatly limited, and many patients stop chemotherapy because of cardiac dysfunction during chemotherapy. This directly affects the quality of life and the incidence of long-term cardiac death of patients receiving chemotherapy (5, 6). Therefore, early monitoring and prevention of anthracyclines-induced cardiotoxicity events are particularly important.

A nearly perfect diagnostic tool for evaluating anthracycline-associated cardiotoxicity needs to meet the characteristics of non-invasiveness, high sensitivity, and low cost. Left ventricular ejection fraction (LVEF) is a commonly used index to monitor ventricular systolic and diastolic function, which can be assessed by echocardiography. At the same time, echocardiography can intuitively show the anatomical structure and hemodynamic changes of the heart, and detect the systolic and diastolic functions of the heart (7). Many studies have shown that heart-specific biomarkers such as N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be valuable in identifying high-risk patients (8–10). The etection of NT-proBNP is convenient, quick and cheap. The purpose of this study is to study and effectively analyze the cardiotoxicity of anthracycline chemotherapy in breast cancer patients by using NT-proBNP and cardiac ultrasound monitoring, and to clarify the predictive value of non-invasive evaluation tools in preventing cardiotoxicity, and to guide clinical practice. The report is shown below.

DATA AND METHODS

General Information

A total of 80 female breast cancer patients from January 2019 to October 2021 were included in our hospital. All patients ranged in age from 30–75 years and weighed 44–80 kg, including 23 patients with hypertension, 19 patients with diabetes and 22 patients without basic disease. Among these 80 patients, 26 patients with cardiotoxicity were classified as the cardiac impairment group, and 54 patients without cardiotoxicity were classified as the normal control group. Diagnostic criteria for cardiotoxicity events are a decrease in LVEF ≥10% measured by radionuclide myocardial perfusion imaging during or at the end of chemotherapy, or an absolute value of LVEF measured by radionuclide after chemotherapy ≤50%. This study was approved by the hospital ethics committee and the patients' informed consent was obtained.

Inclusion Criteria

(1) complete 6 cycles of chemotherapy; (2) those who have not received chemotherapy with other drugs in the past; (3) normal function of liver and kidney; (4) anthracycline antineoplastic drugs are mainly used in chemotherapy; (5) no obvious abnormality was found in echocardiography before chemotherapy.

Exclusions

(1) previous coronary heart disease, valvular heart disease, congenital heart disease, malignant arrhythmia, etc.; (2) before entering the group, receiving chemotherapy or local radiotherapy; (3) withdrawal of drugs due to poor curative effect or intolerance of anthracycline drugs; (4) combined with other cardiotoxic drugs.

Research Methods

Patients were treated with adjuvant chemotherapy with 6 cycles of pirarubicin + cyclophosphamide + fluorouracil or 6 cycles of epirubicin + docetaxel. NT-proBNP levels and cardiac echocardiography were measured before the start of the chemotherapy cycle, in cycle 3 of the chemotherapy, and after the chemotherapy cycle in all cases.

Five milliliters of venous blood was drawn from patients in the morning under fasting conditions, centrifuged at 3500 r/min for 10 min to separate plasma, and NT-proBNP was measured using a chemiluminescent immunoassay.

Echocardiography: Philips IE33 color Doppler ultrasound diagnostic apparatus, s5-1 ultrasound probe with probe frequency of 2.5–4.0 MHz. The patient was placed in the left inclined 30° decubitus position and all sections of the heart were routinely explored. The cardiac morphology, atrioventricular size, valvular activity and left ventricular contraction were observed by two-dimensional echocardiography. The end-diastolic diameter (LVDd) and end-systolic diameter (LVDs) were measured. The left ventricular LVEF was measured by two-plane modified Simpson's method using a four-chamber cusp incision.

Statistical Methods

SPSS22.0 software was used for processing. The experimental data were in accordance with the normal distribution, and the measurement data were expressed as mean standard deviation ($\bar{x} \pm s$). The t test was used for pairwise comparison. The count data were expressed as (%) and the comparison was performed using χ^2 test. Pearson's method was used to analyze the correlation between NT-proBNP and LVEF. The

ROC curve was used to evaluate the predictive value of NT-proBNP and LVEF for cardiac toxicity events. The test level was $\alpha = 0.05$, and $P < 0.05$ 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 age, weight, basic disease and tumor type between the two groups ($P > 0.05$). As shown in **Table 1**.

Changes of NT-proBNP Level in Two Groups

The levels of NT-proBNP in patients of the two groups after three cycles of chemotherapy and chemotherapy were significantly higher than those before chemotherapy ($P < 0.05$). The levels of NT-proBNP in the cardiac impairment group after three cycles of chemotherapy and chemotherapy were higher than those in the normal control group at the same time point ($P < 0.05$). As shown in **Figures 1**, **2**.

Changes of Echocardiography in Patients of Two Groups

There was no significant change in LVDd and LVDs values before and during the 3rd cycle of chemotherapy and after chemotherapy between the two groups, and there was no difference between the two groups ($P > 0.05$). The LVEF of patients in the cardiac impairment group after chemotherapy was lower than that before chemotherapy, and the LVEF after chemotherapy was lower than that in the normal control group, and the differences were statistically significant ($P < 0.05$). As shown in **Figures 3–6**.

Correlation Between NT-proBNP and LVEF

Pearson correlation analysis showed a negative correlation between NT-proBNP and LVEF ($r = -0.549$, $P < 0.001$). As shown in **Figure 7**.

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

Group	*N*	Age (years)	Body weight (kg)	Basic disease (case)		Tumor type (case)	
				hypertension	diabetes	Invasive ductal carcinoma	Invasive lobular carcinoma
Cardiac impairment group	26	52.07 ± 5.96	59.86 ± 7.52	8	7	16	10
Normal control group	54	53.84 ± 6.27	60.28 ± 7.39	15	12	39	15
t/χ^2 value		1.201	0.237	0.019		0.932	
P value		0.233	0.814	0.890		0.334	

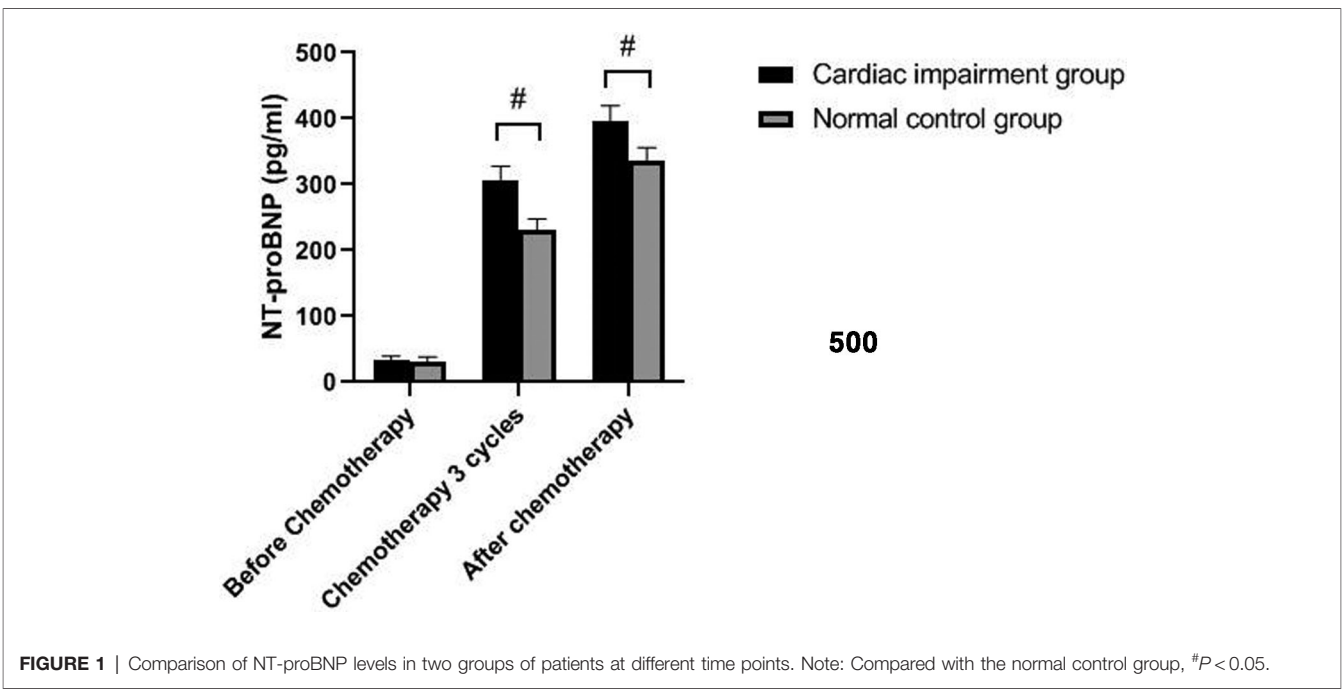

FIGURE 1 | Comparison of NT-proBNP levels in two groups of patients at different time points. Note: Compared with the normal control group, $^{\#}P < 0.05$.

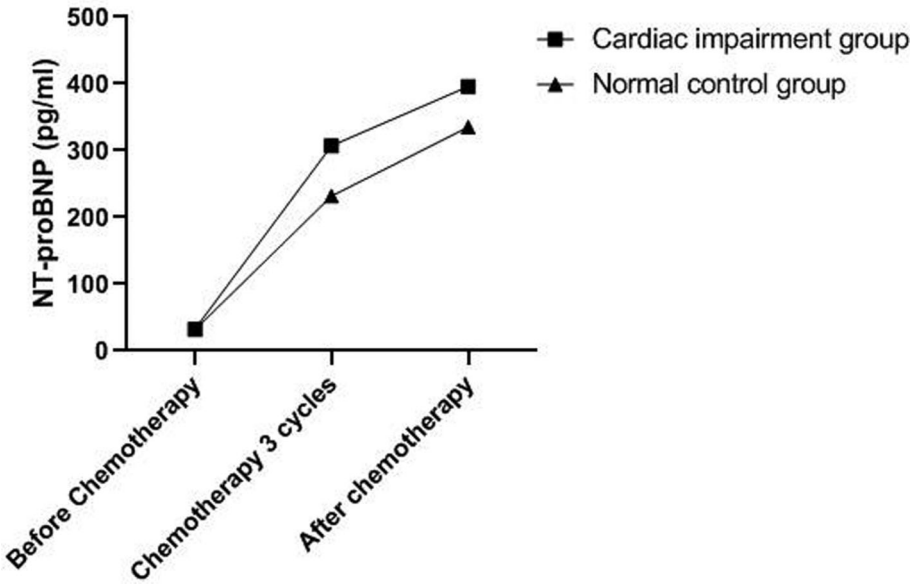

FIGURE 2 | Change trend of NT-proBNP level in patients of two groups.

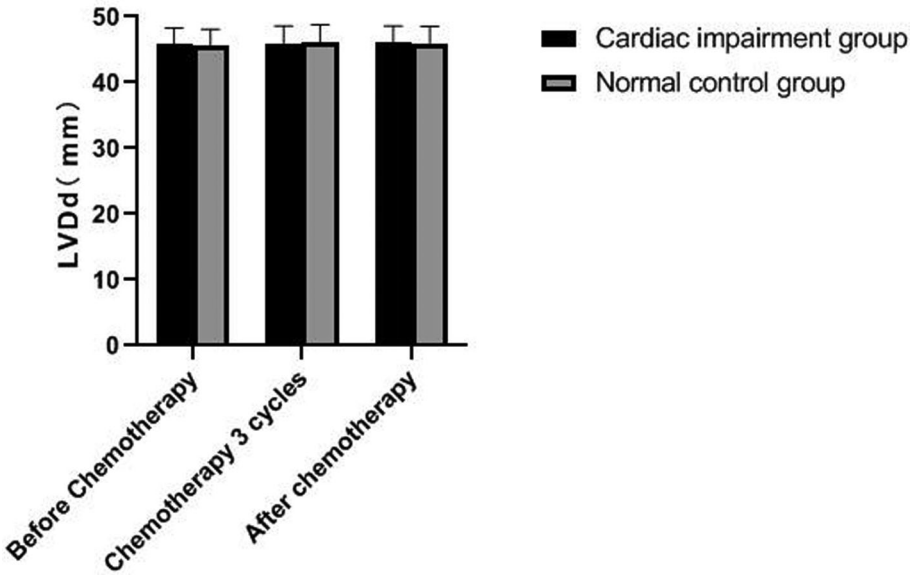

FIGURE 3 | Comparison of LVDd values between the two groups at different time points.

Prediction Value of NT-pro BNP and Echocardiography Monitoring on Cardiac Toxicity in Patients

The AUC of NT-proBNP in combination with LVEF for predicting cardiotoxicity in our patient was 0.898 (95% CI:0.829–0.966), higher than the AUC of NT-proBNP of 0.780 (95% CI: 0.660–0.901) and LVEF of 0.675 (95% CI: 0.526–0.823). As shown in **Figure 8**.

DISCUSSION

Anthracyclines is a kind of cytotoxic drug, which has been widely used in anti-tumor therapy. It can significantly improve the survival rate of patients with breast cancer and other malignant tumors, and has important positive value in prolonging their survival (11). However, in cancer patients treated with anthracyclines chemotherapy drugs, due to the

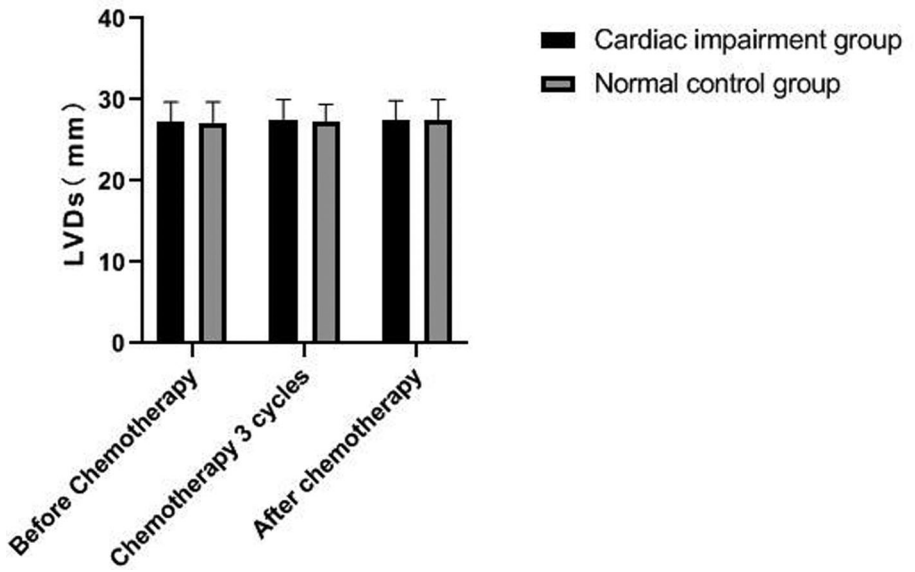

FIGURE 4 | Comparison of LVDs values between the two groups at different time points.

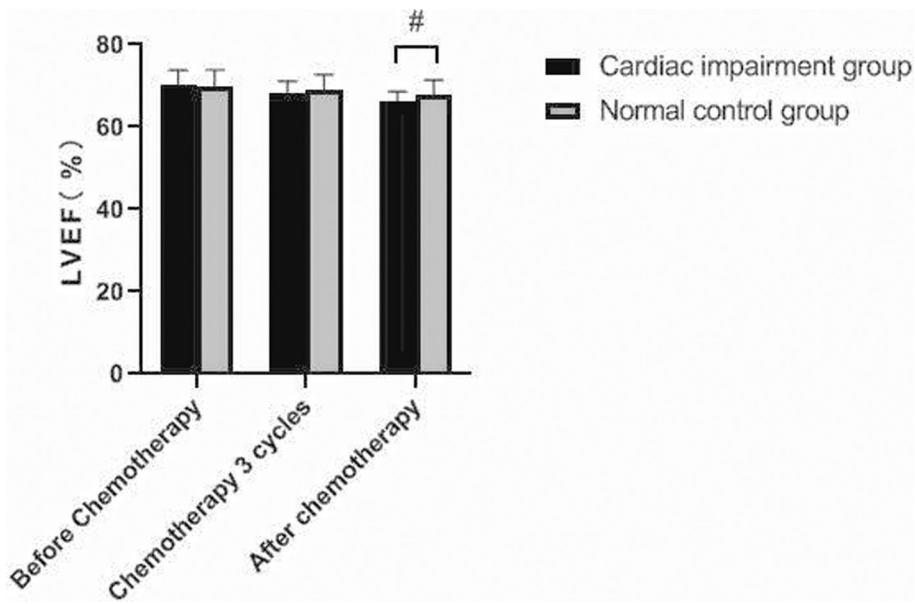

FIGURE 5 | Comparison of LVEF values between the two groups at different time points. Note: Compared with the normal control group, $^{\#}P < 0.05$.

cardiotoxicity of the drug metabolite 1,3-dihydro derivatives, and the influence of susceptible factors such as oxygen free radicals, calcium overload and mitochondrial damage, the excessive accumulation can lead to serious cardiotoxicity, especially in patients with underlying heart diseases in the past (12). At present, more and more evidences (citations) have supported the cardiotoxicity of anthracyclines and their clinical relevance (13–15). The study found that in patients after treatment with anthracyclines, drug-induced congestive heart failure and cardiomyopathy mostly occurred within 0–231d after treatment, and the severity depended on the cumulative dose (16).

The cardiotoxicity caused by anthracyclines is generally divided into acute, chronic and delayed, which represent

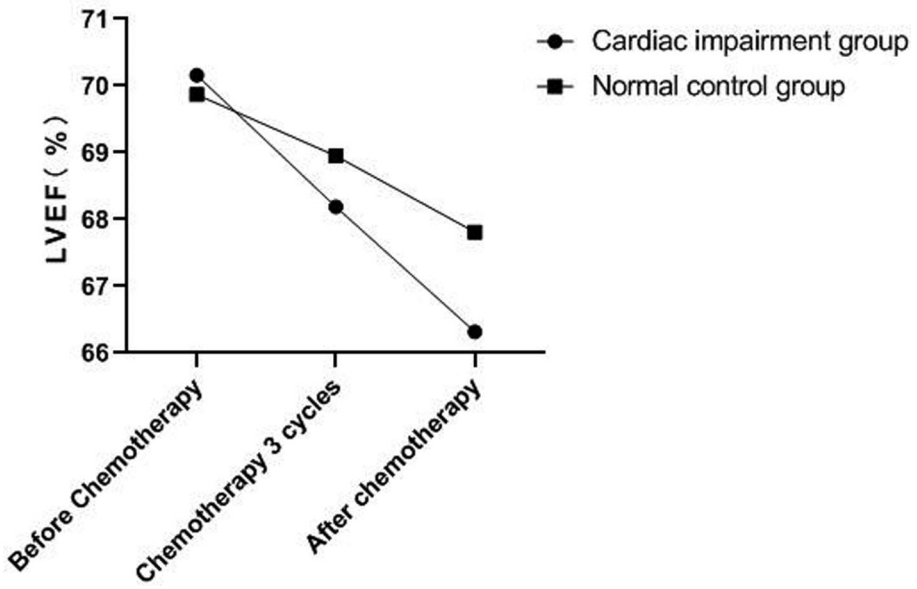

FIGURE 6 | LVEF change trend of patients in two groups.

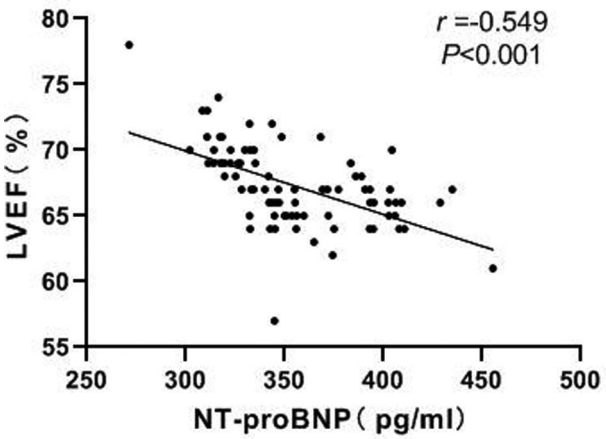

FIGURE 7 | Correlation between NT-proBNP and LVEF.

different pathological processes of myocardial injury. Because the early clinical manifestations of cardiotoxicity are not obvious, once it is diagnosed, obvious myocardial lesions, with poor prognosis and high mortality (17–19). Therefore, during chemotherapy, it is necessary to monitor the cardiac status and toxicity of anthracyclines, find out and intervene in time, and improve the survival rate of patients after chemotherapy.

B-type natriuretic peptide (BNP) is mainly synthesized and secreted by ventricles and contains 32 amino acids, which is a kind of polypeptide cardiac neurohormone. Its release is closely related to ventricular volume expansion and ventricular pressure load, and it can reflect changes of left ventricular function. It is a good biochemical index for clinical diagnosis of heart failure, and reflects the grading of heart function (20). NT-proBNP and BNP were derived from the same precursor. The concentration of BNP can not only reflect the severity of cardiac insufficiency, but also its inactive product NT-proBNP has the same effect. Compared with BNP, NT-Pro BNP has a longer half-life and is more stable, with higher sensitivity and specificity, thus making it easier to achieve the standardization of detection (21–23). This study showed that the levels of NT-proBNP in the two groups were significantly higher after three cycles of chemotherapy and after chemotherapy, and the level of NT-proBNP in the cardiac damage group were significantly higher than those in the normal control group. These results suggest that NT-proBNP played an important role in the early detection of anthracycline cardiotoxicity. Romano et al. (24) studied the predictive value of serum NT-proBNP on long-term cardiotoxicity in low-dose chemotherapy regimens for breast cancer. Through the follow-up observations of 3 months, 6 months and 12 months, the left wentricular function damage in the group with continuously increased of serum NT-proBNP was significantly different from that in the group without increased serum NT-proBNP.

At present, left ventricular function can be evaluated by various non-invasive imaging techniques, including echocardiography. Echocardiography has the advantages of price advantage, non-invasive, simple operation and good repeatability, etc. It can not only visually display the shape, structure and movement of the heart, but also quantitatively display the systolic and diastolic function of the heart. It has been widely used in clinical and research for the detection of cardiac function and early assessment of myocardial damage (25, 26). There are many indexes for evaluating cardiac

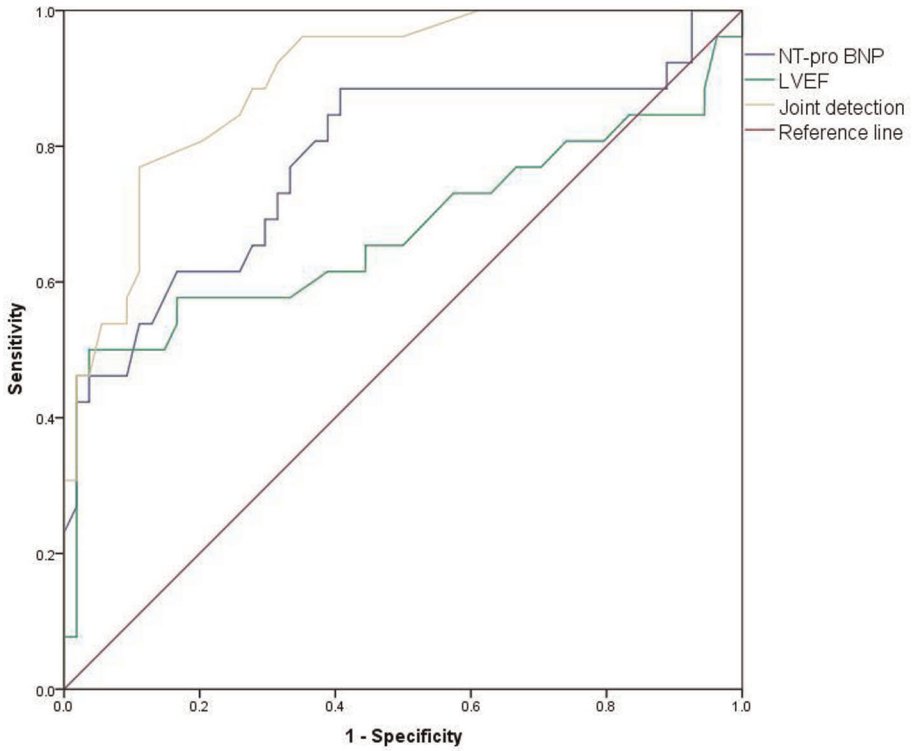

FIGURE 8 | ROC curve of predictive value of NT-proBNP and echocardiography monitoring on cardiotoxicity of patients.

function. Clinically, LVEF is often used to estimate the systolic function of the left wentricle. The decline of LVEF represents irreversible damage, which is of great significance in the evaluation of left ventricular function (27). The results of this study show that the LVEF value of the cardiac impairment group after chemotherapy was lower than that of the normal control group, but the measurement method of LVEF by two-dimensional echocardiography is easy to change, and the confidence interval is 11%. In this study, LVEF decreased by 3.84% after chemotherapy, Considering the individual differences of patients, it cannot be used as a specific indicator of left ventricular systolic function decline in breast cancer patients after anthracyclines therapy.

LVEF is not very sensitive to the early detection of subclinical cardiac injury, and its parameter changes depend on myocardial contractility, preload and afterload, so it is less specific. Further analysis is needed in combination with other clinical indicators (28). Analysis of the value of NT-proBNP and LVEF in predicting cardiotoxic events in patients revealed that AUC 0.898(0.829–0.966) of NT-proBNP combined with LVEF was significantly higher than AUC 0.780 (0.660–0.901) of NT-proBNP and AUC 0.675 (0.526–0.823) of LVEF. The results confirmed the value of NT-proBNP combined with echocardiography in the early diagnosis of cardiac toxicity.

In summary, NT-proBNP combined with echocardiography monitoring has clinical significance in detecting anthracyclines-induced cardiotoxicity, and it can detect myocardial injury caused by anthracyclines at an early stage, which has the value of early prediction and is of great significance in protecting cardiac function and judging 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 This study was approved by the ethics committee of our hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QW is the mainly responsible for the writing, research and data analysis of the article. YD is responsible for the guidance of the entire research. The corresponding author is CH and he is ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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Application of Gestational Blood Glucose Control During Perinatal Period in Parturients with Diabetes Mellitus: Meta-Analysis of Controlled Clinical Studies

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Background: Gestational diabetes mellitus (GDM) is a common metabolic disorder. Hyperglycemia may cause gestational hypertension, increase the probability of infection, abnormal embryonic development, and increase the abortion rate. Oral hypoglycemic drugs may be another effective means of blood glucose control in addition to insulin injection. We included controlled clinical studies for meta-analysis to understand the effect of oral hypoglycemic drugs in gestational diabetes.

Methods: The databases were searched with the keywords "*Glycemic control*" & "*gestational diabetes*": Embase (January, 2000–August, 2021), Pubmed (January, 2000–August, 2021), Web of Science (January, 2000–August, 2021), Ovid (January, 2000–August, 2021), and *ClinicalTrials.org* to obtain the randomized controlled trial (RCT) literatures related to the treatment of gestational diabetes with oral hypoglycemic drugs, after screening, the *R* language toolkit was used for the analysis.

Results: A total of 10 articles with a total of 1,938 patients were included, 7 studies used *metformin* as an hypoglycemic agent. Meta-analysis showed that oral *metformin* had no significant difference in fasting blood glucose levels after the intervention compared with insulin injection [$MD = -0.35$, 95%CI(–0.70,1.40), $Z = 0.66$, $P = 0.51$], with no significant difference in postprandial blood glucose levels after intervention [$MD = -2.20$, 95%CI(–5.94,1.55), $Z = -1.15$, $P = 0.25$], and no statistical difference in glycosylated hemoglobin [$MD = 0.10$, 95%CI(–0.17,–0.04), $Z = -0.94$, $P = 0.31$]. *Metformin* was more conducive to reducing maternal weight during pregnancy than insulin [$MD = -1.55$, 95%CI(–2.77,–0.34), $Z = -2.5$, $P = 0.0123$], *metformin* reduced the abortion rate compared with insulin [$RR = 0.81$, 95%CI(0.63,1.05), $Z = -2.61$, $P = 0.015$], and reduced cesarean section rate [$RR = 0.66$, 95%CI(0.49,0.90), $Z = -3.95$, $P = 0.0001$].

Discussion: The application of oral hypoglycemic drug *metformin* in blood glucose control of gestational diabetes can play a hypoglycemic effect equivalent to insulin

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and can control the weight of pregnant women, reduce the rate of abortion and cesarean section, and improve pregnancy outcomes.

Keywords: gestational diabetes mellitus, glycemic control, insulin, oral hypoglycemic agents, meta-analysis

INTRODUCTION

Gestational diabetes mellitus (GDM) is a common metabolic disorder that refers to varying degrees of abnormal glucose metabolism that occurs for the first time during pregnancy (1). It has been reported its incidence ranges from 1.32% to 3.75%. Gestational diabetes is specific, and the parturient has no history of diabetes before pregnancy (2). But due to a variety of physiological changes during pregnancy, the reabsorption of glucose by the renal tubules is weakened, so that the sugar content in the urine is high, which in turn can cause diabetes, which is gestational diabetes (3). The effect of gestational diabetes on maternal and fetal outcomes is related to the degree of glycemic control (4). Hyperglycemia may cause maternal gestational hypertension, increase the chance of infection, and may also cause abnormal embryonic development and increase the rate of miscarriage (5). Some patients can achieve the expected blood glucose range through lifestyle intervention, including changing lifestyle, reasonable diet, appropriate exercise, prevention of infection, and regular testing of blood glucose levels (6). However, some patients fail to reach the ideal blood glucose level and still need drugs for intervention (7). Injection of insulin is the most common method of blood glucose control. Besides, compared with insulin, that oral hypoglycemic agent is convenient to use and ideal for hypoglycemic effect. And the efficacy and safety of oral hypoglycemic drugs in GDM patients have been reported, but there is still a lack of systematic evaluation and comprehensive analysis in clinical practice (8). In order to understand the efficacy of oral hypoglycemic agents in the treatment of gestational diabetes, we included controlled clinical studies for meta-analysis to provide evidence for the clinical treatment of this disease.

METHOD

Inclusion of Studies

We followed the PICOS principle to develop inclusion criteria (P-participants, I-intervention, C-control, O-outcome, S-study type): (1) Study type: The literatures published after January, 2000 were limited to randomized controlled trials (RCTs), the language was English, and individual cases, guidelines, systematic analysis, and case-control studies of non-RCT studies were excluded. (2) Study subjects: The participants were pregnant women aged 18–45 years, 14–35 weeks of gestational age (GA), diagnosed with diabetes (we did not limit pregnant women to type 1 or type 2 diabetes), fasting blood glucose ≥7.0 mmol/L [126 mg/dl], and HbA1c ≥48 mmol/mol [≥6.5%] (9)). (3) Grouping and control: randomization must be taken in the study, we do not limit the randomization method (computer random number or manual random number), we do not limit the allocation concealment and blind method, but we will perform the quality assessment of the literature. (4) Intervention method: All patients were given routine prenatal care and iron, calcium, folic acid, and vitamin D supplementation after enrollment, all patients were given regulation from the diet and lifestyle, if the regulation failed (fasting blood glucose higher than 95 mg/dl and postprandial blood glucose higher than 40 mg/dl), the intervention was carried out. The control group was given conventional insulin injection, and the observation group was given hypoglycemic drugs (biguanides or Glinides). (5) Outcome indicators: The literature must provide observation indicators and statistical methods, provide outcome data, or indicate the accessible storage address of data.

Literature Search Strategy

Search database: Embase (January, 2000–August, 2021), Pubmed (January, 2000–August, 2021), Web of Science (January, 2000–August, 2021), Ovid (January, 2000–August, 2021), and *ClinicalTrials.org*. The search method was keyword rapid search, and the input keywords were: "*Glycemic control*" and "*gestational diabetes*."

Selection of Literatures

SCREEN and inclusion of articles were done independently by two researchers, and in case of discrepancies during this process, a third person was consulted for agreement. After the initial search, we combined all retrieved articles with ". *Enw*" is reserved with suffix name and is managed uniformly after imported by Endnote X9 software. The software menu of "*References*" -> "*find duplicates*" allows the software to de duplication the retrieved literatures, and then browse the title and author of the literatures by manual method. For the literatures with a similar title and the same author, browse the abstract of the literatures. If the time, place, and number of participants of the study coincide, it is considered that the study is repeated. We only retain the literatures with the later publication time. By reading the title and abstract of the literature for preliminary screening, we remove the literature that obviously does not meet the inclusion requirements; for the remaining literature, we use the "*Find full text*" function of the software to obtain the full text of the literature. For some unobtainable literature, we search the database of the literature or the publication magazine to obtain the full text of the literature; if the literature cannot be obtained through the network, we try to contact the original author (Find via email) to obtain the original text; if it still fails, we exclude the literature. Literatures that were obtained were read and checked for completeness of literature data, and articles with missing data were excluded.

Data Extraction

After obtaining the full text of the literature, we use the self-made data table to extract the data information in the literature. Include the following contents: (1) Basic data of the literature: publication time, author, and region; (2) Characteristics of the study subjects: patient age, race, BMI, family history of diabetes, whether the first pregnancy, hypertension during pregnancy, fasting blood glucose, blood glucose (breakfast, lunch, and dinner), and glycosylated hemoglobin (HbA1c); (3) Literature intervention methods: grouping method, number of participants in each group, grouping intervention method, intervention time, and follow-up time; (4) Outcome data.

Outcome Indicators

Blood glucose control indicators: (a) fasting glycemia; (b) postprandial glycemia after lunch; (c) HbA1c postpartum;

Maternal situation and obstetric outcome indicators: (a) maternal weight gain; (b) abortion rate; (c) cesarean deliveries.

Statistical Methods

We used *R* language development environment (R version 4.1.2 released by "The R foundation for statistical computing") to summarize and analyze the data of multiple studies. We entered the key data into *CSV* files, read the data under *RGUI*, and used Meta tool of *RGUI* environment (metabin/metacont/metainf/metabias/funnel) to obtain the summary data of continuous variables and binary variables. *MD* (mean, difference) effect size was used for continuous variables, and *RR* (Risk Ratio) effect size was used for dichotomous variables, with 95%CI as the confidence interval, and $P < 0.05$ was considered statistically significant. For the heterogeneity among different studies, I^2 test was used for the analysis and *Q* check. The heterogeneity was not statistically significant when $I^2 < 50\%$ or $P \geq 0.1$, that means there was no (or acceptable) heterogeneity among the literatures, otherwise it indicated that there was heterogeneity among the literatures; if there was no statistical heterogeneity among the literatures, the fixed-effect model was used; if there was heterogeneity, the random effect model was used; the analysis results were presented in forest plot; publication bias was reported in the funnel plot.

Heterogeneity Investigation and Sensitivity Analysis

We try to analyze the heterogeneous literatures to determine the source of heterogeneity.

RESULTS

Literature Screening Results

In this search, 1,101 literatures were initially searched, 10 literatures (10–19) were finally included, 1,938 patients were included, and we listed three typical cases for exclusion: (a) the literature (20) was a retrospective observational study, so it was excluded; (b) the literature (21) was a pilot study, the number of patients included was too small, 14 cases in total; (c) the literature (22) was an observational study, without comparative data. The selection flowchart is shown in **Figure 1**.

Basic Characteristics of Literatures

The published years of the studies included in this meta-analysis ranged from 2012 to 2021. The study subjects were all pregnant women with diabetes, aged 18–45 years. The minimum number of patients in the group was 32, and the maximum number was 253. Among them, three studies used *glyburide* as a hypoglycemic drug, while seven studies used *metformin* as a hypoglycemic drug, as shown in **Table 1**.

Bias Risk Assessment and Quality Evaluation of the Included Literatures

The use of Cochrane handbook for systematic reviews of interventions for risk of bias assessment in the included literature is shown in **Table 2**, all literatures had a detailed description for randomization and drop-out cases, without selective reporting of risk of bias and other risks. The literatures (10, 16) reported blindness, while the literatures (18) did not specify allocation concealment, which may cause selective risk.

Meta-Analysis Results

Fasting Blood Glucose (mg/dl)

A total of six literatures (10, 14–17, 19) reported the fasting blood glucose of pregnant women after blood glucose control intervention, with heterogeneity between the literatures ($I^2 = 67\%$, $P < 0.01$). The random effect mode combined analysis was used. There was no statistically significant difference in fasting blood glucose level after intervention between hypoglycemic drugs and insulin [$MD = -0.67$, 95%CI (-3.08,1.75), $Z = 0.87$, $P = 0.25$].

The study was further divided into two subgroups according to hypoglycemic drugs (*metformin* group and *glibenclamide* group). *Metformin* included five literatures. There was no statistically significant heterogeneity between the literatures ($I^2 = 0\%$, $P = 0.80$). The pooled effect size for fasting blood glucose level after the intervention compared with insulin was [$MD = -0.35$, 95%CI(-0.70,1.40), $Z = 0.66$, $P = 0.51$]. The *glibenclamide* group contained only one article, and its effect size on fasting blood glucose compared with insulin was [$MD = -9.40$, 95%CI(-14.49,-4.31), $Z = -3.62$, $P = 0.0003$], as shown in **Figure 2**.

Postprandial Glycemia After Lunch (mg/dl)

A total of six literatures (10, 14–17, 19) reported the blood glucose content of pregnant women after lunch after blood glucose control intervention, with heterogeneity between the literatures ($I^2 = 74\%$, $P < 0.01$). The random effects model combined analysis was used. There was no statistically significant difference in postprandial blood glucose level after intervention between hypoglycemic drugs and insulin [$MD = -2.60$, 95%CI(-5.75,0.56), $Z = -1.61$, $P = 0.11$].

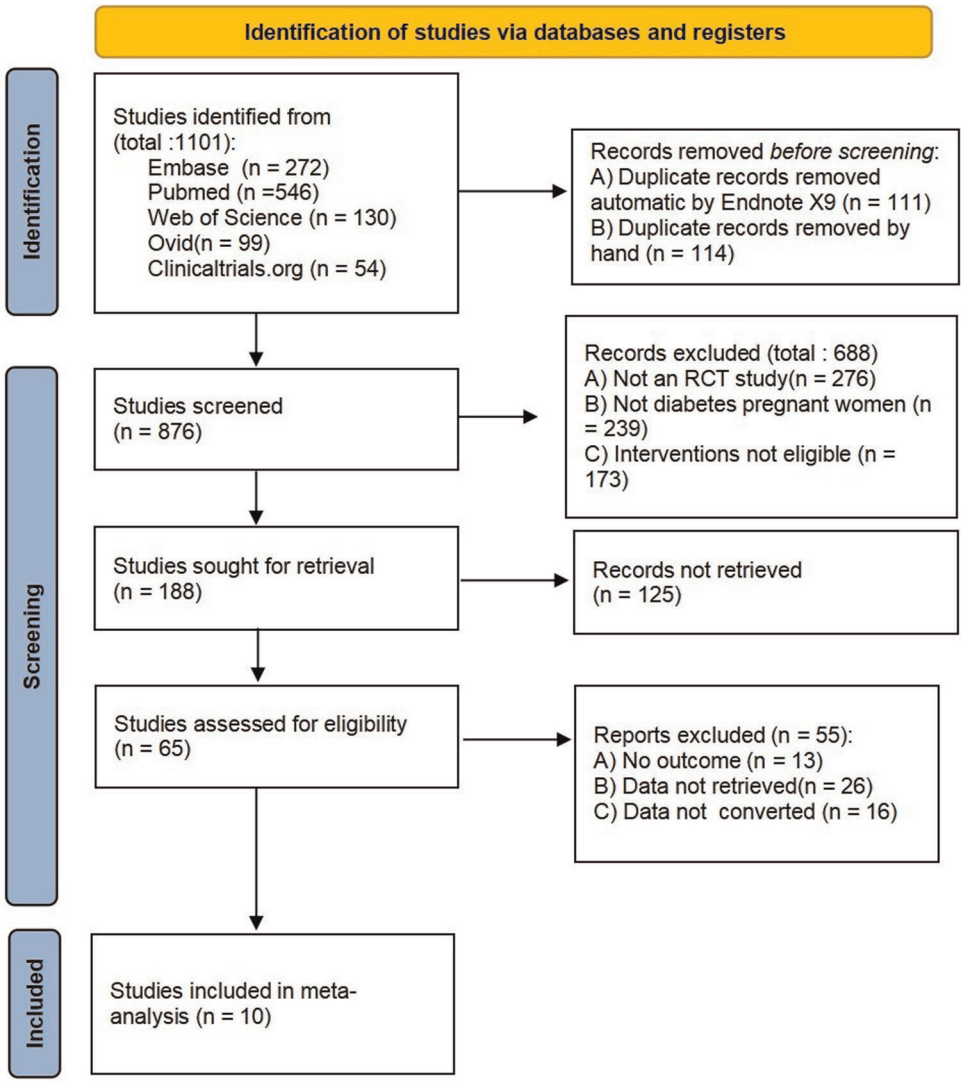

FIGURE 1 | The selection flow chart.

The patients were further divided into two subgroups according to hypoglycemic drugs (*metformin* group and *glibenclamide* group). *Metformin* included five literatures. There was statistically significant heterogeneity between the literatures ($I^2 = 76\%$, $P < 0.01$). The pooled effect size for postprandial blood glucose level after the intervention compared with insulin was [$MD = -2.20$, 95%CI(−5.94,1.55), $Z = -1.15$, $P = 0.25$]. There was only one article in the *glibenclamide* group, and the effect size on blood glucose compared with insulin was [$MD = -4.69$, 95%CI(−8.29, −1.09)], as shown in **Figure 3**.

Glycosylated Hemoglobin (HbA1c) (%)

A total of four literatures (10, 12, 15, 19) reported the changes of glycated hemoglobin index after blood glucose control. All studies used *metformin* as the hypoglycemic agent. Since there was no statistical heterogeneity between the literatures ($I^2 = 45\%$, $P = 0.14$), the fixed-effect mode combined analysis was used. There was no statistical difference in glycosylated hemoglobin between *metformin* and insulin for blood glucose control [$MD = 0.10$, 95%CI(−0.17,−0.04), $Z = -0.94$, $P = 0.31$], as shown in **Figure 4**.

Maternal Weight Gain (kg)

Four literatures (10, 11, 15, 19) reported maternal weight gain indicators after glycemic control with *metformin*. Cause there was statistical heterogeneity between the literatures ($I^2 = 87\%$, $P < 0.01$), the random effects model combined analysis was used. There was a statistical difference in maternal weight gain between *metformin* and insulin for glycemic control [$MD = -1.55$, 95%CI(−2.77,−0.34), $Z = -2.5$, $P = 0.0123$], as shown in **Figure 5**.

TABLE 1 | Basic characteristics, intervention measures, follow-up time, and outcome indicators of the included literatures.

Author	Year of publication	Women age (years)	BMI (kg/m^2)	Population (E/C)	Intervention group	Control group	Outcome indicators
Picón-César MJ et al. (10)	2021	34.86 ± 4.83	30.42 ± 5.42	100/100	Metformina Sandoz 850 mg/d, maximum 2,550 mg/d	Insulin 0.1 IU/kg/meal	(a) (b) (c) (d) (e) (f)
Kulshrestha V et al. (11)	2021	29.7 ± 4.4	25.5 ± 4.0	49/50	Metformin 1,000 mg twice daily	Insulin 0.1 IU/kg/meal	(d) (f)
Feig DS et al. (12)	2016	34.7 ± 5.0	35.0 ± 7.1	253/249	Metformin 1,000 mg twice daily	Insulin 0.1 IU/kg/meal	(c) (e) (f)
Casey BM et al. (13)	2015	31.3 ± 6	29.0 ± 4.8	189/186	Glyburide maximum of 20 mg per day	Insulin 0.1 IU/kg/meal	(d) (e) (f)
Beyuo T et al. (14)	2015	33.51 ± 4.67	33.47 ± 6.95	113/117	Metformin start dose 500 mg/d, max 2,500 mg/d	Insulin 0.1 IU/kg/meal	(a) (b)
Ainuddin J et al. (15)	2015	30.6 ± 2.9	N/A	43/75	Metformin start dose 500 mg/d, max 2,500 mg/d	Insulin 0.1 IU/kg/meal	(a) (b) (c) (d) (e)
Mirzamı M et al. (16)	2015	29.50 ± 4.06	N/A	37/59	1.25 mg glyburide with morning meal	Insulin 0.4 unit/kg	(a) (b)
Spaulonci CP et al. (17)	2013	31.93 ± 6.02	31.96 ± 4.75	47/47	Initial metformin dose of 1,700 mg/d (850 mg three times a day)	Insulin 0.4 unit/kg	(a) (b)
Tempe A et al. (18)	2013	N/A	N/A	32/32	Glyburide 2.5 mg orally as the initial dose	Insulin 0.4 unit/kg	(e) (f)
Niromanesh S et al. (19)	2012	30.7 ± 5.5	28.1 ± 4.0	80/80	initial metformin dose of 500 mg	Insulin 0.7 U/kg/d	(a) (b) (c) (d) (f)

Abbreviation: E indicates the intervention group and C indicates the control group.
Outcomes: (a) Fasting blood glucose; (b) Postprandial glycemia after lunch; (c) HbA1c; (d) Maternal weight gain; (e) Abortion rate; (f) Cesarean section rate.

TABLE 2 | Risk of bias assessment and quality evaluation based on Cochrane Collaboration.

Study	Random sequence generation	Classification hiding	Blind method	Data integrity	Optional reporting	Other bias	Quality evaluation
Picón-César MJ et al. (10)	Low	Low	Unclear	Low	Low	Low	B
Kulshrestha V et al. (11)	Low	Low	Low	Low	Low	Low	A
Feig DS et al. (12)	Low	Low	Low	Low	Low	Low	A
Casey BM et al. (13)	Low	Low	Low	Low	Low	Low	A
Beyuo T et al. (14)	Low	Low	Low	Low	Low	Low	A
Ainuddin J et al. (15)	Low	Low	Low	Low	Low	Low	A
Mirzamı M et al. (16)	Low	Low	Unclear	Low	Low	Low	B
Spaulonci CP et al. (17)	Low	Low	Low	Low	Low	Low	A
Tempe A et al. (18)	Low	Unclear	Low	Low	Low	Low	B
Niromanesh S et al. (19)	Low	Low	Low	Low	Low	Low	A

Abortion Rate

Three literatures (10, 12, 15) reported the indicators of maternal abortion rate after using *metformin* for blood glucose control. Cause there was no statistical heterogeneity between the literatures ($I^2 = 8\%$, $P = 0.34$), the fixed effect mode combined analysis was used. There was statistical difference in maternal abortion rate between *metformin* and insulin for blood glucose control [$RR = 0.81$, 95%CI(0.63,1.05), $Z = -2.61$, $P = 0.015$].

Two literatures (13, 18) reported the indicators of maternal abortion rate after using *glibenclamide* for blood glucose control. Cause there was no statistical heterogeneity between the literatures ($I^2 = 0\%$, $P = 0.57$), the fixed effect mode combined analysis was used. There was no statistical difference in maternal abortion rate between *glibenclamide* and insulin for blood glucose control [$RR = 1.21$, 95%CI (0.81,1.79), $Z = 0.93$, $P = 0.35$], as shown in **Figure 6**.

Cesarean Section Rate

Three literatures (10, 11, 19) reported the indicators of cesarean section rate of parturients after glycemic control with *metformin*. Cause there was statistical heterogeneity between the literatures ($I^2 = 50\%$, $P = 0.14$), the random effects model was used for

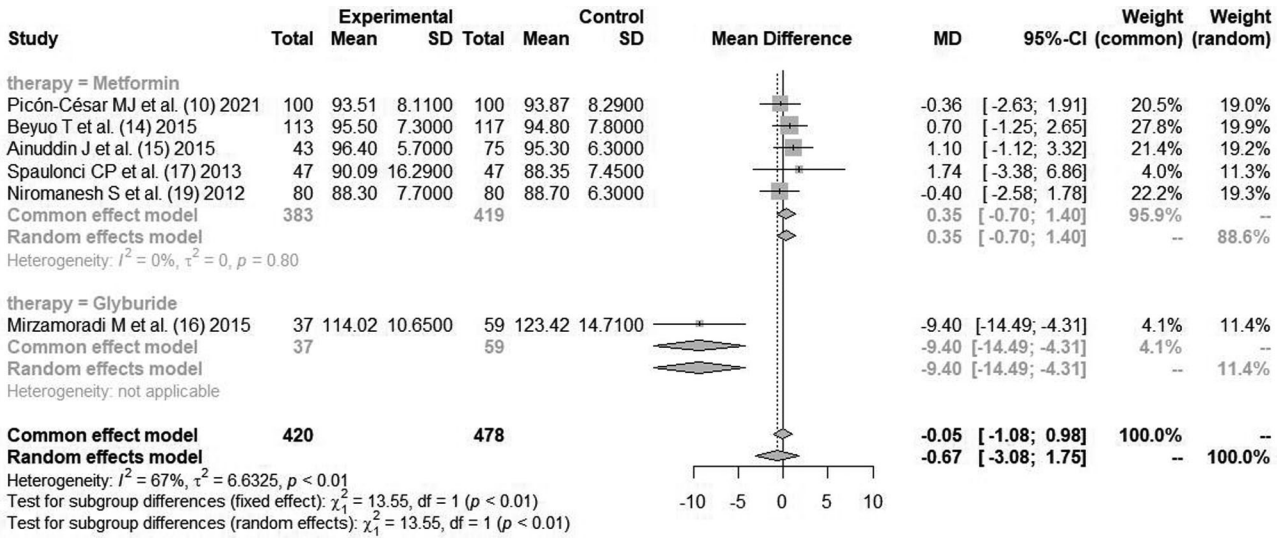

FIGURE 2 | Comparison of fasting glycemia after glycemic control during pregnancy.

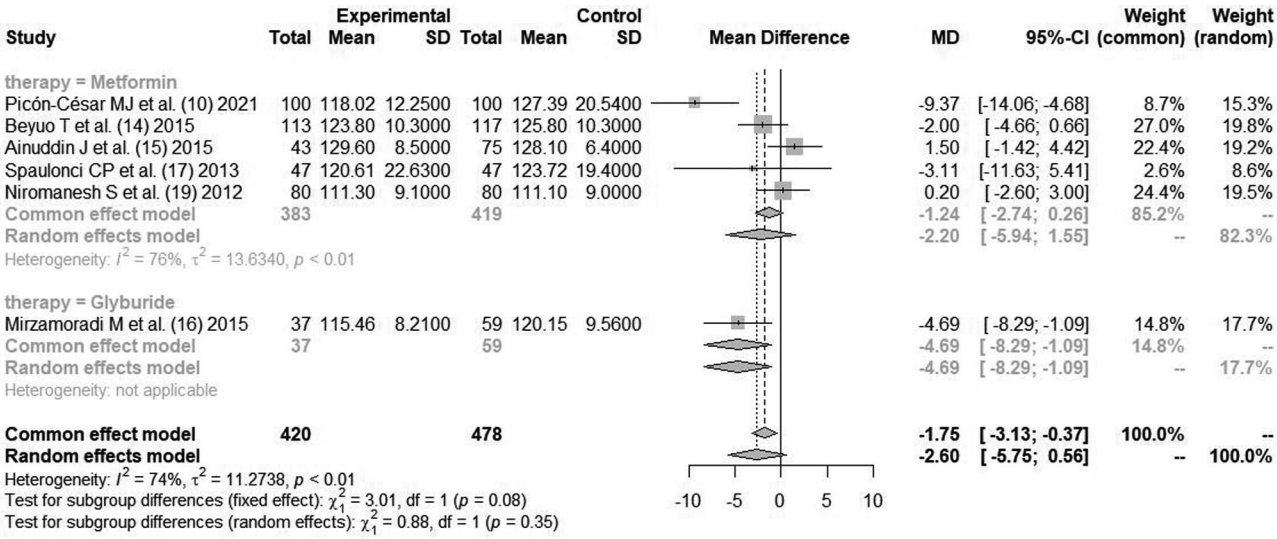

FIGURE 3 | Comparison of postprandial glycemia after lunch during pregnancy.

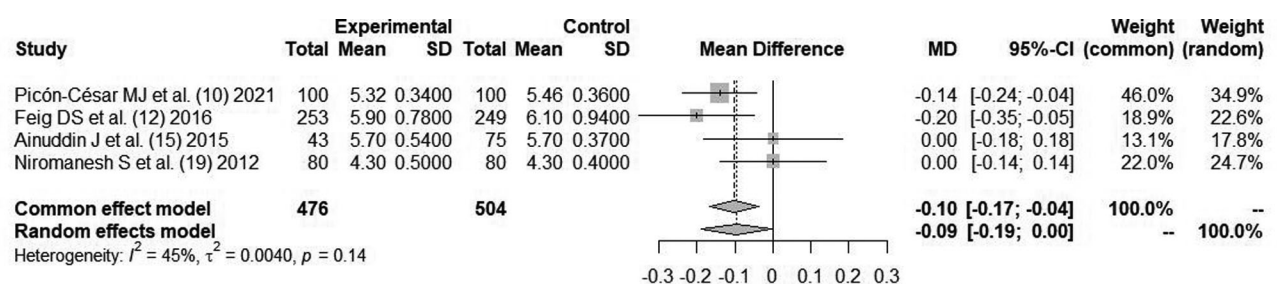

FIGURE 4 | Comparison of postpartum glycosylated hemoglobin (HbA1c postpartum) after glycemic control during pregnancy.

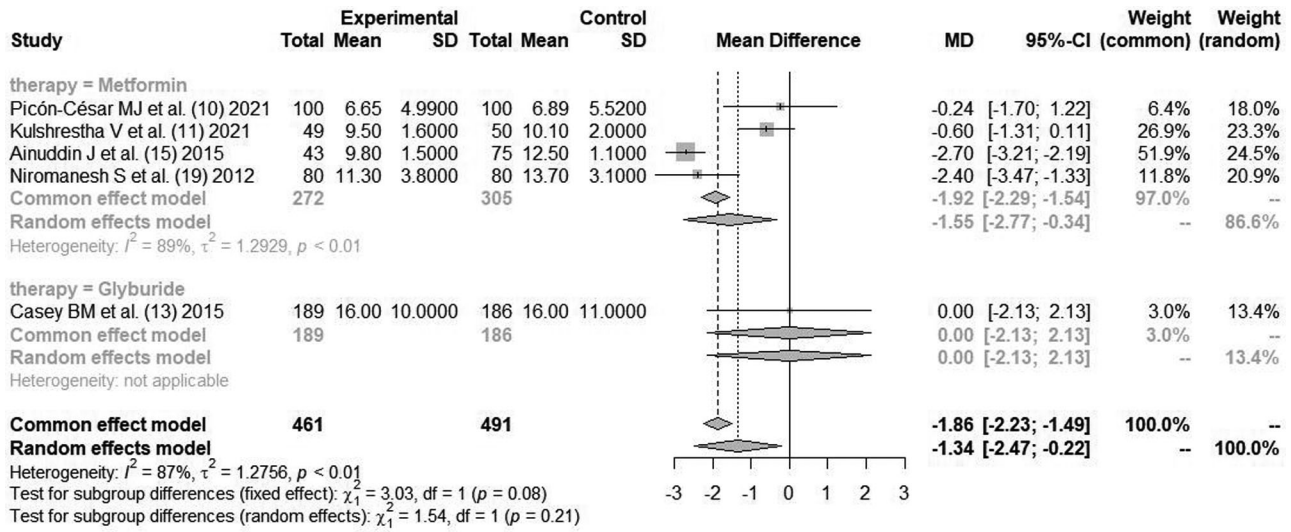

FIGURE 5 | Comparison of maternal weight gain after blood glucose control during pregnancy.

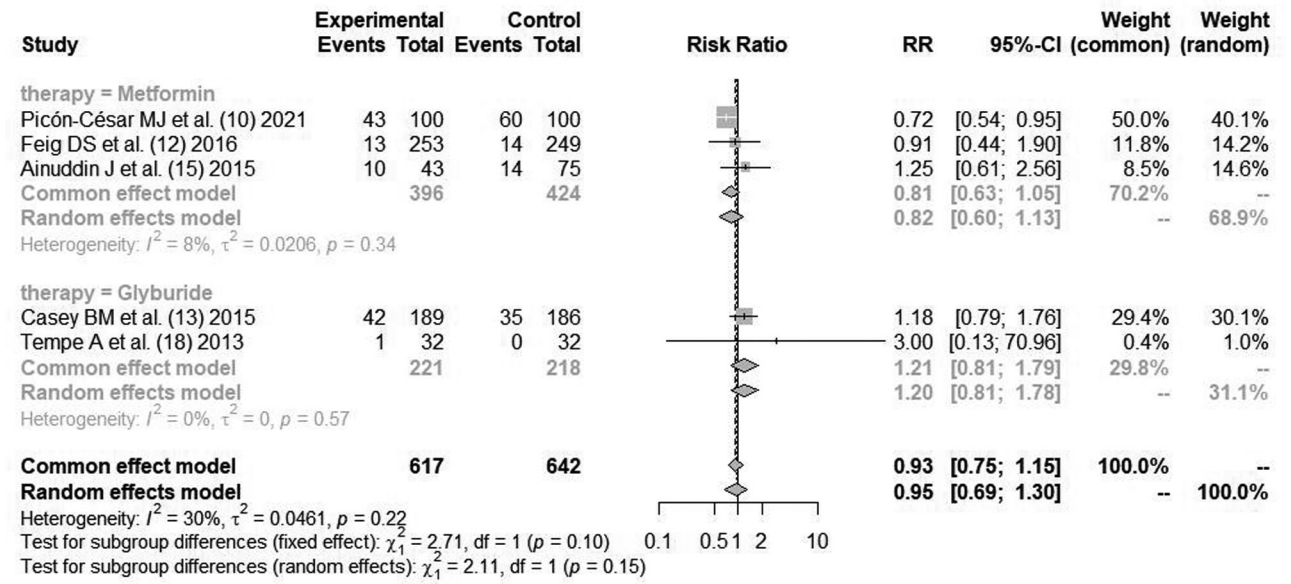

FIGURE 6 | Comparison of maternal abortion rate after blood glucose control during pregnancy.

combined analysis. There was statistical difference in cesarean section rate between *metformin* and insulin for glycemic control [RR = 0.66, 95%CI(0.49,0.90), Z = −3.95, P = 0.0001].

Two literatures (13, 18) reported the indicators of maternal cesarean section rate after using *glibenclamide* for blood glucose control. Cause there was no statistical heterogeneity between the literatures (I^2 = 0%, P = 0.98), the fixed effect mode combined analysis was used. There was no statistical difference in maternal cesarean section rate between *glibenclamide* and insulin for blood glucose control [RR = 0.78, 95%CI(0.66,0.93), Z = 0.88, P = 0.44], as shown in **Figure 7**.

Heterogeneity Investigation and Sensitivity Analysis

In the analysis of fasting blood glucose, six articles (10, 14–17, 19) had heterogeneity (I^2 = 67%, P < 0.01), but after being divided into two subgroups according to glucose-controlling drugs, five articles

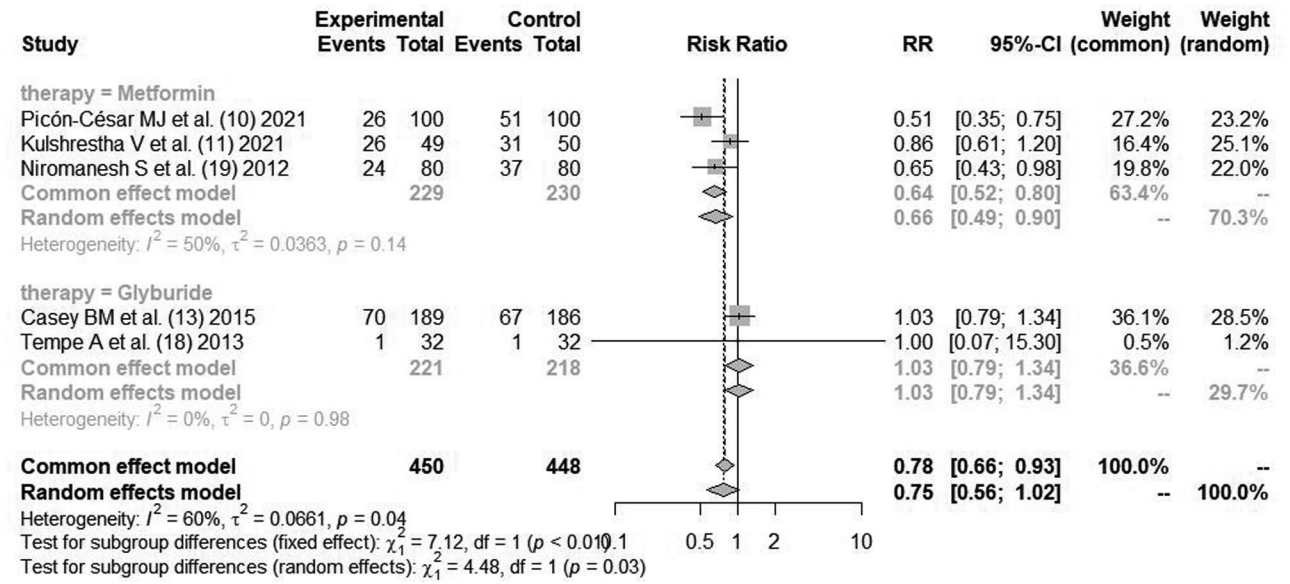

FIGURE 7 | Comparison of cesarean section rate after blood glucose control during pregnancy.

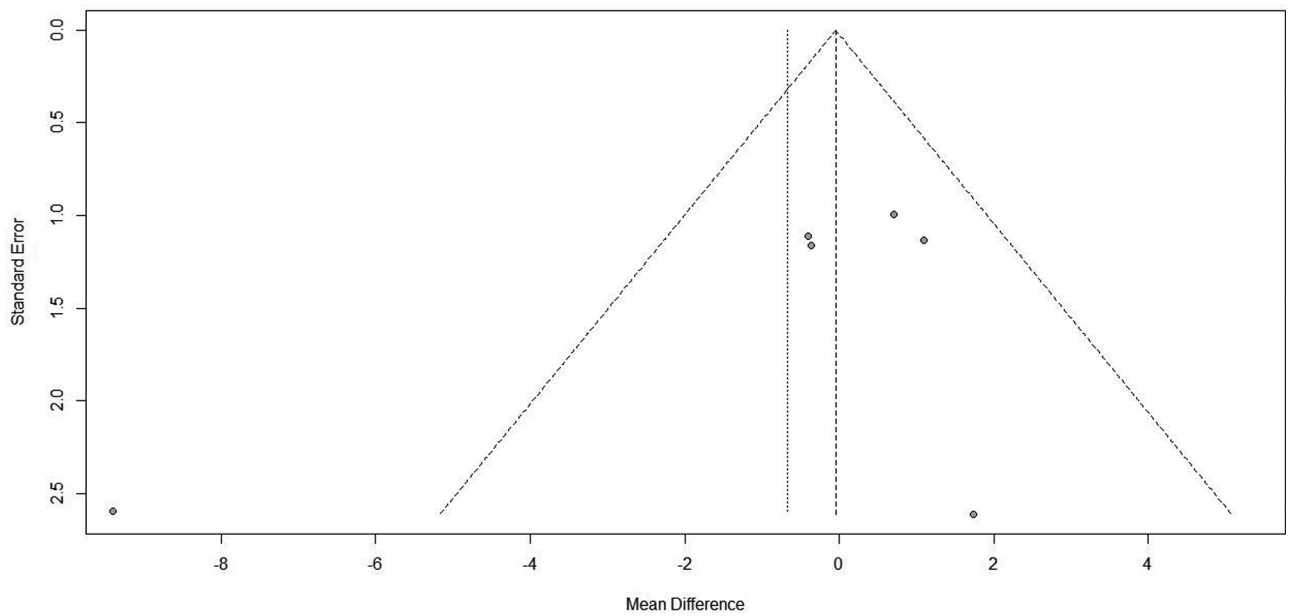

FIGURE 8 | Funnel plot of fasting blood glucose indicators after blood glucose control during pregnancy.

within the *metformin* group had no heterogeneity ($I^2 = 0\%$, $P = 0.80$), which suggested that glucose-controlling drugs were the greatest source of heterogeneity.

Analysis of Publication Bias

In the analysis of fasting blood glucose, the funnel plot showed that the two sides were not evenly distributed, suggesting the presence of publication bias, as shown in **Figure 8**.

DISCUSSION

Ten RCTs with a total of 1,938 participants were included in this study, including seven studies using *metformin* as an oral hypoglycemic agent and three studies using *glibenclamide* as an oral hypoglycemic agent. The results of this study showed that the use of *metformin* as an oral hypoglycemic agent in gestational diabetes had no significant difference in glycemic

control (fasting blood glucose, blood glucose, and glycosylated hemoglobin) compared with the utility of insulin injection, but the use of *metformin* could control maternal weight and improve pregnancy outcomes (reduce the rate of miscarriage and cesarean section). Both domestic and foreign guidelines recommend *metformin* as a first-line hypoglycemic drug. For patients with gestational diabetes, glucose control can be performed by intramuscular injection of insulin. *Metformin*, as a common hypoglycemic agent, promotes glucose uptake by target cells in the body, thereby regulating blood glucose levels (23). Studies (24) have revealed that *metformin* is mainly absorbed by the small intestine after oral administration, is not metabolized by the liver in the body, is mainly excreted unchanged by the kidney with the urine, and *metformin* itself has no hepatorenal toxicity and can be used normally in patients with normal liver and kidney function, so it has no negative impact on maternal and fetal outcomes. In addition, *metformin* belongs to the biguanide class of hypoglycemic agents, which control blood glucose by oral administration and can improve insulin therapy by improving insulin sensitivity, so it can be used in combination with insulin to better control blood glucose (25). But it is worth noting that during insulin therapy, the dose needs to be continuously adjusted, otherwise it will lead to hypoglycemic symptoms in patients, whether the blood glucose level is too high or too low, which will affect the safety of mothers and infants (26).

Glibenclamide is the second generation of sulfonylurea long-acting secretagogue, which produces the hypoglycemic effect by stimulating insulin cells to release insulin. It is suitable for mild and moderate non-insulin-dependent diabetes mellitus with unsatisfactory efficacy when diet is used alone. The results of the literature showed that the *glibenclamide* used as a glucose-controlling drug during pregnancy was superior to insulin therapy in lowering fasting blood glucose, but the evidence was insufficient cause too few articles were included. In a study by Moore LE et al. (27), *metformin* was compared with *glibenclamide* in gestational diabetes and found to have a 2.1-fold higher rate of glucose control failure with *metformin* than with *glibenclamide*. The efficacy and safety of *glibenclamide* remain to be deeply explored by more RCT studies.

The results of the study by Ashoush S et al. (28) showed that *metformin* in combination with insulin may be a better option for some patients whose glycemic control cannot be achieved with *metformin*. Literature (15) counted the cost of oral hypoglycemic agents using *metformin* throughout pregnancy, which was 4.02 ± 1.1 USD, much less than 24.83 ± 8.3 USD using insulin, which shows that *metformin* has the advantage of low price.

In this study, there was still heterogeneity in the *metformin* application group (blood glucose index), which may be related to the dynamic application adjustment of *metformin* in the study. Some patients failed to respond to oral *metformin* in regulating blood glucose and still needed insulin, which may bias the results. Although 10 included literatures were good, some literatures did not describe allocation concealment and blind method, which may cause implementation bias. Funnel plot showed possible publication bias, the number of included literatures was small, and the sample of participants was also small. The relevant studies still need to be supported by evidence from the study with higher quality RCT.

SUMMARY

The results of this meta-analysis showed that the application of oral hypoglycemic drug *metformin* in the blood glucose control of gestational diabetes can play a hypoglycemic effect equivalent to insulin, control the weight of pregnant women, reduce the rate of abortion and cesarean section, and improve pregnancy 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/s.

AUTHOR CONTRIBUTIONS

TW is mainly responsible for the writing, data analysis, and research design of the article. The corresponding author is WZ, and she is responsible for ensuring that the descriptions are accurate and agreed by all authors. All authors contributed to the article and approved the submitted version.

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Different effects of a perioperative single dose of dexamethasone on wound healing in mice with or without sepsis

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Introduction: Sepsis delays wound healing owing to uncontrolled inflammation. A single perioperative dose of dexamethasone is widely used because of its anti-inflammatory effects. However, the effects of dexamethasone on wound healing in sepsis remain unclear.
Methods: We discuss the methods to obtain dose curves and explore the safe dosage range for wound healing in mice with or without sepsis. A saline or LPS intraperitoneal injection was applied to C57BL/6 mice. After 24 hours, the mice received a saline or DEX intraperitoneal injection and full-thickness, dorsal wounding operation. Wound healing was observed by image record, immunofluorescence and histological staining. Inflammatory cytokines and M1/M2 macrophages in wounds were determined by ELISA and immunofluorescence, respectively.
Results: Dose-response curves reflected the safe dosage range of DEX in mice with or without sepsis, from 0.121 to 2.03 mg/kg and from 0 to 0.633 mg/kg, respectively. we found that a single dose of dexamethasone (1 mg/kg, i.p.) promoted wound healing in septic mice, but delayed wound healing in normal mice. In normal mice, dexamethasone delays inflammation, resulting in an insufficient number of macrophages during the healing process. In septic mice, dexamethasone alleviated excessive inflammation and maintained the balance of M1/M2 macrophages in the early and late healing process.
Discussion: In summary, the safe dosage range of dexamethasone in septic mice is wider than that in normal mice. A single dose of dexamethasone (1 mg/kg) increased wound healing in septic mice, but delayed it in normal mice. Our findings provide helpful suggestions for the rational use of dexamethasone.

KEYWORDS
dexamethasone, dose–response curve, macrophage, sepsis, wound healing

1. Introduction

Wound healing is a well-orchestrated process involving many tightly controlled factors that work in concert (1). The healing process consists of four distinct yet overlapping stages: haemostasis, inflammation, proliferation, and remodelling. Many risk factors hamper the tight control of this process, including steroids, systemic inflammation status, and comorbidities.

Sepsis is characterised by a severe systemic inflammation due to an imbalance in the body's response to infection (2, 3). Intra-abdominal infection has the highest mortality rate (30.7%) (4), and surgery is the most viable therapeutic measure to control such infections (5). However, sepsis has been proven in basic research and clinical trials to delay wound healing (6, 7), and patients with sepsis may suffer from impaired healing of the surgical incision.

Dexamethasone (DEX) has potent anti-inflammatory and immunosuppressive effects. The clinical outcomes of corticosteroid treatment in patients with sepsis or septic shock are associated with dosage. While low-dose dexamethasone has been reported to reduce mortality risk in patients with sepsis, high-dose dexamethasone may result in more harm than benefits (8). However, few studies have compared the effects of dexamethasone on wound healing in septic and non-septic conditions.

A perioperative single dose of dexamethasone is widely used to prevent postoperative nausea and vomiting (PONV) (9). However, the routine perioperative use of dexamethasone is still controversial (10, 11). Dexamethasone did not increase the incidence of surgical-site infection within 30 days after nonurgent noncardiac surgery (12) when compared with placebo controls. However, it is uncertain whether dexamethasone affects wound healing in the general surgical population (13).

Therefore, we hypothesised that dexamethasone (1 mg/kg, i.p.) may have different effects on wound healing in septic mice than in normal mice. We also explored the possible mechanism of action of dexamethasone in wound healing in the context of sepsis. Of note, we depicted the differences between the two dose–response curves, which explored the safe dosage range of dexamethasone in mice with or without sepsis.

2. Materials and methods

2.1. Dose–response curves

A total of 260 mice were allocated to two groups and received an intraperitoneal injection of dexamethasone at doses ranging from 0 to 5 mg/kg (9–11 doses per experiment). For normal mice, the complete range of dexamethasone doses was 0, 0.125, 0.25, 0.375, 0.5, 1, 1.25, 2.5, and 5 mg/kg (six mice per dose). Dexamethasone was administered to septic mice at 0, 0.125, 0.25, 0.5, 1, 1.25, 1.6, 2, 2.5, 3, and 5 mg/kg (6–10 mice per dose).

2.2. LPS sepsis model and medication procedure

Male C57BL/6 mice (6–8 weeks) were housed 3–5 per cage and had free access to water and food throughout the experiment; the padding was replaced at least three times a week. The protocol complied with the NIH Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978) and was approved by the Animal Ethics Committee of the Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, and was reported in accordance with the ARRIVE guidelines.

The mice were randomly separated into four experimental groups: control, DEX, sepsis, and sepsis + DEX group (**Figure 1**). The control and DEX groups received an intraperitoneal (i.p.) injection of saline solution, and the other groups received lipopolysaccharide (LPS) (O55:B5, Sigma Aldrich, St. Louis, MO, United States) injection (i.p.) at a dose of 10 mg/kg (14–17). After 24 h, mice with signs of lethargy, piloerection, and tachypnoea were diagnosed with sepsis (6). Dexamethasone (Sigma Aldrich, St. Louis, MO, United States), 1 mg/kg, was injected intraperitoneally into mice in the DEX group and sepsis + DEX group. The control and sepsis groups were injected with saline solution (i.p.).

2.3. Skin wound model and evaluation of wound closure

A mouse full-thickness wound model was generated and all the experiments were performed at 0, 3, 5, 7, and 9 days after the operation.

Before the experiment, the mice were anaesthetised by intraperitoneal administration of 3% pentobarbital sodium, and their back hair was removed. After that, their skin was disinfected with 75% alcohol. Two full-thickness wounds (6 mm diameter) were created on each side of the dorsal midline using a sterilised biopsy punch. The centres of the wounds were located 28 mm cranial from the beginning of the tail and 8 mm lateral to the spine.

Images of the wounds were captured using a digital camera. A ruler was used to standardise the measurements, and the results were quantified using ImageJ software (version 2.0.0, United States). The wound closure% was calculated using the equation $(A_0 - A_n)/A_0 \times 100$, where A_0 is the original wound area and A_n is the wound area on days 3, 5, 7, or 9 post-surgery. At different time points, the mice were euthanised following the approved euthanasia protocol, and the original wound area and 2 mm-wide slices of skin around the wound surface were harvested and sectioned for further investigation.

2.4. Histological analysis

For morphometric analysis, the wound specimens were sectioned, stained with haematoxylin and eosin (H&E) according to the manufacturer's protocol, and observed by light microscopy (Leica DM IL LED, Buffalo Grove, IL, United States). The thickness of granulation tissue was defined as the distance from the wounded dermal upper margin to the bottom of the area that is rich in cellular infiltration and revascularisation (18) (five measurement points per view). The thickness of the epidermis (imaged at ×200), granulation tissue (imaged at ×50), and the number of blood vessels (imaged at ×200) and follicles (imaged at ×50) were calculated in three randomly selected views per specimen using ImageJ software.

2.5. Immunofluorescence analysis

Immunofluorescence staining was performed on the tissue sections to assess vessel regeneration and granulation tissue with the expression of CD31 and α-smooth muscle actin, respectively. Cryosections of the tissue were fixed in paraformaldehyde (4%) for 15 min, washed with phosphate buffered saline (PBS) for 15 min,

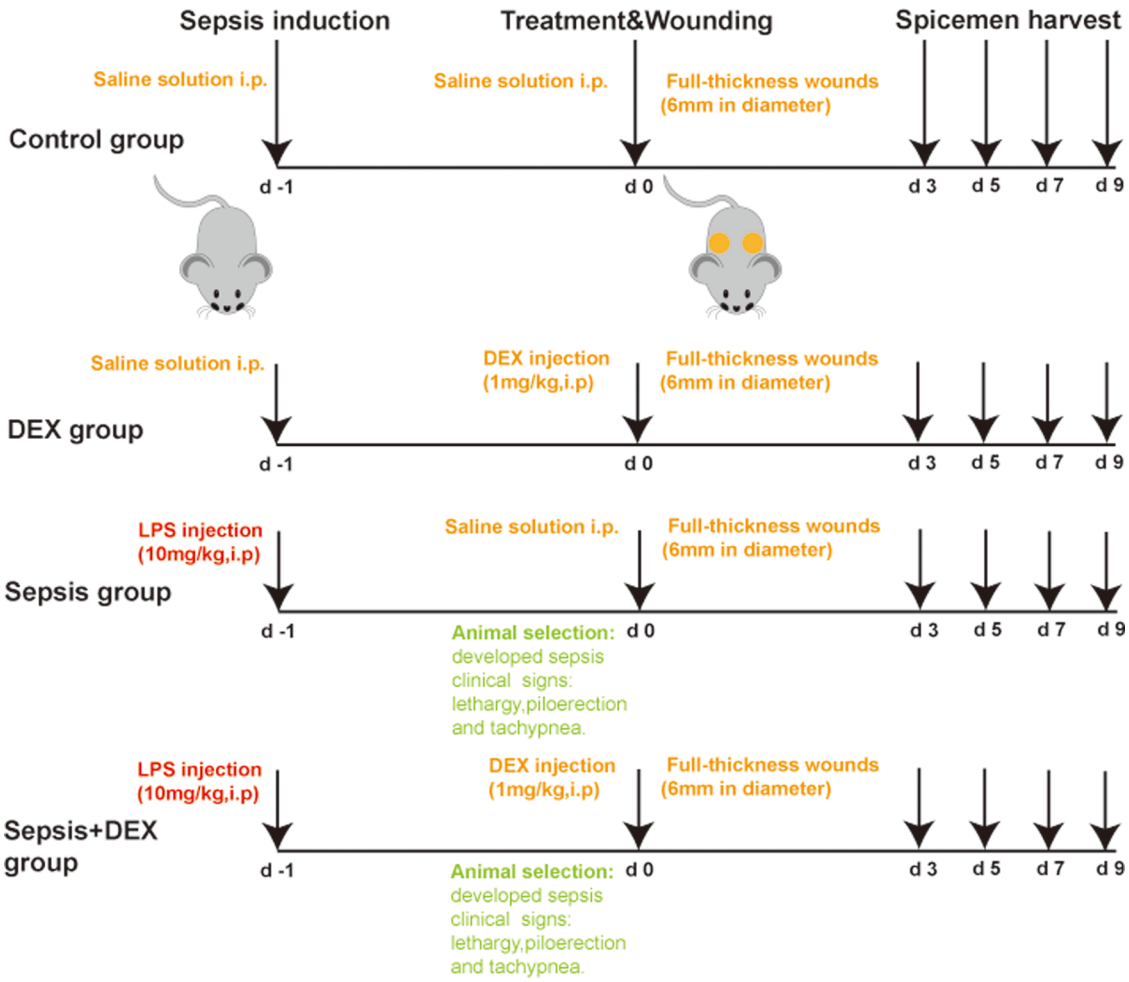

FIGURE 1
LPS sepsis model and medication procedure in the sepsis + DEX group. Medication procedure in 4 groups.

and blocked with 1% goat serum for 1 h before staining with primary antibodies overnight. The slices were incubated with the following primary antibodies: anti-mouse CD31 antibody (BD Pharmingen, clone 550274) 1:100 and anti-mouse α-smooth muscle actin (Cell Signalling Technology, clone 19245) 1:100.

To detect the effect of dexamethasone on macrophage polarisation in wounds, skin slices were processed by immunofluorescence staining with anti-mouse iNOS (Abcam, clone ab178945) 1:50 and anti-mouse Arg-1 (Santa Cruz Biotechnology, sc-271430) 1:500. After the primary antibodies were removed, Alexa Fluor 488- or Alexa Fluor 594-conjugated secondary antibodies (Cell Signalling Technology, MA, United States) 1:500 were used, followed by staining with DAPI (SouthernBiotech, Birmingham, United States).

2.6. Enzyme-linked immunosorbent assay

Wound samples collected on days 3, 5, 7, and 9 were frozen at −80°C. Frozen samples were carefully minced with sharp scissors and homogenised in cold PBS containing protease inhibitors (NCM Biotech, Suzhou, China) at a weight-to-volume ratio of 1 mg/mL. The samples were centrifuged at 2,500 rpm for 10 min at 4°C. The supernatant was analysed using a BCA Protein Assay Kit (Beyotime Biotechnology, Shanghai, China). Tissue levels of IL-6, TNF-α, and IL-10 were measured using enzyme-linked immunosorbent assay (ELISA) kits (Neobioscience Technology, Beijing, China), following the manufacturer's instructions.

2.7. Statistics

Data are presented as the mean ± SEM. All statistical analyses were performed using Prism 9 (GraphPad, San Diego, CA, United States). For the comparison between normal and septic mice or between dexamethasone-treated normal mice and dexamethasone-treated septic mice, a two-way ANOVA followed by Tukey's *post-hoc* test was used. For the safe dosage range of dexamethasone, the dose–response curve in normal mice was generated using a four-parameter nonlinear regression, and the curve in septic mice was generated using a bell-shaped nonlinear regression. Correlations of the dose–response curve in normal mice were assessed with the Pearson correlation coefficient. In all cases, statistical significance was set at $P < 0.05$.

TABLE 1 Different doses of dexamethasone in normal mice (wound closure% on day 9).

	0 mg/kg	0.125 mg/kg	0.25 mg/kg	0.375 mg/kg	0.5 mg/kg	1 mg/kg	1.25 mg/kg	2.5 mg/kg	5 mg/kg
Wound closure% on day 9[a]	94.8 ± 4.73	96.9 ± 2.28	93.3 ± 1.39	92.5 ± 3.31	93.6 ± 2.16	85.9 ± 6.60	87.8 ± 3.17	87.4 ± 1.45	83.4 ± 5.06
Delayed-healing incidence	0/6	0/6	0/6	2/6	3/6	4/6	4/6	6/6	6/6

[a]All values represent mean ± SD, $n = 6$.

3. Results

3.1. Dose curves of DEX for wound healing in mice with and without sepsis

It is challenging to obtain the dose–response curve of dexamethasone for wound healing. The dose variable is always quantitative, and the crux depends on the forms of the dependent variable. Table 1 shows a comparison of the response variables. In plan A, the dependent variable is the event incidence, whereas it is the relative wound closure% in plan B. Usually, the relationship between x and y in a dose–response curve is described by nonlinear regression models. Taking the four-parameter logistic regression model as an example [Equation (1)]

$$y = l + \frac{u - l}{[1 + exp[b(log(x) - log(e))]]} \quad (1)$$

where y is the response variable and x is the dose variable. If y decreases as the dose increases, l is the lower limit of the outcome variable at an infinitely large dose and u represents the upper limit of the outcome variable when the dose is zero. Parameter e indicates the dose inducing a response halfway between u and l parameters (19). In general (e.g., the dependent variable is cell viability), the value of u does not exceed 100% (the formula for cell viability determines the range of this value). Similarly, l was not less than 0% (20, 21). In plan A (Table 1), u and l satisfy the conditions in the model ($u \leq 100\%$ and $l \geq 0\%$). There is only one new parameter to be defined: a certain value of the delayed-healing threshold. In our study, the average wound closure% of the control group was taken as the threshold value, which was used to normalise the data in experimental groups in previous studies (19, 20). However, u and l in plan B (the dependent variable was normalised by the control group) failed to meet the application conditions. Thus, Plan A (Table 1) was a better choice.

To determine the association between dosing and the different effects of dexamethasone mentioned above, we performed a medium-safe dose experiment in mice with and without sepsis (Figure 2A). Taking the average wound closure% (94.8% ± 4.73%) of the control group on day 9 as the standard (when the wound closure% was less than this value, it was determined as delayed healing), we obtained the dose curves (Figures 2B,C). The dexamethasone dose at which delayed healing of 50% of the mice occurred was calculated as 0.633 mg/kg in dexamethasone-treated normal mice, while for dexamethasone-treated septic mice it ranged from 0.121 to 2.03 mg/kg (Figures 2B,C, Tables 2, 3). The safe dosage range for wound healing in mice without sepsis was from 0 to 0.633 mg/kg (Figure 2B), and that in mice with sepsis was from 0.121 to 2.03 mg/kg (Figure 2C). There was a positive correlation between the dose of dexamethasone and the incidence of delayed wound healing ($R^2 = 0.665$, $P = 0.007$) in wounds without sepsis.

3.2. Intraperitoneal injection of dexamethasone (1 mg/kg) promoted wound healing in septic mice but delayed it in normal mice

To explore whether a single dose of dexamethasone (1 mg/kg, i.p.) has different effects on wound healing in normal and septic mice, we compared wound states among four groups of mice (six mice per group): control (intraperitoneal injection of saline solution to C57BL/6 mice), DEX (DEX, i.p.), sepsis (LPS, i.p.), and sepsis + DEX (septic mice with DEX, i.p.) groups. As shown in Figure 3, dexamethasone delayed wound healing from day 3 after wounding in normal mice but accelerated the healing process in septic mice from day 7 (Figure 3E), which was visualised by image records and a schematic diagram (Figures 3A,D). By immunofluorescence staining, we observed less granulation tissue (revealed by αSMA-positive areas) and blood vessels (indicated by CD31 distribution) in the DEX group on day 9 after wounding than in the control group (Figures 3B,C). In contrast, more granulation tissue and blood vessels were seen in the sepsis + DEX group than in the sepsis group.

3.3. Intraperitoneal injection of dexamethasone (1 mg/kg) improved tissue regeneration in septic mice

Next, we assessed the quality of the regenerated tissue in the wounds by histological analysis (Figure 4). Mice in the DEX group expressed thinner epidermis on day 9 than those in the control group (Figures 4A,B). However, wounds in the sepsis + DEX group had thicker epidermis than those in the sepsis group, which indicated that dexamethasone improved epidermal regeneration in septic mice.

Soon after the injury, the fibrin clot is replaced by blood vessel-rich granulation tissue. In general, new vessel formation is essential for tissue repair by delivering nutrients and oxygen to injured tissue and removing waste products and carbon dioxide (22). Thus, blood vessel and granulation tissue conditions are closely related to the healing situation and are often used as evaluation parameters (23, 24). During the entire observation period, dexamethasone promoted angiogenesis and granulation tissue formation in wounds of the sepsis + DEX group, exhibiting a

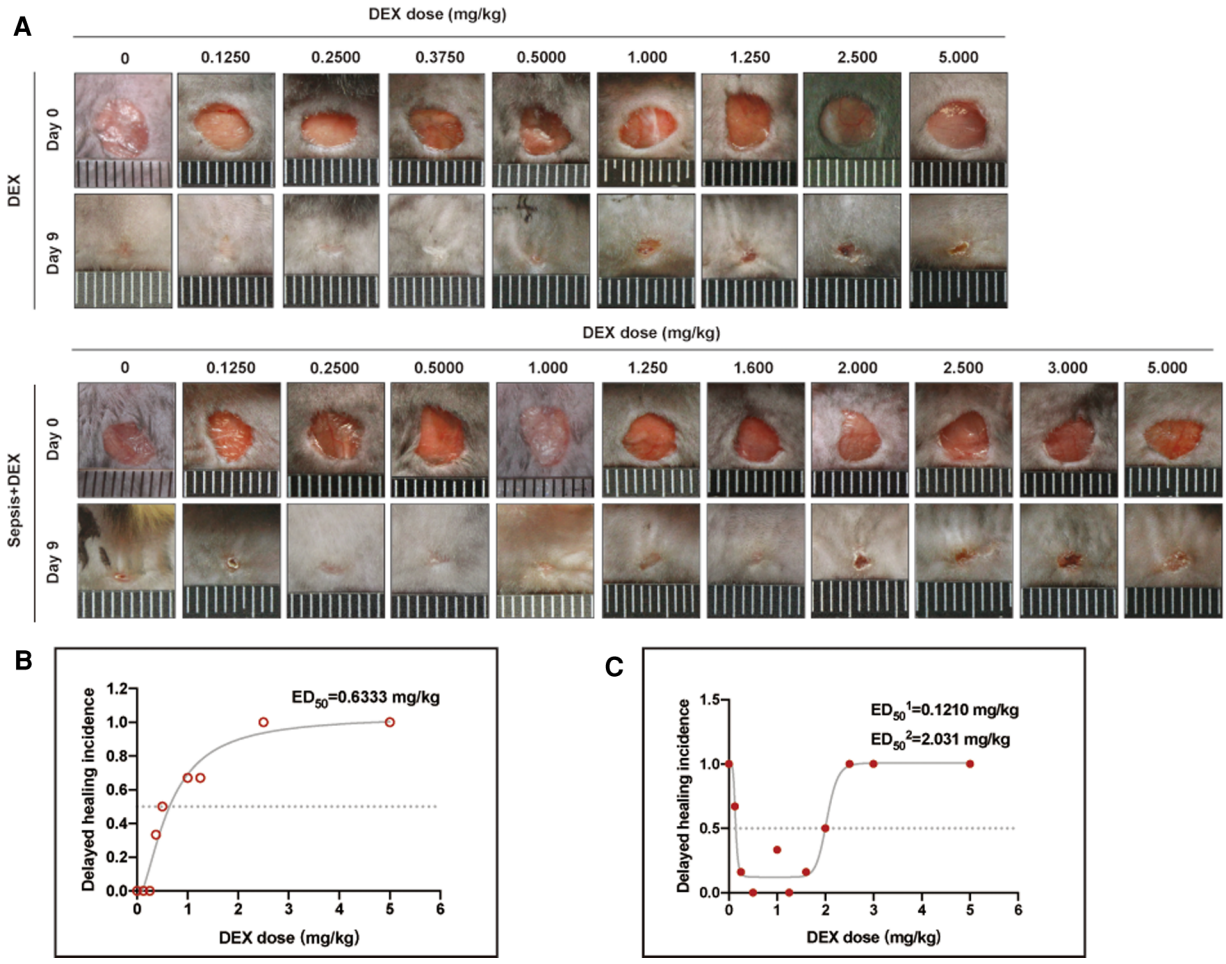

FIGURE 2
Dose curves of dexamethasone for wound healing in mice with and without sepsis. (A) Appearance of wounds on days 0 and 9 for DEX and sepsis + DEX groups. (B) Dose curve of dexamethasone for wound healing in normal mice. R^2 is 0.959. (C) Dose curve of dexamethasone for wound healing in septic mice. R^2 is 0.958. In (B,C), the non-healing wound was defined as that wound closure rate on day 9 was less than 90.1%. Parameter values are presented in Tables 2, 3.

TABLE 2 Different doses of dexamethasone in septic mice (wound closure on day 9).

	0 mg/kg	0.125 mg/kg	0.25 mg/kg	0.5 mg/kg	1.0 mg/kg	1.25 mg/kg	1.6 mg/kg	2 mg/kg	2.5 mg/kg	3 mg/kg	5 mg/kg
Wound closure% on day 9[a]	85.5 ± 1.13	87.8 ± 3.50	93.6 ± 0.0447	97.2 ± 1.56	95.5 ± 5.19	93.7 ± 1.12	92.0 ± 1.37	90.1 ± 3.96	87.9 ± 1.88	86.4 ± 2.73	83.5 ± 7.25
Delayed-healing incidence	6/6	4/6	1/6	0/6	2/6	0/6	1/6	3/6	6/6	6/6	6/6

[a]All values represent mean ± SD, $n = 6$.

larger number of blood vessels and thicker granulation tissue than those in the sepsis group. However, dexamethasone suppressed vessel regeneration in the DEX group (Figures 4A,C).

The hair follicle is another regeneration parameter (as it is rich in several kinds of skin stem cells, which improves wound healing in re-epithelialisation and angiogenesis) (25–28), which was significantly increased by dexamethasone in the sepsis + DEX group compared with that in the DEX group on day 9 (Figure 4E). These results

TABLE 3 The data of wound closure%

Wound closure%	Control group	DEX group	Sepsis group	Sepsis + DEX
Day 3	62.4 ± 6.98	49.8 ± 5.68	31.9 ± 5.67	34.7 ± 7.86
Day 5	63.2 ± 5.48	58.4 ± 8.91	48.4 ± 3.56	33.5 ± 9.39
Day 7	80.0 ± 4.05	64.3 ± 6.53	78.2 ± 2.94	83.5 ± 3.59
Day 9	94.8 ± 4.38	85.9 ± 6.02	85.5 ± 1.06	95.5 ± 4.10

[a]All values represent mean ± SEM, $n = 6$.

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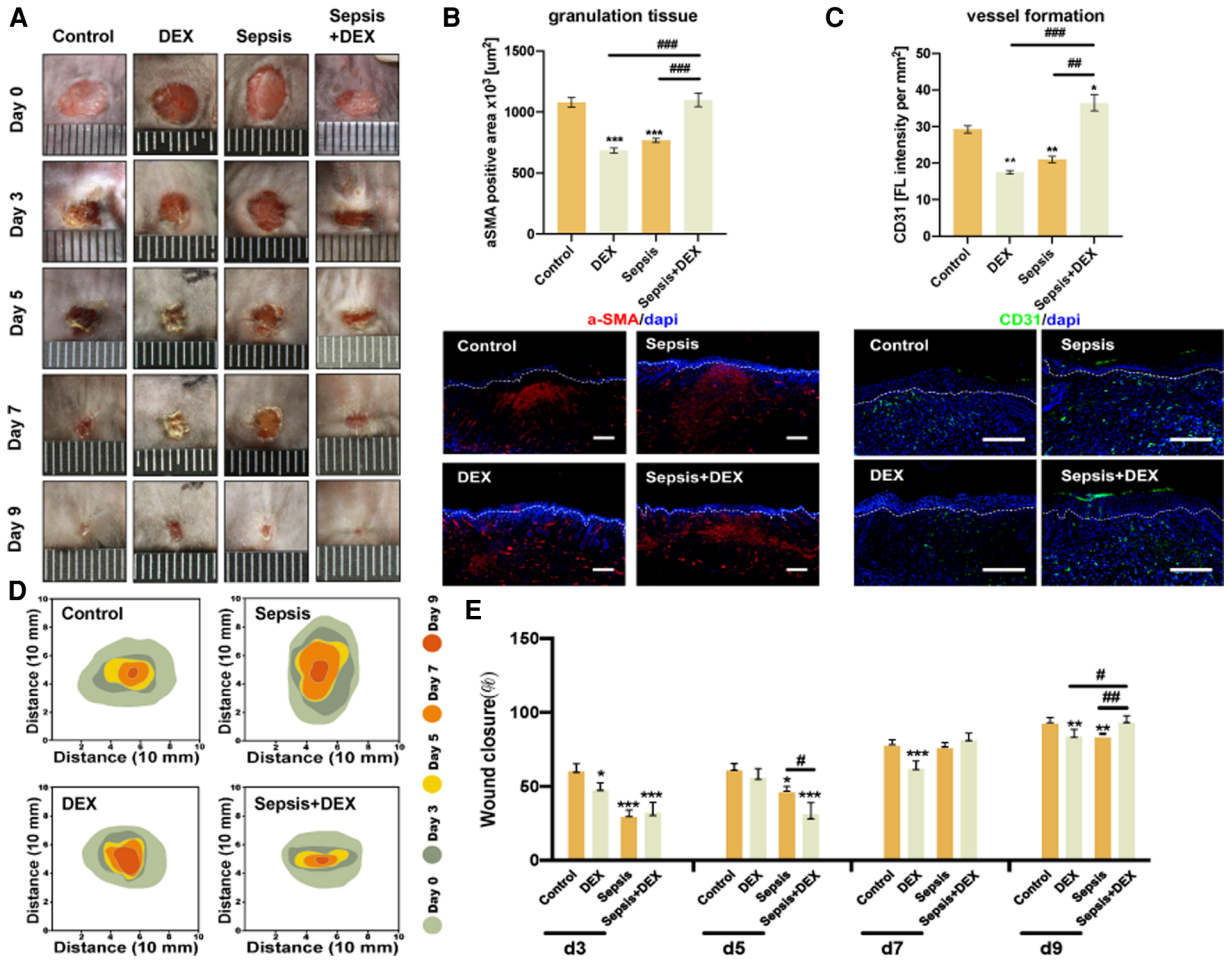

FIGURE 3
Intraperitoneal injection of dexamethasone (1 mg/kg) promoted wound healing in septic mice but delayed that in normal mice. Mice received intraperitoneal LPS (10 mg/kg) injection (sepsis and sepsis + DEX groups) or saline solution (control and DEX groups). After 24 h, dexamethasone was injected (1 mg/kg, i.p.) (DEX and sepsis + DEX groups) or normal saline (control and sepsis groups). Then, all groups had the wounding operation. Observation period included days 0, 3, 5, 7, and 9 after wounding. (**A**) Appearance of wounds on days 0, 3, 5, 7, and 9 for control, sepsis, DEX, and sepsis + DEX groups. (**B**) Granulation on day 9 after wounding. αSMA-IF (scale bar 500 μm), granulation tissue = αSMA-positive area (mean ± SEM, $n = 6$ per group). (**C**) Vessel formation on the 9th day after wounding. CD31-IF (scale bar 500 μm), angiogenesis = CD31 distribution/wound area (mean ± SEM, $n = 3$ per group). (**D**) Schematic diagram of wound area during 9 days for control, sepsis, DEX, and sepsis + DEX groups. Visualised by Adobe Illustrator. (**E**) Wound closure for each group. Quantitative data of image records (mean ± SEM, $n = 6$ per group). Wound closure rate was measured by the equation: $(A_0 - A_n)/A_0 \times 100$, where A_0 is the wound area on day 0, and A_n is the wound area of days 3, 5, 7, or 9 post-wounding. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, vs. control group; $\#P < 0.05$, $\#\#P < 0.01$, $\#\#\#P < 0.001$, vs. other groups. IF, immunofluorescence; αSMA, α-smooth muscle actin.

demonstrate that dexamethasone improved wound healing only in septic mice, but not in normal mice, in terms of enhancing angiogenesis and the formation of granulation and follicles.

3.4. Intraperitoneal injection of dexamethasone impaired the initiation of inflammation in wounds of normal mice but not in septic mice

Accumulating evidence shows that the effect of dexamethasone on wound healing is accompanied by changes in inflammatory cytokines (29–31). To reveal the association between the inflammatory response and the different effects of dexamethasone (1 mg/kg, i.p.) on wound healing in septic and normal mice, we assessed the expression of pro-inflammatory cytokines (IL-6 and TNF-α) and anti-inflammatory cytokine (IL-10) in the wound healing process (3–9 days).

As shown in the ELISA analysis (Figure 5), early in wound healing (days 3 and 5), dexamethasone decreased the expression of inflammatory cytokines in the DEX group (compared to the control group) and the sepsis + DEX group (compared to the sepsis group). Later in the healing process, the DEX group showed persistent inflammation with a higher level of IL-6 on day 7 than that in the control group. In addition, more TNF-α was secreted in the DEX group on days 7 and 9, although there were no statistically significant differences between the DEX and control groups. These results were different in the sepsis + DEX group. Dexamethasone suppressed the secretion of pro-inflammatory cytokines (IL-6 and TNF-α) during the early stages

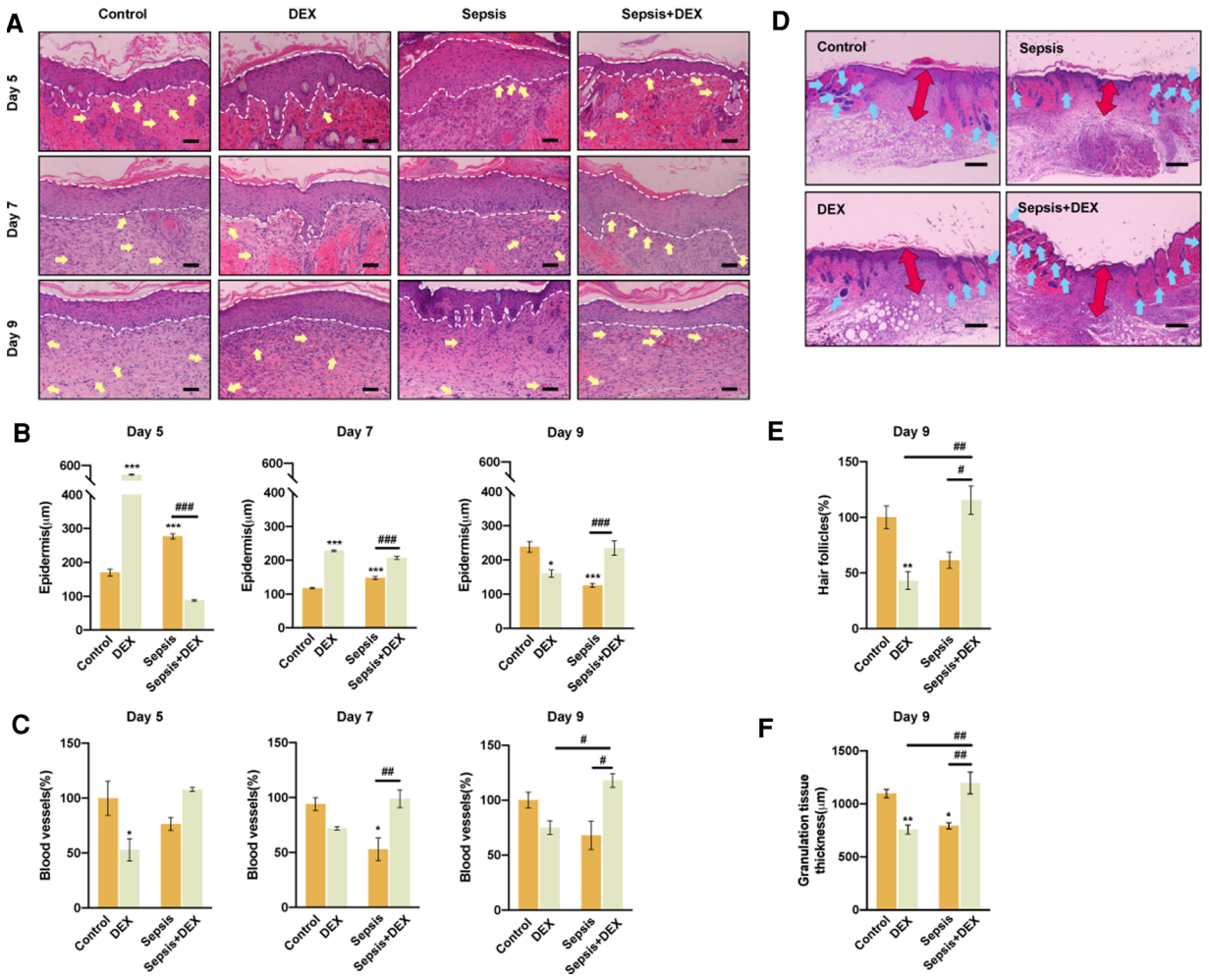

FIGURE 4
Intraperitoneal injection of dexamethasone (1 mg/kg) improved tissue regeneration in septic mice. (A) Wound H&E staining for control, sepsis, DEX, and sepsis + DEX on the 5th, 7th, and 9th day (blood vessels: yellow arrows, hair follicles: blue arrows, boundary of epithelium: white lines). Scale bar: 100 μm. (B) Epidermis thickness assessments for different groups on the 5th, 7th, and 9th day. (C) Blood vessels regeneration on the 5th, 7th, and 9th day. Quantified data were presented by relative number percentage. Control group on 5th day was set as 100%. (D) Granulation tissue (red arrows) thickness and amount of hair follicles (blue arrows) for different groups on the 9th day. Scale bar: 500 μm. (E) Hair follicles for different groups on day 9 post-wounding. Data were shown in relative number percentage. Control group was set as 100%. (F) Quantitative data of granulation tissue thickness. Data are shown as mean ± SEM, $n = 3$.*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, vs. control group; #$P < 0.05$, ##$P < 0.01$, ###$P < 0.001$, vs. other groups.

of wound healing. A higher level of IL-6 on day 7 and a lower level of inflammation (both IL-6 and TNF-α) on day 9 were observed in the Sepsis + DEX group than in the sepsis group.

Of note, IL-10 showed a trend of changes, which were lower on days 3 and 5 in the DEX-treated groups than in the saline groups, and then reached a peak on day 7 but declined again on day 9.

3.5. The initiation of inflammation and subsequent macrophage polarisation towards *M2* relied on adequate *M1* macrophages in early wound healing

Macrophages play a prominent role in tissue repair by balancing the pro- and anti-inflammatory responses. Early in wound repair, *M1* macrophages participate in pro-inflammatory activities and have traditionally been marked with iNOS. *M2* macrophages, which promote inflammation resolution and tissue repair during the later stages of wound healing, are marked with Arg-1. To study how dexamethasone affects inflammation progression, we checked the number of macrophages (*M1* + *M2*) and the *M1*/*M2* ratio in wound sites using immunofluorescence staining (Figure 6).

Throughout the wound healing process, mice in the DEX group had fewer macrophages (*M1* + *M2*) than those in the control group. On day 3, more macrophages were observed in the sepsis group, but fewer were observed in the sepsis + DEX group. There were no significant differences in the number of *M1* + *M2* macrophages between the sepsis and Sepsis + DEX groups on days 5, 7, and 9.

The wounds in the DEX group displayed a higher *M1*/*M2* ratio than those in the control group on day 3. During later tissue repair, a higher *M1*/*M2* ratio was observed in the DEX group than in the control group.

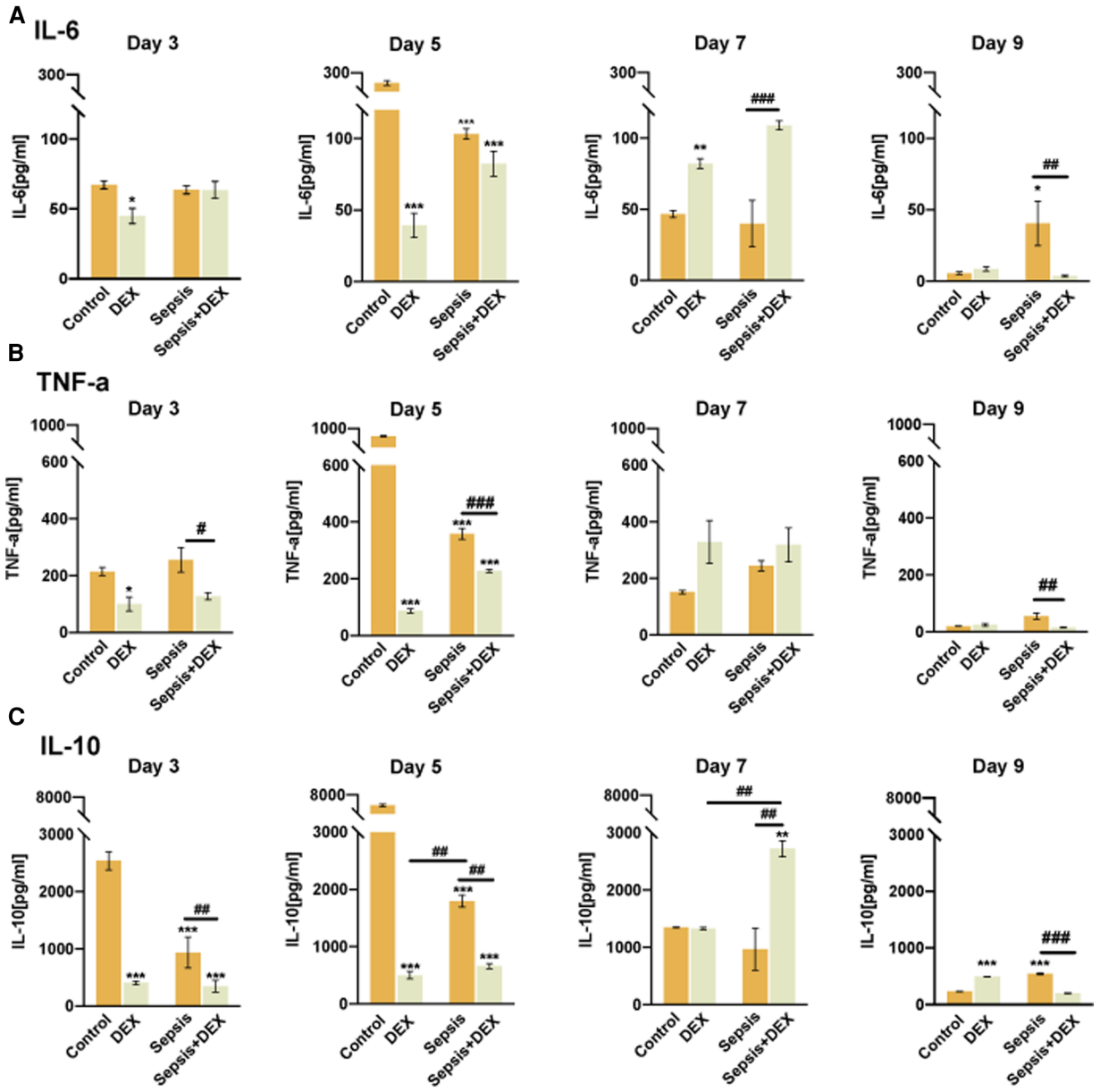

FIGURE 5
Intraperitoneal injection of dexamethasone impaired the initiation of inflammation in wounds of normal mice but not in septic mice. ELISA analysis of IL-6, TNF-α, and IL-10 in wounds. (A) The concentration of IL-6 in skin defects among control, DEX, sepsis, and sepsis + DEX groups on the 3rd, 5th, 7th, and 9th days after wounds creation. (B) TNF-α expression in tissue among the four groups on the 3rd, 5th, 7th, and 9th day after wounding. (C) IL-10 expression of wounds among different groups on the 3rd, 5th, 7th, and 9th day after the operation. All values represent mean ± SEM, $n = 3$.*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, vs. control group; #$P < 0.05$, ##$P < 0.01$, ###$P < 0.001$, vs. other groups. TNF-α, tumour necrosis factor-α; ELISA, enzyme-linked immunosorbent assay.

On the other hand, there was a higher *M*1/*M*2 ratio in wounds of the sepsis + DEX group than in the sepsis group on day 3. Wounds in the sepsis + DEX group had a lower *M*1/*M*2 ratio on day 9 than those in the sepsis group.

These results indicate that dexamethasone decreased *M*1 macrophages in early wound healing, which may result in the phenotypic switch of macrophages from *M*1 to *M*2 being delayed or failing to occur.

4. Discussion

Dexamethasone, an approved corticosteroid medication, is widely used for prophylaxis and treatment of PONV. However, the safe dosage of dexamethasone for wound healing in the perioperative period, particularly in patients with sepsis, remains unknown.

Herein, we found that the differences between normal and septic mice were dose-related and described them in the dose–

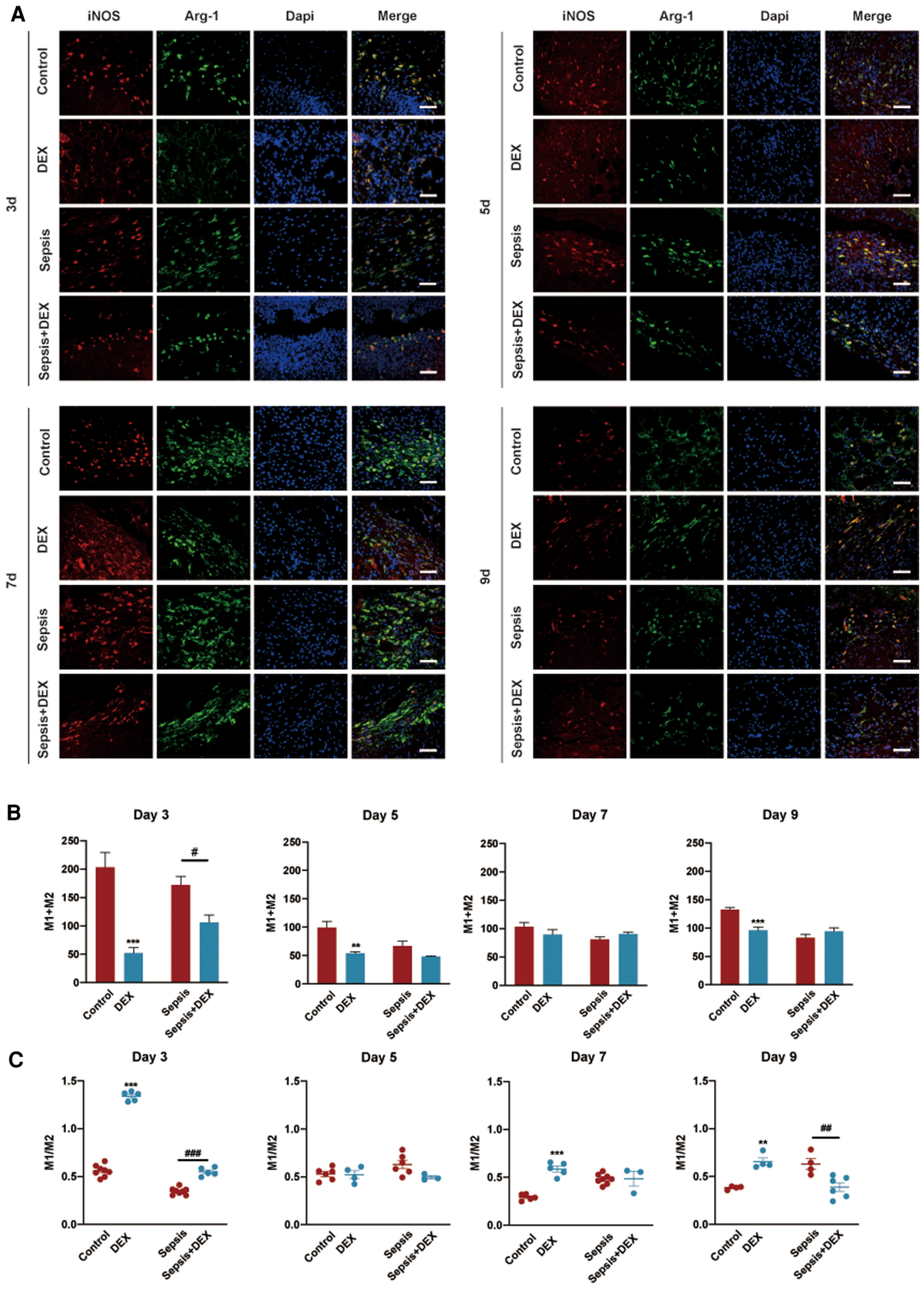

FIGURE 6
The initiation of inflammation and subsequent macrophage polarisation towards *M2* relied on adequate *M1* macrophages in early wound healing. Immunofluorescence staining analysis of *M1* and *M2* macrophages in wounds in various groups on the 3rd, 5th, 7th, and 9th day. (**A**) Representative histological slices of wounds stained by immunofluorescence: red (iNOS, *M1* macrophages marker), green (Arg-1, *M2* macrophages marker), and blue (DAPI). Scale bar: 100 μm. (**B**) Number of *M1* and *M2* macrophages. (**C**) *M1*/*M2* ratio. (**B**,**C**) are quantised data of (**A**). All values represent mean ± SEM, $n > 3$.*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, vs. control group; #$P < 0.05$, ##$P < 0.01$, ###$P < 0.001$ vs. sepsis group. iNOS, inducible nitric oxide synthase; Arg-1, arginase-1.

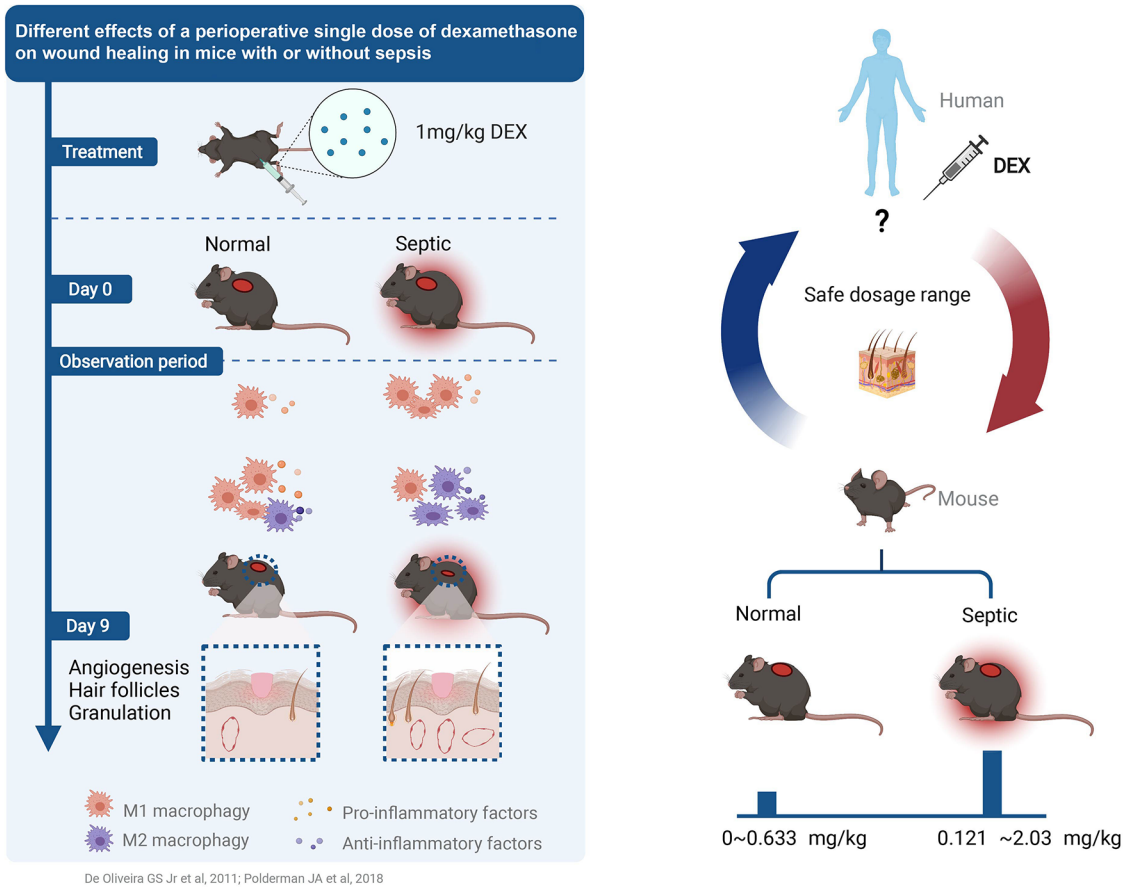

FIGURE 7
Different effects of a perioperative single dose of dexamethasone on wound healing in mice with or without sepsis (50, 51).

TABLE 4 Selection of the dependent variable in dose–response curves.

	The dependent variable is the event incidence (A)	The dependent variable is relative wound closure rate (B)	The better one
Supporting evidence[a]	Yes	No	A
Data	Transformed	Transformed	—
Curve-fitting model	Yes	Yes	—
Number of new parameters	1	2	A
The literature support of new parameter(s)	Yes	No	A

[a]Carvalho et al. (33) and Ginosar et al. (34) have defined the event incidence as the dependent variable in the dose–response curve.

response curves. By comparing the incidence of delayed healing, we demonstrated that the therapeutic window of dexamethasone in septic mice was broader. Identification of the relationship between inflammatory response and wound healing may provide a plausible explanation for dose-related discrepancies.

Significantly, these curves may be beneficial for a rational plan of dexamethasone use. The differences between them highlight some important considerations regarding perioperative dexamethasone administration, namely, dosing and disease of the body.

By observing the dose–response curves, we found that intraperitoneal injection of dexamethasone (1 mg/kg) played a positive role in wound repair in septic mice but impaired it in normal mice. Previous studies have focused on either the association of wound healing and sepsis (6) or wound healing and dexamethasone (32); however, few investigations have focused on the impact of single-dose dexamethasone on wound repair under septic status. This is, so far as we know, the first study to explore the single dose of dexamethasone (1 mg/kg, i.p.) on wound healing in mice with and without sepsis and found the different effects of dexamethasone. Durmus et al. (32) identified that a single dose of dexamethasone at 1 mg/kg may have negative effects on wound healing in a prospective, randomised, experimental rat model. Our experiments confirmed these findings, and we found that a low dose of dexamethasone may benefit wound healing in septic mice.

Here, we monitored the progression of wound healing in two aspects: wound performance and the quality of tissue regeneration, and evaluated them using diverse parameters: wound closure, epidermal proliferation, angiogenesis, and the formation of granulation tissue and follicles. Moreover, we

compared the results with those of their septic counterparts and found different effects of dexamethasone, which were visualised by multiple experimental methods: image recording, H&E staining, and immunofluorescence staining.

The dose–response curve in normal mice was generated using a four-parameter nonlinear regression; Carvalho et al. (33) and Ginosar et al. (34) used this model to describe the relationship between dose and response in dose–response curves, and correlations were assessed with the use of linear regression in their studies. For wounds without sepsis, there was a positive correlation between the dose of dexamethasone and the incidence of delayed wound healing in our study. The curve in septic mice was generated using a bell-shaped nonlinear regression; Owen et al. (35) and Zhu et al. (36) used this model to describe the relationship between dose and response in dose–response curves. They performed statistical analyses of the dose–response curves, However, the forms of the response in our study are different from theirs, and the bell-shaped model is the sum of two dose–response curves; the relationship between the dose of dexamethasone and the incidence of delayed wound healing is not suitable to describe with simple positive/negative correlation. If we perform statistical analyses of the dose–response curves, the other form of the response (relative wound closure rate) will be chosen, which may produce more problems that we discuss in **Table 4**.

The process of wound healing involves a programmed local inflammatory reaction that requires precise coordination and is dictated mainly by macrophages in response to tissue damage. Early in wound healing, the initial inflammatory response is characterised by macrophage tissue destruction, production of inflammatory cytokines, and clearance of pathogens and debris. This is followed by the resolution of inflammation and initiation of tissue repair. The timing of both initiation and resolution of inflammation is essential for restoring tissue integrity after injury. Macrophages, which initiate and resolve inflammation, play an indispensable role in wound healing and contribute to tissue regeneration. The transition from pro-inflammatory to reparative phenotypes is required for effective wound healing in an orderly manner (32, 37). However, in the pathological status, the phenotypic switch of macrophages can be perturbed, resulting in the insufficiency and imbalance of pro-inflammatory and anti-inflammatory macrophages, preventing wound repair (36, 38, 39).

Our study demonstrated that a single dose of dexamethasone reduced pro-inflammatory cytokine levels and the number of macrophages in the wounds of normal mice in the early healing stage. This failure to generate an initial inflammatory response negatively impacts the downstream orchestration of subsequent phases, resulting in ongoing inflammation instead of proceeding into the proliferative phase (39, 40).

Our data suggest that dexamethasone impairs the initiation of inflammation in normal mice by reducing the number of macrophages, which may result from the inhibition of macrophage polarisation towards the *M*1 phenotype.

Unlike in normal mice, dexamethasone decreased the inflammatory response in the early healing of septic mice, and in the later stage, the wounds expressed a lower level of inflammatory cytokines. During the wound healing process, the total number of *M*1 and *M*2 macrophages was equal in the sepsis and sepsis + DEX groups. However, we found that there were sufficient *M*1 macrophages in the early stages and *M*2 macrophages in later wound healing in dexamethasone-treated septic mice, exhibiting a higher *M*1/*M*2 ratio and a lower *M*1/*M*2 ratio, respectively. This ensures that macrophages function in both pro-inflammatory and reparative phenotypes (41–43). These data indicate that dexamethasone alleviated the degree of inflammation rather than impairing the initiation of inflammation in wounds of dexamethasone-treated septic mice in the early stages; thus, healing progressed with resolving inflammation.

During wound healing, the local inflammatory response to injury may be influenced by dysregulation of systemic inflammation. In the current study, we found that dexamethasone reduced excessive inflammation by reducing the number of macrophages but maintained the balance between *M*1 and *M*2 macrophages in wounds in the context of sepsis. This may be because of the following reasons. First, DEX may disturb macrophage polarisation in wounds. Indeed, using *in vitro* and *in vivo* models, prior studies have demonstrated that glucocorticoids have an inhibitory effect on the polarisation of macrophages towards a pro-inflammatory phenotype (44–46). Second, DEX may perturb the migration of macrophages from the circulation; however, this hypothesis contradicts the observations of Chatzopoulou et al. (47) and Xie et al. (44) that glucocorticoids have a limited effect on the migration of macrophages in the zebrafish tail amputation model.

In the peritonitis model, a systemic inflammatory response occurs with large numbers of *M*1 macrophages (44, 48), which may provide a pre-inflammatory environment. After wounding, large numbers of monocytes are recruited from circulation into the wound bed, and such monocytes may differentiate into pro-inflammatory macrophages in response to the pre-inflammatory environment. Dexamethasone treatment, however, reduced the expression of inflammatory cytokines and the polarisation of macrophages in early stages (29, 49) and had limited effects on specific macrophages (pre-inflammatory environment maker), which maintained the coordination of the initiation and resolution of inflammation in wound healing. However, the effect of dexamethasone may be conditional, and further investigation is warranted.

Our study offers insight into the rational use of dexamethasone. However, this study has some limitations that must be addressed. Since we know that the effects of DEX on wound healing are associated with macrophages, further studies are necessary to clarify the regulatory mechanism by which DEX affects phenotypic changes in macrophages during the wound healing process in sepsis. In addition, rodent models have limitations in the evaluation of the effects of drugs in clinical practice and do not completely reflect human disease; thus, more forms of disease models and injections should be investigated.

In conclusion, wound healing was promoted in septic mice but delayed in normal mice following a single-dose intraperitoneal injection of dexamethasone. Dexamethasone reduced

inflammation without impairing the *M*1-induced initiation of inflammation and polarisation towards *M*2 in septic mice but impaired inflammation in normal mice. The two curves reflect the dose-related differences, which may provide considerable suggestions for the rational use of dexamethasone.

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 animal study was reviewed and approved by Animal Ethics Committee of the Sixth People's Hospital Affiliated to Shanghai Jiao Tong University.

Author contributions

YC designed the research and wrote the article. YC and XC acquired and analysed data. QZ supervised the entire research. All authors contributed to the article and approved the submitted version.

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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.

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