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Clinical teaching and practice in intensive care medicine and anesthesiology

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Clinical teaching and practice in intensive care medicine and anesthesiology

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Editorial: Clinical teaching and practice in intensive care medicine and anesthesiology

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Editorial on the Research Topic
Clinical teaching and practice in intensive care medicine and anesthesiology

This special topic is a Research Topic opened by Frontiers in Medicine in the field of critical care medicine and anesthesiology, focusing on the research and discussion of clinical teaching and practice. The main purpose of this Research Topic is to promote the development of teaching and practice in the field of critical care medicine and anesthesiology, improve the teaching and practice level of medical staff, so as to provide safer and more effective medical services for critically ill patients. This Research Topic finally contains 16 articles in total, 11 of which are original articles. The studies covers many research areas related to clinical teaching and practice, including but not limited to: education system and teaching methods of critical care medicine and anesthesiology, teaching quality assessment and improvement, clinical skills training and practical operation standards, Clinical research and translational research related to critical care medicine and anesthesia, as well as clinical case analysis and study protocol.

First of all, this Research Topic contains many researches and reflections on critical care medicine and anesthesiology education. O'Connor and Doyle reviewed methods for the assessment of undergraduate clinical placements in anesthesia and critical care. The results of the study show that there are various evaluation methods, including scoring sheets, questionnaires, reflection logs, etc., but these methods lack consistency and comparability and need further improvement and unification. Only adequate assessment will lead to an appropriate educational program for the residents to improve their skills and confidence in critical situations (O'Connor and Doyle). Su et al. conducted a survey on the training status of analgesia and sedation in China. The study found the necessity of improving physicians' cognition and practice of analgesia and sedation, and provided a reference for improving related education and training in mainland China (Su et al.). Brewster et al. the leadership in airway management

needs to be further strengthened, and at the same time, it is necessary to pay attention to the teamwork ability in the airway management process (Su et al.). In addition, the Research Topic also introduced the development and training of palliative medicine in China, opened up the extension of intensive care medicine treatment, and explained the possible methods of how to realize palliative care in intensive care medicine (Brewster et al.). These articles highlight the critical role of education in improving the quality and safety of critical care healthcare and provide physicians with educational resources on best practices and new technologies.

Second, this Research Topic contains several articles related to the diagnosis and management of critically ill patients. Among them is an analysis of septic shock in plateau areas from China. Studies have explained that septic shock is mainly caused by pathogens such as pneumonia, abdominal infection, and urinary tract infection, and has a high prevalence rate. In addition, patients with septic shock at high altitude often have challenges in airway management, hemodynamics, and fluid management (Li Q. et al.). This clarifies the direction of future related plateau medical training. In addition, severe disease-related technologies are developing rapidly, and two studies are from Long's Team. Their case report on the diagnosis of massive atelectasis and pneumothorax using electrical impedance imaging demonstrated the powerful diagnostic power of EIT (Zhou et al.); another article described a standard method for esophageal pressure measurement (Jiang et al.), which is relevant Training and dissemination of technology is critical care. In addition, it is of great significance to improve the treatment of patients who cannot tolerate non-invasive mechanical ventilation. Altinkaya Cavus et al. revealed the appropriate sedative agent to effectively reduce discomfort and improve the therapeutic effect, breaking through the past situation where we did not dare to use sedation for related patients (Altinkaya Cavus et al.). These studies provide important information on how to quickly and accurately diagnose and treat diseases in critical situations, helping doctors better understand how to respond to critical situations.

In addition, this Research Topic includes diagnostic and evaluation studies, articles aimed at improving the quality and safety of critical care healthcare. Among them, Mahmoodpoor et al. explored the prognostic value of using the National Early Warning Score (NEWS) and the Modified Early Warning Score (MEWS) for readmission and death in intensive care unit (ICU) patients. The conclusion highlighted that MEWS performed better in predicting death in ICU patients (Mahmoodpoor et al.). Chen et al. established an early warning scoring system for the assessment and prediction of septic shock in patients with gastrointestinal perforation. It can be seen that the evaluation of critically ill patients is very important clinically, and the scoring system needs to be paid attention to in teaching. These articles provide practical advice to help physicians refine and improve their practice in clinical setting.

Due to the characteristics of the anesthesia profession itself, this Research Topic contains many articles about the clinical practice of perioperative anesthesia. Benefits of paraspinal nerve block anesthesia (Fei et al.), fentanyl can improve poor outcome of ProSeal^{TM} laryngeal mask insertion (Rahmat Ameen Noorazyze et al.), use of tapered cuff endotracheal tube in anterior cervical spine surgery can control air leaks and complications (Li Y-S. et al.), Sumodexin to reduce the incidence of postoperative nausea and vomiting (Mat et al.), spinal analgesia in cesarean section provides a more accurate reference for the use of bupivacaine dosage (Manouchehrian et al.). These results are of great significance to the teaching of anesthesia.

The teaching of intensive care and anesthesia is a long-term and arduous systematic project, and good training and education directly affect the quality of patient treatment. Through this Research Topic, we feel that we should continue to strengthen our understanding and investment in teaching, and constantly adjust teaching methods and directions according to clinical needs, so as to respond to changes without change.

Author contributions

PP wrote this article. MK, LS, LM-L, and LS contributed the idea of this topic. All authors contributed to the article and approved the submitted version.

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REVIEW
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A Scoping Review of Assessment Methods Following Undergraduate Clinical Placements in Anesthesia and Intensive Care Medicine

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Introduction: Anesthesia and intensive care medicine are relatively new undergraduate medical placements. Both present unique learning opportunities and educational challenges to trainers and medical students. In the context of ongoing advances in medical education assessment and the importance of robust assessment methods, our scoping review sought to describe current research around medical student assessment after anesthesia and intensive care placements.

Methods: Following Levac's 6 step scoping review guide, we searched PubMed, EMBASE, EBSCO, SCOPUS, and Web of Science from 1980 to August 2021, including English-language original articles describing assessment after undergraduate medical placements in anesthesia and intensive care medicine. Results were reported in accordance with PRISMA scoping review guidelines.

Results: Nineteen articles published between 1983 and 2021 were selected for detailed review, with a mean of 119 participants and a median placement duration of 4 weeks. The most common assessment tools used were multiple-choice questions (7 studies), written assessment (6 studies) and simulation (6 studies). Seven studies used more than one assessment tool. All pre-/post-test studies showed an improvement in learning outcomes following clinical placements. No studies used workplace-based assessments or entrustable professional activities. One study included an account of theoretical considerations in study design.

Discussion: A diverse range of evidence-based assessment tools have been used in undergraduate medical assessment after anesthesia and intensive care placements. There is little evidence that recent developments in workplace assessment, entrustable activities and programmatic assessment have translated to undergraduate anesthesia or intensive care practice. This represents an area for further research as well as for curricular and assessment developments.

Keywords: intensive care, undergraduate education best practices, assessment and education, anesthesia, scoping review methodology

INTRODUCTION

The inclusion of anesthesia and intensive care medicine (ICM) in undergraduate medical student placements is a relatively new development (1). Recent publications have sought to define suitable curricula in these disciplines (2, 3). With expanding placement opportunities come an ever-increasing obligation to ensure that student learning is effective and efficient, that student time is "well-spent," and that we "maximize assessment for learning while at the same time arriving at robust decisions about learner's progress" (4).

The ICU and the anesthetic room can be challenging areas for student learning. Opportunities for history-taking and clinical examination are variable (1, 5). Patients undergoing anesthesia require a focused history and examination tailored to the upcoming anesthetic and surgical procedure (5). ICM patients are commonly sedated and/or confused, impeding history-taking. Clinical examination in the intensive care unit (ICU) is more challenging in the context of an immobile, unresponsive patient on extracorporeal devices (dialysis, mechanical ventilation). Furthermore, in both disciplines, procedural learning is often limited by the complex, high-stakes, time-sensitive aspects of common tasks (1, 5).

Conversely, anesthesia and ICM share learning opportunities not readily available during other placements. They are ideal environments for the vertical integration of primary and clinical sciences (6). Many learning topics are unique to these disciplines (e.g., acute respiratory distress syndrome, clinical brainstem death evaluation, inhalation anesthesia, pharmacological neuromuscular blockade). Other key elements of their curricula (e.g., the management of acute respiratory failure, shock, acute airway emergencies, sedation administration) are generic, high-stakes, transferrable clinical skills that could be viewed as important competencies for all doctors.

Current evidence suggests that ICM and anesthesia placements can achieve effective student learning outcomes (7). Nonetheless, the unique nature of their curricula may require a bespoke approach to learner assessment. Furthermore, valid and reliable tools are central to assessment decisions regarding high stakes competencies such as effective acute and perioperative patient care. Despite this, three recent papers on curriculum and effective teaching in the ICU and anesthetic room make no recommendations about student assessment (2, 3, 5). The first objective of our review therefore was to evaluate the nature and robustness of published assessment strategies in these high-stakes clinical specialties, incorporating an analysis of the theoretical bases for these publications.

The expansion of undergraduate anesthesia and ICM placements has occurred contemporaneously with an evolution in medical education assessment. Accordingly, practice is moving away from evaluating low-level cognitive learning objectives such as knowledge and understanding (using MCQs, written examinations) toward knowledge application (using extended matching questions, OSCEs) and most recently to clinical performance, either in a simulated or workplace environment (8–11). Furthermore, longitudinal methods such as programmatic assessment have in recent years gained in popularity (12). The extent to which this evolution has translated to assessment in undergraduate anesthesia and ICM education was the second objective of our review.

A scoping review methodology was used for two reasons. First, the authors had prior knowledge of the research topic and recognized that the range of published literature was unlikely to yield research of sufficient quality to enable a systematic review or a meta-analysis. Second, in light of recent advances in assessment practice, we anticipated a knowledge and/or research gap in the areas of anesthesia and ICM assessment. Our study methodology therefore needed to be tailored to identifying these gaps were they to exist (13, 14).

METHODS

We used the 6-step adaptation of Arksey and O'Malley's (15) scoping review framework as proposed by Levac et al. (13). These steps are (1) identifying research questions, (2) identifying relevant articles, (3) study selection, (4) charting the data, (5) collating, summarizing, and reporting the results and (6) consulting with stakeholders. In addition, we applied a scoping review quality checklist to enhance the rigor of our findings (16). The overarching purposes of our scoping review were (a) to describe the nature of existing research about undergraduate assessment after anesthesia/ICM placements and (b) to identify research gaps in this area.

The following six steps were applied.

1. Identifying Research Questions

The scoping research questions were:

1. What methods and practices of assessment have been reported in the literature for students undertaking clinical placements in anesthesia and/or intensive care medicine?
2. What educational theories have been articulated for the assessment methods published in the literature?

2. Identifying Relevant Articles

Using five online databases (EMBASE, SCOPUS, EBSCO, PubMed, Web of Science) we conducted a search for all available papers from January 1980 to 31/12/2020, using the search terms "medical student," and several variations on "anesthesia" and "intensive care" to account for differences in regional terminology (see **Figure 1**). A librarian was used to assist with accessing articles. Reference lists of relevant articles were also included in the search. Due to the pandemic, the high intensive care and anesthesia workload in early 2021 led to a reallocation of research to clinical time, delaying the completion of the scoping review. Accordingly, a further search was performed up to 31/08/2021.

To be included, studies had to describe original research using an assessment tool following an undergraduate placement in anesthesia and/or intensive care medicine. Studies were excluded if they were not published in English, if they enrolled postgraduate or non-medical learners, or if the assessment followed a standalone courses rather than a clinical placement.

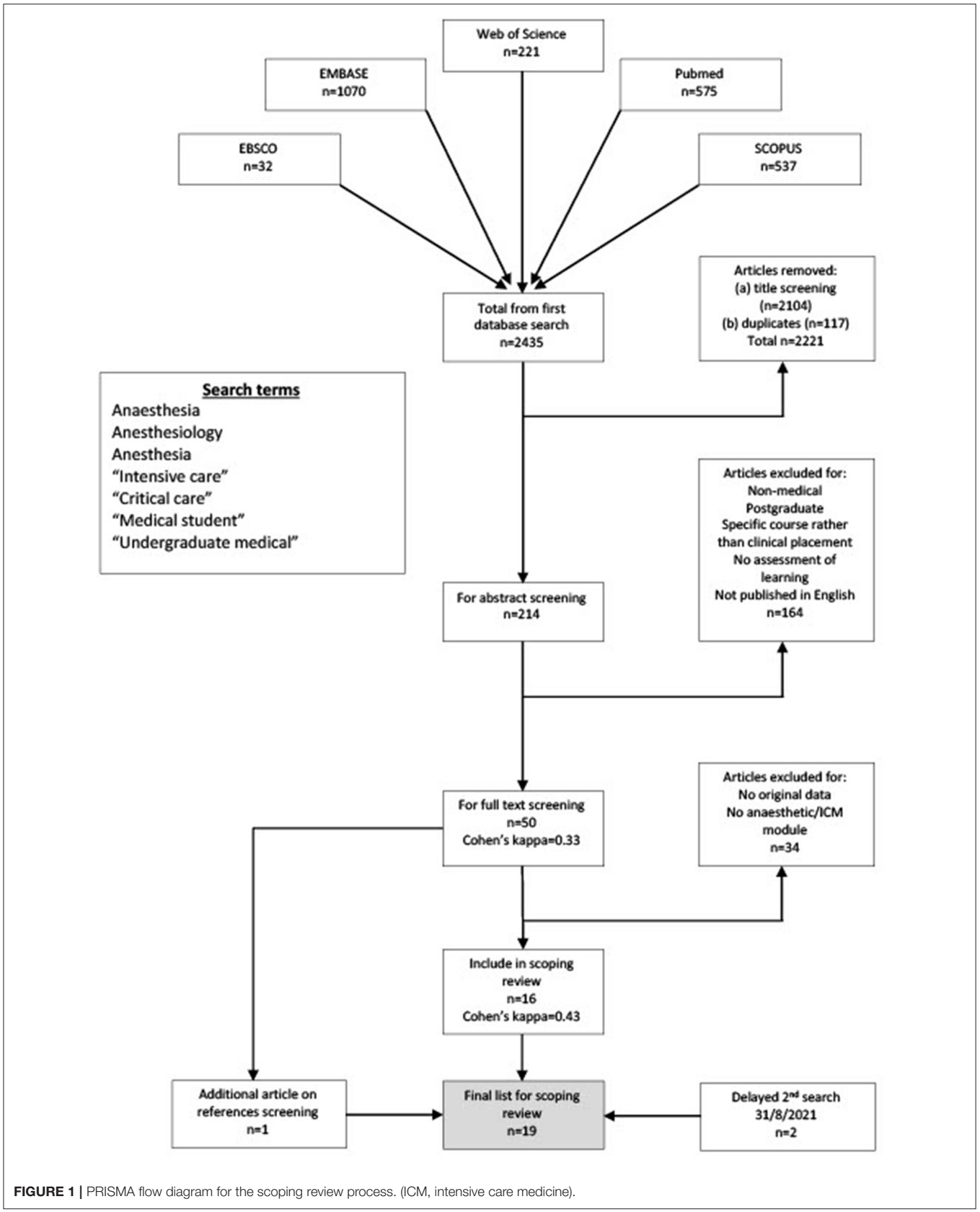

FIGURE 1 | PRISMA flow diagram for the scoping review process. (ICM, intensive care medicine).

3. Study Selection

The three stages of study selection were based on title, abstract, and full-text searches respectively. Mendeley© software was used. The two authors independently screened the publications for study inclusion. A Cohen's kappa coefficient was calculated to quantify author agreement at each stage of study selection. The authors met regularly to discuss and resolve any disagreements about study inclusion. The number of studies included in each stage of selection, and the exclusion criteria are shown in the flowchart in **Figure 1**.

4. Charting the Data

Evaluating each study involved a combination of numerical description and general thematic analysis. For the former, the following information was extracted from each article: lead author; country of authorship; journal title; the year of publication; study design; number of research sites; sample size; assessment tools used; quantitative outcomes; Miller's learning outcomes (17); MERQSI score (18). Through thematic analysis, other details about the studies were recorded, including qualitative outcomes, important author's quotes, theoretical considerations and any insights pertinent to the research area. In accordance with Levac et al. (13) scoping review methodology, the 2 authors met following data extraction of the first 6 articles to determine whether the approach was "consistent with the research question and purpose" (page 4). Study authors were contacted directly if further information or clarification about their findings were deemed appropriate.

5. Collating, Summarizing and Reporting the Results

The information drawn from each article was summarized and tabulated (see **Table 1**).

6. Consulting With Stakeholders

Consultation was undertaken via email with 3 stakeholders involved in undergraduate education and/or anaesthesiology/intensive care medicine teaching, each working in a different academic institution. Preliminary study results were shared with them. The purpose of the consultation was to seek opinions about any omitted sources of study information, to gain additional perspectives on the study topics, and to invite opinions about the study findings.

RESULTS

A total of 2,435 results were returned from the initial search between the 5 databases, of which 17, published between 1983 and 2020, were selected for full-text review (6, 20–34, 36). The second search performed in August 2021 returned 2 further studies published in 2021 (19, 35). The findings of these 19 studies are shown in **Table 1**.

Of the 19 studies, 9 (47.4%) involved anesthesia (21, 23–25, 28–32), 8 (42.1%) intensive care medicine (6, 19, 20, 26, 27, 33–35) and 2 (10.5%) a combination of both disciplines (22, 36). The primary research focus was on the assessment instrument and on student learning in 9 (22–26, 28–30, 36) and 7 (19–21, 27, 32, 33, 35) studies respectively. The remaining 3 studies had equal research focus on learning and the assessment tool.

All were single-center studies, 14 of which (73.7%) were conducted in Canada, USA and Hong Kong. The average sample size across all studies was 119 students (range 5–466). Clinical placements lasted 2–12 weeks, with a median duration of 4 weeks. Fourteen studies (73.7%) had 2 or 4 week placements.

Twelve of 19 studies (63.2%) had a non-randomized design and collected assessment data at one timepoint only (20–25, 28–32, 36). Conversely, the remaining 7 studies (36.8%) were either RCTs and/or had a pre-/post-test study design (6, 19, 26, 27, 33–35). Despite all studies reporting solely or mainly quantitative data, none conducted a power analysis to evaluate the required sample size. Ten studies (52.6%) considered the issues of the reliability and/or validity of their assessment tools (6, 21–26, 28, 30, 31). Two additional studies used standardized assessment questions from the Society of Critical Care Medicine and the American College of Physicians (20, 35). The average MERQSI score was 12.3 (range 5–15) out of a maximum of 18.

Q1: What Methods of Undergraduate Assessment Have Been Reported for Medical Students Undertaking Clinical Placements in Anesthesia and/or Intensive Care Medicine?

A wide variety of student assessment tools were used across the 19 included studies. These are shown in **Table 2**. The most common methods were multiple choice questions (7 studies; 36.8%) (19, 22, 26, 27, 29, 32, 35), written assessment (6 studies; 31.6%) (20, 22, 23, 29, 32, 34) and simulation (6 studies; 31.6%) (21, 23, 25, 26, 30, 31).

Seven studies (36.8%) used a combination of more than one assessment tool (22, 23, 25, 26, 29, 30, 32), which in 3 studies included final end-of-year examinations (22, 25, 30).

All 7 studies with a pre-/post-test design showed an improvement in assessment outcomes after clinical placements. All had a 4 week/1 month clinical placement and all were in intensive care medicine. Only 2 of these 7 studies evaluated student performance using simulation and/or OSCE stations (6, 26). The remaining 5 studies evaluated student knowledge using MCQs or written assessment tools (19, 27, 33–35).

Q2: What Educational Theories Are Evident in Studies of Undergraduate Medical Assessment After Anesthesia and/or Intensive Care Medical Placements?

Of the five studies with a primary research focus on student learning, contextual learning theory was used as the theoretical basis for one study (20). No other study made any methodological references to an underlying educational theory.

Though seldom articulated, Miller's Pyramid of learning outcomes was an important theoretical foundation in most of the studies (17). Nine studies (47.4% evaluated learning outcomes in the "shows how" level 3 domain using simulation

TABLE 1 | Summary of studies included in the scoping review.

Reference **Country**	**Study title**	**Journal** **Year** **Specialty site: single or multi-medical schools** **Assessment or Education**	**Study design** **Single arm or not** **Main data type(s)**	**Sample size** **Description of intervention** **Data collection tool(s)**	**Key messages from study findings** **Miscellaneous**	**Levels of learning outcomes assessed** **Educational theory if described** ***Validity/Reliability?***
Critchley et al. (19) Hong Kong	An adaptation of the objective structured clinical examination to a final year medical student course in anesthesia and intensive care	Anesthesia 1995 Anesthesia/ICM Single school Assessment	Descriptive account of 4 academic years – observational Single group having OSCE (no control) Quantitative (student performance and course feedback)	466 students in 4 years. Learning curriculum in place 4 week rotation → OSCE adaptation for skills, knowledge and communication. Summative (for final exam). Criterion-based marking Student survey/OSCE exam results	No student failed exam based on OSCE. Different domains of learning assessed in one examination Students perceived it a fair format (equally with other formats) but more stressful Assessment mapped to learning objectives derived from curriculum (knowledge and skills)	Miller's "Shows how" Assesses performance in simulated environment.
Lofaro et al. (20) US	An innovative course in surgical critical care for second-year medical students	Academic Medicine 1994 ICM Single school Education	Description of 12-week SICU rotation in 1990/91 Single arm, no control group Quantitative (rudimentary)	13 "sophomore" students 12 week SICU rotation Ax: "A shelf test from SCCM" (postgrad equivalent - ?format) Course evaluation by students	No student got <70% in SCCM test Student ratings were "uniformly high" Good description of range of teaching and learning methods	Miller's "Knows how" Contextual learning theory *Reliabilty/Validity NO but used an Society of Critical Care Medicine "Shelf" test*
Moll-Khosrawi et al. (21) Germany	Anaesthesiology students' Non-Technical skills: development and evaluation of a behavioral marker system for students (AS-NTS)	BMC Medical Education 2019 Anesthesia/EM Single school Education	4-steps of literature RV, focus groups/interviews, field observation and implementation/ validation Quant and qual	98 simulation activities with groups of 3 students (?yr, ?total number) Study describes the design of AS-NTS tool and evaluated feasibility, validity and inter-rater reliability of it Not summative Ax	Assessing 3 NTS: planning tasks, teamwork, and team orientation New Ax tool was feasible, valid and had good inter-rater reliability No Ax of technical skills or knowledge	Miller's "Shows how" for non-technical skills *Reliability YES* *Validity YES* *Intraclass correlation and Cohen's kappa* *Content validity index* *High validity and reliability*
Shams et al. (22) Saudi Arabia	Assessment of current undergraduate anesthesia course in a Saudi University	Saudi J Anesthesia 2013 Anesthesia/ICM Single school Assessment	Comparison of 3 different Ax tools (MCQs, portfolios and OSCEs) 3 Ax tools (quant) Short essays as well Student evaluation of course (quant)	154 students on 5-week OR/Anesthesia rotation described 20 question MCQ (validity and reliability) OSCE 6 stations Portfolio of presentations, logbook and trainer feedback (marks for each aspect) Correlation with final mark	Strong correlation between 3 Ax tools, and between each Ax tool and the overall outcome of the examination (r coeff >0.85 for all 3 tools). The MCQ exam was the highest predictor of overall exam mark, followed by OSCE and then portfolio.	Miller's "Shows how" *Reliability/Validity YES* *Cronbach alpha* *Cohen's kappa coefficient*

(Continued)

TABLE 1 | Continued

Reference **Country**	**Study title**	**Journal** **Year** **Specialty site: single or multi-medical schools** **Assessment or Education**	**Study design** **Single arm or not** **Main data type(s)**	**Sample size** **Description of intervention** **Data collection tool(s)**	**Key messages from study findings** **Miscellaneous**	**Levels of learning outcomes assessed** **Educational theory if described** ***Validity/Reliability?***
Morgan and Hogg (23) Canada	Evaluation of medical students' performance using the anesthesia simulator	Medical Education 2000 Anesthesia Single school Assessment	Pilot study, single arm interventional study, no control Faculty training to try to standardize Quantitative inter-rater reliability intra-class coefficient correlation between different Ax tools (Pearson) student evaluation	2 week anesthesia rotation with apprenticeship model in OR 24 students had sim assessment (to test reliability) and to compare with clinical and written exams for the rotation 6 scripted case scenarios linked to the learning objectives and outcomes of the anesthetic course	Strong IRR (ICC 0.87) Poor correlation between sim & written exam and between sim & clinical evaluation Better correlation between clinical & written exams Reliable assessment even if raters have not seen students during the rotation High student evaluation scores Authors did not expect written and sim to be well correlated but did hope for this between clinical and sim exams.	Miller's "Shows how" in simulated setting correlated with knows and knows how *Reliability YES* *Intraclass coefficient* *High inter-rater reliability*
Hamid et al. (24) Canada	The lack of construct validity when assessing clinical clerks during their anesthesia rotations	Can J Anesthesia 2020 Anesthesia Single school Assessment	Observational single arm study Quantitative (2 different numerical exams – anesth 1-10 and MCCQE part 1)	205 medical students undergoing 2 week anesthesia rotation Daily clinical evaluation (1-10 scale for 8 domains of medical competence) averaged over the 2 weeks period (average of 9 total daily evaluations per student)	No score of 1-4 (5=meets expectations) Mean score 7.1 DFA (discrimant function analysis) showed that anaes scores could identify weakest clerks "Failure to fail" phenomenon shown. A clear results of having subjective, workplace environment Ax tool Call for more valid, reliable and predictive assessments	Miller's "Does" observed in the workplace *Validity YES* *Discriminant Factor Analysis*
Morgan et al. (25) Canada	High-fidelity patient simulation: validation of performance checklists	BJA 2004 Anesthesia Single school Assessment	Quantitative Student scores on Sim Student feedback Single arm study	135 students 2 week anaesth rotation 1 day of Sim during this. 2 independent raters (0.97) 10 management Sim scenarios based on critical event [See (31)]. Wide faculty RV to decide "expected" and "critical performance items" (80% cutoff for inclusion) Internal consistency (compared with end of year clinical and anaes examination mark)	85% students agreed/strongly agreed the scenarios reflected rotation's learning objectives. Good face and content validity 5 of 10 scenarios had good internal consistency	Miller's "Shows how" *Reliability/Validity YES* *Cronbach's alpha* *Item analysis* *Variable validity (50% of scenarios had satisfactory validity and internal consistency)*

(Continued)

TABLE 1 | Continued

Reference **Country**	**Study title**	**Journal** **Year** **Specialty site: single or multi-medical schools** **Assessment or Education**	**Study design** **Single arm or not** **Main data type(s)**	**Sample size** **Description of intervention** **Data collection tool(s)**	**Key messages from study findings** **Miscellaneous**	**Levels of learning outcomes assessed** **Educational theory if described** ***Validity/Reliability?***
Rogers et al. (26) US	Quantifying learning in medical students during a critical care medicine elective: a comparison of 3 evaluation instruments.	CCM 2001 Intensive Care Medicine Single school Assessment	One student cohort with pre-/post- data collection. Ax tools randomized Quantitative data only Marks scored on 3 Ax tools	24 medical student volunteers 1 months ICM placement Ax using written exam (MCQs), OSCE and simulation (pre- and post-elective). All students received all 3 assessments at both time-points (order randomized)	Written test scores did not correlate with students' ability to perform (Sim) or apply their knowledge (OSCE). Scores reduced moving from knows, to knows how to does. Knowledge does not imply skills. Written tests overestimate achieving learning objectives OSCE has "grouping" or "compartmentalisation" of learning. Also, they are presented info rather than having to collect/deduce it themselves. Sim applies it all at once, thereby is harder.	Miller's "Shows how" *Validity discussion but no calculations*
Skinner et al. (27) UK	The use of computerized learning in intensive care: an evaluation of a new teaching program	Medical Education 1983 Medical ICM Single school Education	RCT of computer-assisted learning in addition to standard learning Quantitative Qualitative questionnaire	28 students (14 in each of 2 groups) Old-fashioned computer programme MCQ test pre- and post- learning.	From similar baseline, CAL showed 2-3 times higher post-test scores Computer familiarity associated with higher post-test scores Early study of eLearning/TeL Study focuses more on the learning rather than the assessment	A qualified doctor is "a highly complex blend of knowledge, attitudes and skills"(p53) Miller's "Knows"
Sharma and White (28) Canada	The use of multi-source feedback in assessing undergraduate students in a general surgery anaesthesiology clerkship	Medical Education 2010 (abstr) Anaesthesiology Single school Assessment	Feasibility study using MSF for student Ax Single arm Basic quant and qual data	Uncertain size ("groups of 20-24 students"). MSF using physicians, nurses, peers, patients and administrators 1-page MSF summary for each student	Each student had average of 25 assessments over 6 weeks. Concerns raised about validity of MSF assessments	Miller's "Does" Authors contacted but no response *Validity YES but no calculations*
Critchley et al. (29) HK	Web-based formative assessment case studies: role in a final year medicine 2-week anesthesia course	Anesthesia and Intensive Care 2009 Anesthesia Single school Assessment	Quantitative Feedback qualitative Single arm study – no control or comparator group No pre-/post-data collection	2 week anesthesia rotation Ax: 40-item MCQ and 2 written case reports 149 volunteer students with 6 online FACS (81% used it) Use of FACS during 2006-2007, with milestone MCQs integrated in each case Login and participation details MCQ scores in the FACS	Wide variation in FACS usage, time spent on each FACS. FACS comparable to in-class teaching on feedback Weak correlation between FACS usage and summative MCQs, but stronger correlation with written case reports.	Miller's "Knows how" Low stakes formative

(Continued)

TABLE 1 | Continued

Reference Country	Study title	Journal Year Specialty site: single or multi-medical schools Assessment or Education	Study design Single arm or not Main data type(s)	Sample size Description of intervention Data collection tool(s)	Key messages from study findings Miscellaneous	Levels of learning outcomes assessed Educational theory if described *Validity/Reliability?*
Morgan et al. (30) Canada	Validity and Reliability of undergraduate performance assessments in an anesthesia simulator	CJA 2001 Anesthesia Single school Assessment	Single arm study of students doing simulation Quantitative data (student performance scores, validity and reliability calculations)	140 students 10 day anesthesia rotation with simulator on Day 8 Faculty "marked" students on sim performance, each marking 25-34 students 25-point criterion-based marking form Reliability and validity assessed	High inter-rater reliability in the faculty assessments Poor correlation with students' final clinical and written exam results Concerns about low validity of assessment Low internal consistency of checklist assessments	Knowledge vs "hands-on medical management problems" (p230) Miller's "Shows how" *Validity/reliability YES* *Intraclass coefficient* *Item-total correlation coefficient* *Acceptable reliability with 2 assessors*
Rogers et al. (7) US	Medical Students can learn the basic application, analytic, evaluative and psychomotor skills of critical care medicine	CCM 2000 ICM Single school Education/Assessment	Pre- and Post- elective design using 2 clinical scenarios at 5 OSCE stations (randomized to be pre- or post-) Small randomized control group (n=3) All quantitative	1 month CCM elective OSCE Ax tool on D1 and last day of elective 2 independent assessors of videotaped OSCEs Pre-/Post- comparison	40 students doing elective 3 students not doing elective Only 27 videos were usable 80% of assessments had adequate reliability Consistent improvement in pre- and post-elective scores (except OSCE I = initial patient assessment)	Written exams reliable but not valid (if "we are training students to perform") *Reliability/Validity YES* *Kappa coefficient* *Good reliability for 80% of tools used* Miller's "Shows How"
Morgan et al. (31) Canada	Identification of gaps in the achievement of undergraduate anesthesia educational objectives using high fidelity patient simulation	Anaesth Analges 2003 Anesthesia Single school Education/Assessment	Single arm No control One data collection point Quantitative	135 students – 165 scenarios 2 week anesthesia course. 1 day simulation during this. Development of 10 Sim scenarios based with 3-8 learning items for each. Expert opinion about expected and critical items in these scenarios (80% minimum) Faculty score student performance in Sim sessions	"Expected performance criteria" of students vs "Critical management items" (p1690). 11 of 18 learning items performed by 75% of students. Sim effectively identified critical management items not performed Minimal focus on how teaching delivered. Sim = learning and assessment in one = assessment for learning.	*Reliability YES;* *Inter-rater reliability* *High reliability scores* Sim enables identification of "discrepancies between expected and actual educational outcomes" (p1694) Miller's "Shows how"

(Continued)

TABLE 1 | Continued

Reference **Country**	**Study title**	**Journal** **Year** **Specialty site: single or multi-medical schools** **Assessment or Education**	**Study design** **Single arm or not** **Main data type(s)**	**Sample size** **Description of intervention** **Data collection tool(s)**	**Key messages from study findings** **Miscellaneous**	**Levels of learning outcomes assessed** **Educational theory if described** ***Validity/Reliability?***
Leung et al. (32) HK	Evidence of virtual patients as a facilitative learning tool on an anesthesia course	AHSE 2015 Anesthesia Single school Education	Quantitative student scores Student feedback (Likert) Non-randomized 2x2 groups	VPs used to enhance learning. This is a study of learning, NOT assessment. Ax used: MCQs (60-item), SAQ paper, and "modified essay paper"	VPs improved assessment scores	Miller's "Knows How"
Kapur et al. (33) US	Implementation of a formal medical intensive care unit curriculum for medical students	AJRCCM 2019 (abstr) ICM Single school Education	Quantitative Student feedback	4 week MICU rotation Pre- and Post- rotation tests of knowledge and attitudes	Knowledge improved (67%→81%) "Comfort" taking history and managing common ICU scenarios improved but no demonstration of this.	Miller's "Knows how" Contacted author but no response
Rogers et al. (34) US	Teaching medical students complex cognitive skills in the intensive care unit	CCM 1995 ICM Education/Assessment	Single group Pre-/Post- design Randomized crossover trial Quantitative	1 month SICU rotations 33 students ICU curriculum designed with PbL. Cognitive learning emphasized. Written examinations	Knowledge and application improved	Miller's "Knows How"
Ho et al. (19) US	Developing the eMedical Student (eMS) – a pilot project integrating medical students into the tele-ICU during the COVID-19 Pandemic and beyond	Healthcare 2021 ICM Education	Single group Non-randomized Pre-/post-test design	5 students 4 week rotation MCQ assessment	Improved knowledge on MCQ test	Miller's "Knows"
Gergen et al. (35) US	Integrated critical care curriculum for the third-year internal medicine clerkship	MedEdPortal 2021 ICM Education	Single group Non-randomized with pre-/post-test design	41 3rd year students Seven sessions, over 4 weeks 15 Written short answer questions	Improved knowledge on SAQ test	*No specific reliability/validity but used standardized tests from American College of Physicians question bank* Miller's "Knows"

ICM, intensive care medicine; OR, operating room; IRR, interrater reliability; MCCQE, Medical Council of Canada Qualifying Examination; Sim, simulation; OSCE, objective structured clinical examination; MCQ, multiple choice question; RCT, randomised controlled trial; MSF, multisource feedback; FACS, formative assessment case studies; VPs, virtual patients; MICU, medical intensive care unit; SICU, surgical intensive care unit; SAQ, short-answer question; EM, emergency medicine.

TABLE 2 | Assessment tools used following clinical placements in Anaesthesia and Intensive Care Medicine.

MCQs: 7 studies (19, 22, 26, 27, 29, 32, 35)
Written assessment (not including OSCEs, MCQs or correlation with end of year exams): 6 studies (20, 22, 23, 29, 32, 34)
Simulation: 6 studies (21, 23, 25, 26, 30, 31)
OSCEs: 4 studies (6, 22, 26, 36)
Clinical assessment: 3 studies (23, 25, 30)
Other: FACS 1 (29), Portfolio 1 (22), MSF 1 (28), SAQs 1 (32), Unknown (33)
More than one assessment tool: 7 studies (22, 23, 25, 26, 29, 30, 32)

MCQs, multiple choice questions, OSCEs, objective structured clinical examinations; FACS, formative assessment case studies; MSF, multisource feedback; SAQs, short answer questions.

(21, 23, 25, 26, 30, 31) and/or OSCEs (6, 22, 26, 36). Ten studies had learning outcomes in the "knows" or "knows how" domains, using a combination of MCQs, SAQs, essay questions or online case studies (19, 20, 22, 23, 26, 27, 29, 32, 34, 35). One study did not describe the assessment tool used (33). Finally, two studies evaluated student performance in the workplace using subjective observation (24) and multi-source feedback (28), thereby targeting Miller level 4 "does" learning outcomes. No study used workplace assessment tools (WPAs) to assess undergraduate learning outcomes.

DISCUSSION

Our scoping review illustrates the heterogeneity of literature around assessment in undergraduate anesthesia and intensive care medicine. Published studies used numerous assessment instruments targeting learning outcomes that were either knowledge-based (using selected-response MCQs and constructed-response written tests) or performance-based (using OSCEs or a simulated clinical environment). The findings of the review also attest to the meaningful undergraduate learning that can occur in these clinical settings.

Though heterogenous, a majority of the included studies used evidence-based assessment strategies insofar as either the chosen tools have strong evidence supporting their use in UGME (MCQs, written exams, simulation, OSCEs) or more than one method was used to inform assessment decisions (8, 9, 37). Furthermore, all except one study (33) used an assessment strategy appropriate to the learning outcomes mapped to Miller's pyramid.

A key objective of undergraduate medical education is to equip students with the competencies to deliver effective and safe patient care in their first year of medical practice and beyond. The assessment of knowledge, or the theoretical application of that knowledge alone may not be sufficient to judge whether students are equipped with those skills (38). Accordingly, 9 studies in our review adopted a competency-based approach and used OSCEs or simulation to evaluate student performance. Only 3 of these studies however used complementary tools to evaluate learning in the domains of knowledge and understanding as well as competence (22, 23, 26). These are the most informative studies in our review for educators making instructional design decisions about student assessment after anesthesia and ICM placements.

The most frequent tool used to evaluate student performance in our review was simulation, whereby learners were assessed in the "show how" learning domain. Performance in a simulated environment however correlated poorly with written assessments, suggesting a role for both tools in reaching a more complete assessment decision about a student's learning outcomes. There was scant evidence in the studies however of observed performance assessment *in the workplace*–the "does" domain of Miller's pyramid–which likely reflects a lack of active student work in ICUs and anesthetic rooms; students in these environments are more likely to learn by observing than by doing.

Nonetheless, recent trends in undergraduate assessment have led to greater emphasis on workplace performance and to the use of entrustable professional activities (EPAs) (39–41). EPAs entail assessors observing students performing "units of work" (42) (p2) thereby judging the level of supervision each student needs with that activity–the entrustment decision (11). They are mapped to learning curricula and are commonly informed by assessment in the workplace (11). To date, most EPA studies in UGME centre around internal medicine and general surgery. While we identified no studies using EPAs solely for the purposes of undergraduate anesthesia/ICM assessment, some include anesthesia or ICM placements as part of a broad learning curriculum (43–45). Furthermore, of the 13 undergraduate EPAs published by the Association of American Medical Colleges, 3 (e.g., recognize a patient requiring urgent or emergent care and initiate evaluation and management) have direct relevance to ICM and anesthesia (46). The use of EPAs also helps address long-standing concerns about graduating student's readiness to commence internship (47). A strong case can therefore be made for applying EPAs to anesthesia and ICM.

We did not identify any studies using a programmatic approach to assessment, though our literature search may not have found studies which included anesthesia or ICM as part of a broader programme-wide assessment strategy. Moreover, programmatic assessment challenges the "module-specific" nature of traditional UGME, viewing a clinical placement within a broader context of an overall curriculum (12). Therefore, it does not readily apply to our review, which *ab initio* focused on the assessment of a specific placement in anesthesia or ICM.

A common criticism of education research is that theoretical considerations are not brought to the fore. This also applies to the majority of articles in our review. Notwithstanding this, most of the included studies were designed in such a way that the use of a theoretical paradigm could be implied. Moreover, some of the studies used instructional design methodology. The primary use of technology to enhance learning in 3 studies (27, 29, 32) draws from eLearning theory (48). Adopting problem-based learning in 3 further studies acknowledged the importance of constructivism in effective education (6, 26, 34). Aspects of workplace learning theory were evident in the numerous studies that promoted learning within the operating theater and/or the

intensive care unit (6, 20, 22, 23, 26, 29, 30, 33, 34, 36). The 6 studies using simulation for assessment (21, 23, 25, 26, 30, 31) likely reflected the importance of experiential learning theory and reflection (49).

A recent development that is difficult to ignore is the impact of the COVID-19 pandemic on undergraduate education. Accounts of formal assessment in the context of students working or learning during the pandemic appear to be rare (19). This likely reflects the time constraints and staff redeployment during the pandemic when clinical activities took precedence over faculty pursuits (50). Paradoxically, when viewed through the lens of Miller's pyramid, at a time when students may have been more actively involved in clinical care–in "doing" work–they were least likely to be formally assessed.

Our study therefore highlights a gap between published research in anesthesia/ICM assessment and recent advances in undergraduate assessment. However, for practice to change in these disciplines, the approach to student education in anesthetic rooms and ICUs must first evolve to allow more active student participation in daily clinical activities. Observed workplace assessment can only occur in environments where learners play a legitimate role in patient care. This is the main research gap identified in our review and is an important area for future research into the undergraduate study of anesthesia and intensive care medicine.

Our study results may be limited by the omission of some relevant articles. Each author however individually performed the search and results were then combined. Studies were individually evaluated for inclusion and though Cohen's coefficient showed a suboptimal correlation, author discussion at each step of study selection addressed any differences in opinion. We included any study where discussion did not resolve perceived differences. To improve the rigor of our study, we used the guidelines published by Maggio et al. in all stages of our review (16). We consulted with key external stakeholders but this step yielded no additional information.

In conclusion, our findings yield three useful insights. First, they act as a practice guide for educators directly involved in the design, delivery, and assessment of undergraduate learning in anesthesia and intensive care medicine. Second, they are informative for university educators tasked with the general organization and design of undergraduate medical education, helping them position anesthesia and intensive care medicine in strategies around programmatic assessment and workplace-based entrustable decision-making. Finally, they identify a large research gap for future studies to focus upon.

AUTHOR CONTRIBUTIONS

EO'C and ED were equally involved in all aspects of this study including design, literature searches, data collection, and manuscript writing. Both authors contributed to the article and approved the submitted version.

REFERENCES

1. Whereat S, McLean A. Survey of the current status of teaching intensive care medicine in Australia and New Zealand medical schools. *Crit Care Med.* (2012) 40:430–4. doi: 10.1097/CCM.0b013e31823295fe
2. Smith A, Brainard J, Campbell K. Development of an undergraduate medical education critical care content outline utilizing the delphi method. *Crit Care Med.* (2020) 48:98–103. doi: 10.1097/CCM.0000000000004086
3. Smith A, Carey C, Sadler J, Smith H, Stephens R, Frith C. Undergraduate education in anaesthesia, intensive care, pain, and perioperative medicine: the development of a national curriculum framework. *Med Teach.* (2018) 41:340–6. doi: 10.1080/0142159X.2018.1472373
4. van der Vleuten C, Schuwirth L, Driessen E, Dijkstra J, Tigelaar D, Baartman L, et al. A model for programmatic assessment fit for purpose. *Med Teach.* (2012) 34:205–14. doi: 10.3109/0142159X.2012.652239
5. Doyle S, Sharp M, Winter G, Khan M, Holden R, Djondo D, et al. Twelve tips for teaching in the ICU. *Med Teach.* (2021) 43:1005–9. doi: 10.1080/0142159X.2020.1859097
6. Rajan S, Jacob T, Sathyendra S. Vertical integration of basic science in final year of medical education. *Int J Appl Basic Med Res.* (2016) 6:182. doi: 10.4103/2229-516X.186958
7. Rogers P, Jacob H, Thomas E, Harwell M, Willenkin R, Pinsky M. Medical students can learn the basic application, analytic, evaluative, and psychomotor skills of critical care medicine. *Crit Care Med.* (2000) 28:550–4. doi: 10.1097/00003246-200002000-00043
8. Norcini J, Anderson B, Bollela V, Burch V, Costa M, Duvivier R, et al. Criteria for good assessment: consensus statement and recommendations from the Ottawa 2010 conference. *Med Teach.* (2011) 33:206–14. doi: 10.3109/0142159X.2011.551559
9. Norcini J, Anderson M, Bollela V, Burch V, Costa M, Duvivier R, et al. 2018 Consensus framework for good assessment. *Med Teach.* (2018) 40:1102–9. doi: 10.1080/0142159X.2018.1500016
10. Heeneman S, de Jong L, Dawson L, Wilkinson T, Ryan A, Tait G, et al. Ottawa 2020 consensus statement for programmatic assessment – 1. agreement on the principles. *Med Teach.* (2021) 43:1139–48. doi: 10.1080/0142159X.2021.1957088
11. ten Cate O, Chen H, Hoff R, Peters H, Bok H, van der Schaaf M. Curriculum development for the workplace using entrustable professional activities (EPAs): AMEE guide No. 99. *Med Teach.* (2015) 37:983–1002. doi: 10.3109/0142159X.2015.1060308
12. Torre D, Schuwirth L, Van der Vleuten C. Theoretical considerations on programmatic assessment. *Med Teach.* (2019) 42:213–20. doi: 10.1080/0142159X.2019.1672863
13. Levac D, Colquhoun H, O'Brien K. Scoping studies: advancing the methodology. *Implement Sci.* (2010) 5:69. doi: 10.1186/1748-5908-5-69
14. Munn Z, Peters M, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? guidance for authors when choosing between a systematic or scoping review approach. *BMC Med Res Methodol.* (2018) 18:143. doi: 10.1186/s12874-018-0611-x
15. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res Methodol.* (2005) 8:19–32. doi: 10.1080/1364557032000119616
16. Maggio L, Larsen K, Thomas A, Costello J, Artino A. Scoping reviews in medical education: a scoping review. *Med Educ.* (2020) 55:689–700. doi: 10.1111/medu.14431
17. Miller G. The assessment of clinical skills/competence/performance. *Academic Medicine.* (1990) 65:S63–7. doi: 10.1097/00001888-199009000-00045
18. Reed D, Beckman T, Wright S, Levine R, Kern D, Cook D. Predictive validity evidence for medical education research study quality instrument scores: quality of submissions to JGIM's medical education special issue. *J Gen Intern Med.* (2008) 23:903–7. doi: 10.1007/s11606-008-0664-3
19. Ho J, Susser P, Christian C, DeLisser H, Scott M, Pauls L, et al. Developing the eMedical Student (eMS)—a pilot project integrating medical students into the tele-ICU during the COVID-19 pandemic and beyond. *Healthcare.* (2021) 9:73. doi: 10.3390/healthcare9010073

20. Lofaro M, Abernathy C. An innovative course in surgical critical care for second-year medical students. *Acad Med.* (1994) 69:241–3. doi: 10.1097/00001888-199403000-00022
21. Moll-Khosrawi P, Kamphausen A, Hampe W, Schulte-Uentrop L, Zimmermann S, Kubitz J. Anaesthesiology students' non-technical skills: development and evaluation of a behavioural marker system for students (AS-NTS). *BMC Med Educ*. (2019) 19:205. doi: 10.1186/s12909-019-1609-8
22. Shams T, El-Masry R. al Wadani H, Amr M. Assessment of current undergraduate anaesthesia course in a Saudi University. *Saudi J Anaesth.* (2013) 7:122. doi: 10.4103/1658-354X.114049
23. Morgan PJ, Cleave-Hogg D Evaluation of medical students' performance using the anaesthesia simulator. *Med Educ*. (2000) 34:42–5. doi: 10.1046/j.1365-2923.2000.00462.x
24. Hamid A, Schmuck M, Cordovani D. The lack of construct validity when assessing clinical clerks during their anesthesia rotations. *Can J Anesth.* (2020) 67:1081–2. doi: 10.1007/s12630-020-01597-5
25. Morgan P, Cleave-Hogg D, DeSousa S, Tarshis J. High-fidelity patient simulation: validation of performance checklists. *Br J Anaesth.* (2004) 92:388–92. doi: 10.1093/bja/aeh081
26. Rogers P, Jacob H, Rashwan A, Pinsky M. Quantifying learning in medical students during a critical care medicine elective: a comparison of three evaluation instruments. *Crit Care Med.* (2001) 29:1268–73. doi: 10.1097/00003246-200106000-00039
27. Skinner J, Knowles G, Armstrong R, Ingram D. The use of computerized Learning in intensive care: an evaluation of a new teaching program. *Med Educ.* (1983) 17:49–53. doi: 10.1111/j.1365-2923.1983.tb01093.x
28. Sharma N, White J. The use of multi-source feedback in assessing undergraduate students in a general surgery/anesthesiology clerkship. *Med Educ.* (2010) 44:5–6. doi: 10.1111/j.1365-2923.2010.03702.x
29. Critchley L, Kumta S, Ware J, Wong J. Web-based formative assessment case studies: role in a final year medicine two-week anaesthesia course. *Anaesth Intensive Care.* (2009) 37:637–45. doi: 10.1177/0310057X0903700408
30. Morgan P, Cleave-Hogg D, Guest C, Herold J. Validity and reliability of undergraduate performance assessments in an anesthesia simulator. *Can J Anesth.* (2001) 48:225–33. doi: 10.1007/BF03019750
31. Morgan PJ, Cleave-Hogg D, DeSousa S, Tarshis J. Identification of gaps in the achievement of undergraduate anesthesia educational objectives using high-fidelity patient simulation. *Anesth Analg.* (2003) 97:1690–4. doi: 10.1213/01.ANE.0000086893.39567.D0
32. Leung J, Critchley L, Yung A, Kumta S. Evidence of virtual patients as a facilitative learning tool on an anesthesia course. *Adv Health Sci Educ.* (2014) 20:885–901. doi: 10.1007/s10459-014-9570-0
33. Kapur N, Birk V, Trivedi A. Implementation of a formal medical intensive care unit (MICU) curriculum for medical students. *Am J Respir Crit Care Med.* (2019) 199:A4789. doi: 10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A4789
34. Rogers P, Grenvik A, Willenkin R. Teaching medical students complex cognitive skills in the intensive care unit. *Crit Care Med.* (1995) 23:575–81. doi: 10.1097/00003246-199503000-00025
35. Gergen D, Raines J, Lublin B, Neumeier A, Quach B, King C. Integrated critical care curriculum for the third-year internal medicine clerkship. *MedEdPORTAL*. (2020) 16:11032. doi: 10.15766/mep_2374-8265.11032
36. Critchley L, Short T, Buckley T, Gin T, O'Meara M, Oh T. An adaptation of the objective structured clinical examination to a final year medical student course in anaesthesia and intensive care. *Anaesthesia.* (1995) 50:354–8. doi: 10.1111/j.1365-2044.1995.tb04617.x
37. Gordon C, Ryall T, Judd B. Simulation-based assessments in health professional education: a systematic review. *J Multidiscip Healthc.* (2016) 9:69–82. doi: 10.2147/JMDH.S92695
38. Shumway JM, Harden RM, AMEE. education guide No 25: the assessment of learning outcomes for the competent and reflective physician. *Med Teach.* (2003) 25:569–84. doi: 10.1080/0142159032000151907
39. Shorey S, Lau T, Lau S, Ang E. Entrustable professional activities in health care education: a scoping review. *Med Educ.* (2019) 53:766–77. doi: 10.1111/medu.13879
40. Meyer E, Chen H, Uijtdehaage S, Durning S, Maggio L. Scoping review of entrustable professional activities in undergraduate medical education. *Acad Med.* (2019) 94:1040–9. doi: 10.1097/ACM.0000000000002735
41. Pinilla S, Lenouvel E, Cantisani A, Klöppel S, Strik W, Huwendiek S, et al. Working with entrustable professional activities in clinical education in undergraduate medical education: a scoping review. *BMC Med Educ*. (2021) 21:172. doi: 10.1186/s12909-021-02608-9
42. Peters H, Holzhausen Y, Maaz A, Driessen E, Czeskleba A. Introducing an assessment tool based on a full set of end-of-training EPAs to capture the workplace performance of final-year medical students. *BMC Med Educ*. (2019) 19:207. doi: 10.1186/s12909-019-1600-4
43. Barrett J, Trumble S, McColl G. Novice students navigating the clinical environment in an early medical clerkship. *Med Educ.* (2017) 51:1014–24. doi: 10.1111/medu.13357
44. Jonker G, Booij E, Otte W, Vlijm C, Ten Cate O, Hoff R. An elective entrustable professional activity-based thematic final medical school year: an appreciative inquiry study among students, graduates, and supervisors. *Adv Med Educ Pract.* (2018) 9:837–45. doi: 10.2147/AMEP.S176649
45. ten Cate O, Graafmans L, Posthumus I, Welink L, van Dijk M. The EPA-based Utrecht undergraduate clinical curriculum: development and implementation. *Med Teach.* (2018) 40:506–13. doi: 10.1080/0142159X.2018.1435856
46. Englander R, Flynn T, Call S, Carraccio C, Cleary L, Fulton T, et al. Toward defining the foundation of the MD degree: core entrustable professional activities for entering residency. *Acad Med.* (2016) 91:1352–8. doi: 10.1097/ACM.0000000000001204
47. Bosch J, Maaz A, Hitzblech T, Holzhausen Y, Peters H. Medical students' preparedness for professional activities in early clerkships. *BMC Med Educ*. (2017) 17:140. doi: 10.1186/s12909-017-0971-7
48. Mayer RE. Elements of a science of e-learning. *J Educ Comput Res.* (2003) 29:297–313. doi: 10.2190/YJLG-09F9-XKAX-753D
49. Kolb D. *Experiential Learning*. Englewood Cliffs, NJ: Prentice Hall (1984).
50. Bosveld M, van Doorn D, Stassen P, Westerman D, Bergmans D, van der Horst I, et al. Lessons learned: contribution to healthcare by medical students during COVID-19. *J Crit Care.* (2021) 63:113–6. doi: 10.1016/j.jcrc.2020.09.015

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Effects of Sugammadex and Neostigmine on Post-operative Nausea and Vomiting in ENT Surgery

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We aim to compare the effects of sugammadex on postoperative nausea and vomiting (PONV) with those of neostigmine–atropine mixture. A total of 136 American Society of Anesthesiology (ASA) I or II patients, aged 18 to 65 years who underwent ear, nose, and throat (ENT) surgery under general anesthesia, were recruited in this prospective, randomized, double-blind study to receive either sugammadex 2 mg/kg or neostigmine 2.5 mg with atropine 1 mg for reversal of neuromuscular blockade. PONV scores and the need for the rescue of anti-emetic were assessed upon arrival in the post-anesthesia recovery unit and at 1-, 6-, 12-, and 24-h post-reversal. The incidence of PONV was significantly lower in patients who received sugammadex (3%) compared to patients who received neostigmine–atropine mixture (20%) at 6 h postoperative ($p = 0.013$). The incidence of PONV was comparable at other time intervals. None of the sugammadex recipients require rescue antiemetic whereas two patients from the neostigmine–atropine group required rescue antiemetic at 1 and 6 h post-reversal, respectively. The need for the rescue antiemetic was not statistically significant. We concluded that reversal of neuromuscular blockade with sugammadex showed lower incidence of PONV compared to neostigmine–atropine combination in the first 6 h post-reversal.

Keywords: sugammadex, neostigmine, postoperative nausea and vomiting, reversal of neuromuscular block, ENT surgery

INTRODUCTION

Postoperative nausea and vomiting (PONV) are one of the most unpleasant experience for patients undergoing surgery under general anesthesia and remains a significant problem in modern anesthetic practice because of the adverse consequences such as delayed recovery, unexpected hospital admission, delayed return to work of ambulatory patients, pulmonary aspiration, wound dehiscence, and dehydration (1).

General incidence of PONV reported is in the range of 20–30% but can increase up to 80% in high-risk patients (2). Ear, nose, and throat (ENT) surgeries have a high incidence of postoperative emesis when no prophylaxis is given and the occurrence of nausea or vomiting postoperatively can worsen patients' condition and hence delay recovery and discharge from the hospital (3).

Neostigmine is an anticholinesterase inhibitor used to antagonize muscle paralysis caused by non-depolarizing muscle relaxants through the formation of carbamylated enzyme complex causing increase in the concentration of acetylcholine at the neuromuscular junction (4). It is known to cause bradycardia, increase gastrointestinal motility, and increase gastric secretions (5). Neostigmine is postulated to increase the risk of PONV by provoking gastric spasms, lowering barrier pressure and heighten afferent input to central vomiting center (4). There are several types of receptor for emetogenic neurotransmitters such as dopamine (D_2) receptors, histaminic (H_1) receptors, 5-hydroxytryptamine$_3$ (serotonin) receptors, and muscarinic cholinergic receptors (6). On this theoretical basis, cholinesterase inhibitor (neostigmine in particular) has been associated with increased PONV (7). Previous study has shown the neostigmine dose of up to 2.5 mg or more increased the risk for PONV (8). However, a meta-analysis of 10 clinical studies involving 933 patients by Cheng et al. demonstrated inconclusive evidence that neostigmine increased nausea or vomiting when given with atropine or glycopyrrolate (9).

Sugammadex is a selective gamma-cyclodextrin drug that terminates the action of muscle paralysis by encapsulating aminosteroid non-depolarizing muscle relaxant (10). It is a fast-onset drug without the muscarinic side effects of neostigmine (11). The well-known side effects of sugammadex were nausea and vomiting but these side effects had been shown to be well-tolerated in adult patients (12). A meta-analysis involving 17 randomized clinical trials that recruited 1,553 patients were unable to conclusively confirm any evidence for the differences in PONV effects between sugammadex and neostigmine (13). Due to these findings, we conducted this study with the aim of comparing the PONV effects when neuromuscular blockade was antagonized with sugammadex compared to neostigmine–atropine combination after ENT surgery.

MATERIALS AND METHODS

This was a prospective, double-blinded, randomized clinical study conducted at Universiti Kebangsaan Malaysia Medical Centre (UKMMC) between November 2019 to November 2020. This study was approved by the Research Committee of Department of Anesthesiology and Intensive Care, UKMMC as well as the Medical Research & Ethics Committee, UKMMC (JEP 2019-542).

Patients

A total of 136 patients aged between 18 and 65 years, American Society of Anesthesiologists (ASA) physical status I or II scheduled for elective ENT surgery, were recruited in the study. Patients who were obese (body mass index >30 kg/m^2), pregnant, had history of PONV, Apfel score (2) more than 2, impaired renal function (creatinine clearance <30 ml/min), required postoperative ventilation, and allergic to any drugs used in this study were excluded. Patients who underwent middle ear surgery requiring nerve monitoring were also excluded from the study.

TABLE 1 | Patients and clinical characteristics. Data presented as mean ± SD or number (percentage).

	Group N ($n = 68$)	Group S ($n = 68$)	p-value
Age (year)	42.9 ± 13.6	39.8 ± 14.3	0.198
BMI (kg m^{-2})	25.9 ± 2.9	25.0 ± 2.6	0.066
Gender			0.732
Male	33 (49%)	35 (51%)	
Female	35 (51%)	33(49%)	
ASA			0.863
I	37 (54%)	39 (57%)	
II	31 (46%)	29 (43%)	
Apfel score			0.678
0	8 (12%)	5 (7%)	
1	27 (40%)	29 (43%)	
2	33 (48%)	34 (50%)	
Type of surgery			0.543
Ear	10 (15%)	6 (9%)	
Nose	38 (56%)	39 (57%)	
Pharyngeal	20 (29%)	23 (34%)	
Duration of surgery (min)	137.9 ± 70.3	129.1 ± 62.6	0.441
Morphine consumption (mg)	3.29 ± 1.50	3.62 ± 1.30	0.180

BMI, body mass index; ASA, American Society of Anesthesiologists.

Recruitment and Randomization

During preoperative assessment, patients eligible for the study were assessed for risk of PONV using Apfel score. Patients were then randomized using computer generated sequence to either received neostigmine (Group N) or sugammadex (Group S). Patients were not given sedative premedication prior to their surgery. About 1 g of oral paracetamol was given to the patients prior to operating theater call.

Methodology

In the operating room, all patients were monitored with standard 3-lead electrocardiogram (ECG), peripheral oxygen saturation (SpO2), and non-invasive blood pressure (NIBP). Baseline pulse rate, systolic blood pressure, diastolic blood pressure, and peripheral oxygen saturation were recorded. Patients received crystalloid infusion of normal saline 0.9% or Hartmann solutions throughout the surgery to replace the loss from dehydration. All patients given general anesthesia were preoxygenated for 3–5 min, followed by administration of intravenous (IV) fentanyl 2 mcg/kg and propofol 2 mg/kg, and paralyzed with rocuronium 0.9 mg/kg before orotracheal intubation. Anesthesia was maintained with sevoflurane to achieve a minimum alveolar concentration of 1.0–1.2 in oxygen and air in a 1:1 ratio.

All patients received prophylactic antiemetics, IV dexamethasone 8 mg on induction of general anesthesia, and IV granisetron 1 mg at the end of surgery. Intravenous parecoxib 40 mg was given 30 min before the end of the procedure as a part of multimodal analgesia management. Additional analgesia of morphine up to 0.1 mg/kg used intraoperatively was recorded. At the end of procedure, volatile agent was terminated, and the

patients were ventilated with 100% oxygen. Reversal agent was administered depending on which group the patients have been randomized to receive. Patients in Group N received neostigmine 2.5 mg in combination with atropine 1 mg and patients in Group S received sugammadex 2 mg/kg at the end of surgery. Patients were extubated after suctioning of oropharyngeal secretions and transferred to the postanesthesia recovery unit.

Postoperative nausea and vomiting were assessed by an investigator not involved in the intraoperative care. The incidence of PONV and the need for rescue antiemetics were evaluated for 24 h after surgical procedure. In the postanesthesia recovery unit, nausea and vomiting were assessed using a 4-point verbal descriptive scale as described in previous studies: 0 = not nauseated, 1 = nauseated, not vomiting, 2 = nauseated, one to two episodes of vomiting, 3 = nauseated, more than two episodes of vomiting during the observation period (13). Patients who had vomiting of three or more episodes (PONV score of 3) were given IV metoclopramide 10 mg as rescue antiemetic. Patients were ensured to have stable hemodynamic and adequate pain control prior to discharge to general ward. In the ward, PONV was monitored at 6-, 12-, and 24-h post-reversal with test drugs. Any antiemetic drug given within the first 24 h was recorded. Time to first oral intake that was defined as the time patients started taking food or fluids after the surgery was also recorded.

Statistical Analysis

In the previous study by Yagan et al. (14), the incidence of PONV was reported as 27% with neostigmine and 7% with sugammadex. Using Schlesselman formula, 62 patients in each group would be required to detect 20% change with 80% power and 5% significance ($\alpha = 0.05$, $\beta = 0.80$). We recruited 136 patients in this study to allow for 10% dropouts. Data collected in the study were analyzed using SPSS for MAC version 27.0 (IBM Corp, Armonk, NY, USA). Descriptive statistics were presented as mean ± standard deviation for continuous variable and as number and percentage for nominal variables. Independent sample *t*-test was used for age, BMI, opioid consumption, and duration of surgery. Categorical data such as gender, ASA physical status, and rate of PONV were tested using chi-square or Fisher's exact test. A p-value < 0.05 was considered as statistically significant.

RESULTS

A total of 136 patients were recruited with no dropouts. The demographic data shown in **Table 1** were comparable in both groups. There was no statistical significance seen between both groups in terms of PONV risk scores, type of surgery, duration of surgery as well as total morphine consumption intraoperatively.

Table 2 shows the incidence and severity of PONV on arrival to postanesthesia recovery unit and at 1-, 6-, 12-, and 24-h post-reversal. The incidence and severity of PONV were statistically significant only at 6 h post-reversal ($p = 0.013$). Rescue antiemetic was only required in the neostigmine group at 1- and 6-h post-reversal. The need for rescue PONV was not statistically significant. All patients that scored at least one episode of vomiting in the neostigmine group received neostigmine dose of <45 μg/kg and had received similar amount of morphine intraoperatively (0.05 mg/kg). There was no vomiting noted in either group from 12 h post-reversal onward. None of the patients had PONV by 24 h post-reversal. Time to first oral intake was comparable between both groups. All patients had minimal pain in the first 24 h post-reversal.

TABLE 2 | Incidence and severity of PONV in groups. Data presented as number (percentage).

	Group N ($n = 68$)	Group S ($n = 68$)	p-value
On arrival to recovery area			0.381
PONV SCORE 0	35 (52%)	41 (60%)	
1	28 (41%)	25 (37%)	
2	5 (7%)	2 (3%)	
3	0 (0%)	0 (0%)	
1 h post-reversal			0.158
PONV SCORE 0	35 (52%)	38 (56%)	
1	26 (38%)	28 (41%)	
2	5 (7%)	2 (3%)	
3	2 (3%)	0 (0%)	
6 h post-reversal			0.013*
PONV SCORE 0	54 (80%)	66 (97%)	
1	8 (11%)	2 (3%)	
2	4 (6%)	0 (0%)	
3	2(3%)	0 (0%)	
12 h post-reversal			0.500
PONV SCORE 0	66 (97%)	67 (99%)	
1	2 (3%)	1 (1%)	
2	0 (0%)	0 (0%)	
3	0 (0%)	0 (0%)	
24 h post-reversal			1.000
PONV SCORE 0	68 (100%)	68 (100%)	
Timing of first oral intake			0.220
Less than 6 h	63 (93%)	66 (97%)	
More than 6 h	5 (7%)	2 (3%)	

0 = no nausea or vomiting, 1 = nauseated, no vomiting 2 = nauseated, one or two episodes of vomiting, 3 = nauseated, more than two episodes of vomiting.
**$p < 0.05$ is statistically significant.*

DISCUSSION

Nausea and vomiting occur more commonly following middle ear or nasal surgery, and least frequently after pharyngeal surgery (15). The incidence of PONV is reported as 62–80% after middle ear surgery and 34–65% after nasal surgery without prophylactic antiemetic medication (16). The higher incidence of PONV in ENT surgery was likely due to the sensory stimulation of the ophthalmic and maxillary divisions of trigeminal nerve in the nose, vagal stimulation from head and neck region, and stimulation of afferent fibers of the vestibular apparatus (15).

Despite middle ear surgery being more emetogenic, our study did not report any severe PONV in either group. Patients who reported severe PONV and required rescue antiemetic at first hour post-reversal were both women in their 30s and underwent nasal (trans-sphenoidal surgery for cerebrospinal fluid leak) and

pharyngeal (tonsillectomy) surgery, respectively. Another two patients who needed rescue antiemetic within 6 h post-reversal were in their 30s, one of whom was a woman. Both of them had nasal (septoturbinoplasty) and pharyngeal (tonsillectomy) surgery, respectively as well. We found that all 4 patients had received pharyngeal throat pack insertion during the procedures, and we postulated that the pharyngeal packing may have caused pharyngeal mucosal trauma leading to discomfort and exacerbate PONV (16).

In our study, the average incidence of PONV between 0 and 1 h postoperative was 48% for neostigmine and 40–44% for sugammadex recipients which was comparable between both groups. The rate of PONV in both groups showed similar pattern of decline over time with none of the patients having PONV by 24 h post-reversal. The higher PONV rate for both groups in the early postoperative period in our study was likely attributed to the effects of volatile anesthesia. In a randomized controlled trial by Apfel et al. (17) it was shown that volatile agent was pro-emetogenic and was considered the primary cause of early PONV (0–2 h) with no impact on delayed PONV (2–24 h). As ENT surgery is an emetogenic procedure, prescribing 2 prophylactic antiemetics in our study to mitigate the incidence of PONV have likely reduced the rate of delayed PONV seen in our study (18). Using a combination of dexamethasone and serotonin antagonist, the ability to reduce PONV has been shown to be greater than a single antiemetic agent since these antiemetics act at different receptors (18, 19). Studies have shown that dexamethasone is effective against late PONV (20). In a study done by Rajeeva et al. (21) it was shown that delayed vomiting was better controlled, and nausea score was lesser with combination of ondansetron 4 mg and dexamethasone 8 mg in female patients who underwent laparoscopic gynecology surgery.

In our study, sugammadex showed significantly less incidence of PONV (3%) compared to neostigmine (20%) at 6 h post-reversal. Theoretically, the short duration of action of neostigmine should not give rise to PONV beyond the first hour postreversal. However, cholinesterase inhibitors may decrease esophageal sphincter pressure and increase the secretion of stomach fluid and intestinal movement (7). Unlike what was found in our study, Yagan et al. (14) demonstrated that sugammadex 2 mg/kg showed significantly lower incidence of PONV (8%) compared to neostigmine 50 μg /kg with atropine in the first hour post-operative and less antiemetic used in 24 h of monitoring in a mixed surgical population. The higher incidence for PONV between 0 and 6 h in both of our groups compared to Yagan et al. (14) could be due to the longer duration of surgery in our study averaging 130 min compared to 50 min by Yagan et al. (14). A total of one patient in our study who had severe PONV from 1 h until 6 h post-reversal was found to have a longer duration of nasal surgery (4.5 h compared to 2 h in average for other patients). Apfel et al. (17) had also demonstrated a strong dose–response relationship between duration and use of volatile anesthesia which is pro-emetogenic. It has been established that an increase in surgery duration may increase the incidence of PONV whereby each 30-min increase in duration increases PONV risk by 60%, so that a baseline risk of 10% is increased to 16% after 30 min (22). Tas Tuna et al. (23) reported no significant difference in the incidence of PONV at all time intervals between patients receiving neostigmine 40 μg /kg (with atropine) vs. patients receiving sugammadex 2 mg/kg undergoing laparoscopic cholecystectomy (24). In their study, none of their patients received antiemetic prophylaxis. Similarly, Paech et al. (23)also found no significant difference in PONV between sugammadex 2 mg/kg and neostigmine 40 μg/kg in patients undergoing laparoscopic gynecological procedure. In their study, their patients only received one prophylactic antiemetic (dexamethasone 4 mg) and ondansetron was not given routinely. Instead of atropine, glycopyrrolate was used in combination with neostigmine as reversal agent. In a study by Chhibber et al. (25), neostigmine with atropine was found to be associated with less incidence of PONV compared to neostigmine with glycopyrrolate due to the central anticholinergic action of atropine on antiemesis effect. Similarly, Cheng et al. also found that atropine was associated with a statistically significant decreased risk for PONV compared to glycopyrrolate (9).

Conflicting findings have been reported by several clinical studies regarding the dose of neostigmine used as reversal agent and its relationship with PONV. Koyuncu et al. (5) compared the effects of neostigmine 70 μg/kg and sugammadex 2 mg/kg on PONV in 100 patients undergoing extremity surgery. In their study, patients were not prescribed intraoperative antiemetic, but the author demonstrated that PONV scores were lower only upon arrival in post-anesthesia care area in patients who received sugammadex. PONV was observed in 60% of patients assigned to sugammadex compared to 58% of those that received neostigmine during the initial 24 h postoperative. Higher dose of neostigmine compared to conventional dose of 50 μg/kg might be a contributory factor. Some pieces of literature have linked the higher dose of neostigmine to be a causative factor of PONV (26). High dose of neostigmine (>2.5 mg) is associated with increased PONV (8). Løvstad et al. (27) investigated the effects of neostigmine 50 μg /kg to placebo on PONV on patients with laparoscopic gynecology and found significant increase in PONV during the first 6 h postoperative. In our study, neostigmine was given in a standard dose of 2.5 mg (average of 36 μg/kg). Even though the dose of neostigmine received by patients in our study was lower than the dose used in the previous studies, none of our patients reported any residual paralysis postoperatively, and a study by McCourt et al. showed that neuromuscular blockade induced by rocuronium can be safely antagonized using a neostigmine dose as low of 35 μg/kg (28).

Reducing modifiable risk factors can significantly decrease the rate of PONV. However, clinicians rarely consider the risk of PONV when choosing reversal agents because residual paralysis is a more common concern than PONV. In terms of health economics, Parra-Sanchez et al. performed a comprehensive economic analysis of PONV in patients undergoing ambulatory surgery and they reported an incremental hospital expenditure of $75 per patient which was comparable to the cost that patients would be willing to pay to avoid PONV (29). In a cost analysis study done by Hurford et al. (30), sugammadex would only be a cost-saving strategy in comparison with neostigmine only if neostigmine cost exceeding $84 and a very high likelihood of PONV (30). The conclusion from the study is that they do not

support the routine use of sugammadex in patients as a strategy to reduce PONV.

Our study is limited by the fact that it was a single-center study in Malaysia. Also, a shorter assessment time interval within the first 6 h postoperative may be needed to ascertain the peak of PONV due to the short duration of action of neostigmine. Another limitation was that we did not measure any objective biochemical parameters of PONV such as C-reactive protein, ketones, and aldehydes.

CONCLUSION

Our study showed that there was significantly less PONV at 6 h post-reversal with sugammadex compared to neostigmine–atropine mixture. We do not advocate the routine use of sugammadex as a means of reducing PONV due to the cost. However, sugammadex when used as a reversal agent in selected cases when poor reversal may be a concern confers the added benefit of reducing PONV, and these dual benefits may far outweigh the cost which cannot be reflected in this 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 Medical Research & Ethics Committee, UKMMC. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NM and CY made substantial contribution to the conceptualization, design, methodology, resources, and writing of original draft preparation to this study. CY, MM, JZ, and JO contributed substantially to the review, revision, analysis, and interpretation of data to this study. All authors contributed to the revised final manuscript.

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REFERENCES

1. Shaikh SI, Nagarekha D, Hegade G, Marutheesh M. Postoperative nausea and vomiting: a simple yet complex problem. *Anesthesia, Essays Res.* (2016) 10:388–96. doi: 10.4103/0259-1162.179310
2. Apfel CC, LCC, E, Koivuranta M, Greim C-A, Roewer N, A. simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *J Am Soc Anesthesiol.* (1999) 91:693–693. doi: 10.1097/00000542-199909000-00022
3. Mishra AR, Srivastava U, Kumar D, Saraswat N, Kumar A, Payal YS, et al. Nausea and vomiting after ENT surgeries: a comparison between ondansetron, metoclopramide and small dose of propofol. *Indian J Otolaryngol Head Neck Surg.* (2010) 62:29–31. doi: 10.1007/s12070-010-0012-x
4. Peck T, Harris B. *Pharmacology for Anaesthesia and Intensive Care*. Cambridge; New York, NY: Cambridge University Press (2021). ISBN: 11087 10964.
5. Koyuncu O, Turhanoglu S, Akkurt CO, Karc Karc M, Ozkan M, Ozer C, et al. Comparison of sugammadex and conventional reversal on postoperative nausea and vomiting: a randomized, blinded trial. *J Clin Anesth.* (2015) 27:51–6. doi: 10.1016/j.jclinane.2014.08.010
6. Sweis I, Yegiyants SS, Cohen MN. The management of post-operative nausea and vomiting: current thoughts and protocols. *Aesthetic Plast Surg.* (2013) 37:625–33. doi: 10.1007/s00266-013-0067-7
7. Lee O, Choi G, Kang H, Baek C, Jung Y, Woo Y, et al. Effects of sugammadex vs. pyridostigmine–glycopyrrolate on postrolate on postx vs. C, Jung Y, Woo Yhts and protocols. *Acta Anaesthesiologica Scandinavica*. (2017) 61:39–45. doi: 10.1111/aas.12813
8. Tramer M, Fuchs-Buder T. Omitting antagonism of neuromuscular block: effect on postoperative nausea and vomiting and risk of residual paralysis. A systematic review. *Br J Anaesthesia.* (1999) 82:379–86. doi: 10.1093/bja/82.3.379
9. Cheng C-R, Sessler DI, Apfel CC. Does neostigmine administration produce a clinically important increase in post-operative nausea and vomiting? *Anesth Analg.* (2005) 101:1349. doi: 10.1213/01.ane.0000180992.76743.c9
10. Bom A, Bradley M, Cameron K, Clark JK, Van Egmond J, Feilden H, et al. novel concept of reversing neuromuscular block: chemical encapsulation of rocuronium bromide by a cyclodextrina cyclodextri cyclodext*Angewandte Chemie Int Ed.* (2002) 41:265–70. doi: 10.1002/1521-3773(20020118)41:2%3C265::aid-anie265%3E3.0.co;2-q
11. Abrishami A, Ho J, Wong J, Yin L, Chung F. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. *Cochrane Database Sys Rev*. (2009) 4:7362. doi: 10.1002/14651858.CD007362.pub2
12. McDonagh DL, Benedict PE, Kovac AL, Drover DR, Brister NW, Morte JB, et al. Efficacy, safety, and pharmacokinetics of sugammadex for the reversal of rocuronium-induced meeting abstracts in elderly patients. *J Am Soc Anesthesiol.* (2011) 114:318–29. doi: 10.1097/ALN.0b013e3182065c36
13. Abad-Gurumeta A, Ripollés-Melchor J, Casans-Francés R, Espinosa A, Martínez-Hurtado E, Fernández-Pérez C, et al. systematic review of sugammadex vs neostigmine for reversal of neuromuscular blockade. *Anaesthesia.* (2015) 70:1441–52. doi: 10.1111/anae.13277
14. Yagan Ö, Taş N, Mutlu T, Hanci V. Comparison of the effects of sugammadex and neostigmine on postoperative nausea and vomiting. *Rev Bras Anestesiol.* (2017) 67:147–52. doi: 10.1016/j.bjane.2015.08.003
15. Korkut AY, Erkalp K, Erden V, Teker AM, Demirel A, Gedikli O, et al. Effect of pharyngeal packing during nasal surgery on postoperative nausea and vomiting. *Otolaryngol–Head Neck Surg.* (2010) 143:831–6. doi: 10.1016/j.otohns.2010.08.030
16. Jin HJ, Kim S, Hwang SH. Can pharyngeal packing prevent postoperative nausea and vomiting in nasal surgery? *Laryngoscope.* (2019) 129:291–8. doi: 10.1002/lary.27189
17. Apfel C, Kranke P, Katz M, Goepfert C, Papenfuss T, Rauch S, et al. Volatile anaesthetics may be the main cause of early but not delayed postoperative

vomiting: a randomized controlled trial of factorial design. *Br J Anaesth.* (2002) 88:659–68. doi: 10.1093/bja/88.5.659
18. Gan TJ. Postoperative nausea and vomiting—can it be eliminated? *JAMA*. (2002) 287:1233–6. doi: 10.1001/JAMA.287.10.1233
19. Habib AS, El-Moalem HE, Gan TJ. The efficacy of the 5-HT3 receptor antagonists combined with droperidol for PONV prophylaxis is similar to their combination with dexamethasone. A meta-analysis of randomized controlled trials. *Canadian J Anesth.* (2004) 51:311oflydoi: 10.1007/BF03018234
20. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analgesia*. (2000) 90:186–94. doi: 10.1097/00000539-200001000-00038
21. Rajeeva V, Bhardwaj N, Batra Y, Dhaliwal L. Comparison of ondansetron with ondansetron and dexamethasone in prevention of PONV in diagnostic laparoscopy. *Canadian J Anesth.* (1999) 46:40–4. doi: 10.1007/BF03012512
22. Gijsenbergh F, Ramael S, Houwing N, van Iersel T. First human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. *J Am Soc Anesthesiol.* (2005) 103:695–703. doi: 10.1097/00000542-200510000-00007
23. Paech M, Kaye R, Baber C, Nathan E. Recovery characteristics of patients receiving either sugammadex or neostigmine and glycopyrrolate for reversal of neuromuscular block: a randomised controlled trial. *Anaesthesia.* (2018) 73:340–7.doi: 10.1111/anae.14174
24. Tas Tuna A, Palabiyik O, Orhan M, Sonbahar T, Sayhan H, Tomak Y. Does sugammadex administration affect postoperative nausea and vomiting after laparoscopic cholecystectomy: a prospective, double-blind, randomized study. *Surg Laparosc Endosc Percutan Tech.* (2017) 27:237–40. doi: 10.1097/sle.0000000000000439
25. Chhibber AK, Lustik SJ, Thakur R, Francisco DR, Fickling KB. Effects of anticholinergics on postoperative vomiting, recovery, and hospital stay in children undergoing tonsillectomy with or without adenoidectomy. *J Am Soc Anesthesiol.* (1999) 90:697–700. doi: 10.1097/00000542-199903000-00010
26. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, et al. Society for Ambulatory A. Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg.* (2014) 118:85–113. doi: 10.1213/ANE.0000000000000002
27. Løvstad R, Thagaard K, Berner N, Raeder J. Neostigmine 50 μg kg– 1 with glycopyrrolate increases postoperative nausea in women after laparoscopic gynaecological surgery. *Acta Anaesthesiologica Scandinavica*. (2001) 45:495–500. doi: 10.1034/j.1399-6576.2001.045004495.x
28. McCourt K, Mirakhur R, Kerr C. Dosage of neostigmine for reversal of rocuronium block from two levels of spontaneous recovery. *Anaesthesia*. (1999) 54:651–5. doi: 10.1046/j.1365-2044.1999.00893.x
29. Parra-Sanchez I, Abdallah R, You J, Fu AZ, Grady M, Cummings K, et al. A time-motion economic analysis of postoperative nausea and vomiting in ambulatory surgery. *Canadian J Anesth/J canadien d'anesthésie*. (2012) 59:366–75. doi: 10.1007/s12630-011-9660-x
30. Hurford WE, Welge JA, Eckman MH. Sugammadex vs. neostigmine for routine reversal of rocuronium block in adult patients: a cost analysis. *J Clin Anesth.* (2020) 67:110027. doi: 10.1016/j.jclinane.2020.110027

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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A Tapered Cuff Tracheal Tube Decreases the Need for Cuff Pressure Adjustment After Surgical Retraction During Anterior Cervical Spine Surgery: A Randomized Controlled, Double-Blind Trial

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Background: Surgical retraction to expose the vertebrae during anterior cervical spine surgery increases tracheal tube cuff pressure and may worsen postoperative sore throat and dysphonia. This randomized double-blind study investigated the effect of cuff shape on intraoperative cuff pressure and postoperative sore throat and dysphonia.

Methods: Eighty patients were randomized to tracheal intubation with a tapered cuff or a conventional cylindrical high-volume low-pressure cuff (control) during anesthesia. Intraoperative cuff pressures were compared. The primary outcome was the incidence of pressure adjustment needed when the cuff pressure increased to > 25 mm Hg after surgical retraction. The secondary outcome was the incidence of postoperative sore throat and dysphonia.

Results: The incidence of pressure adjustment after surgical retraction was significantly lower in the tapered group than in the control group (13% vs. 48%; $P = 0.001$; relative risk reduction, 74%). The median [interquartile range (IQR)] cuff pressure (mm Hg) was significantly lower for the tapered cuff than for the control cuff before surgical retraction [9 (7–12) vs. 12 (10–15); $P < 0.001$] and after retraction [18 (15–23) vs. 25 (18–31); $P = 0.007$]. The median (IQR) postoperative dysphonia score assessed by a single

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speech-language pathologist was lower in the tapered group than in the control group [4 (3–6) vs. 5.5 (5–7); $P = 0.008$].

Conclusion: A tapered cuff tracheal tube decreased the need for the adjustment of cuff pressure after surgical retraction during anterior cervical spine surgery, thereby avoiding intraoperative pressure increase. It also has a better outcome in terms of dysphonia.

Clinical Trial Registration: [www.clinicaltrials.gov], identifier [NCT04591769].

Keywords: anterior cervical spine surgery, dysphonia, GRBAS, tapered cuff, tracheal tube cuff pressure

INTRODUCTION

Sore throat, dysphonia, and dysphagia can occur after neck surgery due to direct surgical injury or prolonged tissue compression (**Supplementary Table 1**) (1–4). In anterior cervical spine surgery, retractors are used to expose the vertebrae by spreading apart the medial border of the longus colli muscle. As a result, the tracheal tube and surrounding tissues are pulled laterally and compressed (**Figure 1A**). Compression forces increases the cuff pressure which are then transmitted to the tracheal mucosa and recurrent laryngeal nerve (**Figure 1B**), thereby increasing the risk of nerve paresis or palsy and subsequent dysphonia (5–7). Investigators reported methods to mitigate compressive forces, including monitoring and limiting the tracheal tube cuff pressure (8), transiently adjusting the cuff pressure by deflating and then reinflating the cuff after retractor placement (6), or use of nasotracheal intubation (9, 10). However, it is not always possible to routinely adjust the cuff pressure after surgical retractor placement because of the proximity of the surgical site to the tracheal tube. Reaching for the tracheal tube could result in contamination of the surgical site or failure to optimize the cuff pressure leading to an accidental air leak from the cuff with a loss of delivered tidal volume.

A tracheal tube with a tapered cuff is designed to minimize longitudinal folds during inflation, improve the tracheal seal, and prevent the leak of secretions and air, even under high airway pressures (**Figure 1C**). Fluid or air leak was less around a tapered cuff than around a conventional cylindrical high-volume low-pressure cuff (11, 12). Tapered cuffs also achieve a better air seal with reduced cuff pressure (13), thereby leading to a smaller change in cuff pressure during compressive forces such as pneumoperitoneum in laparoscopic surgery (14). There is evidence suggesting tapered cuffs reduce the incidence of postoperative sore throat and dysphonia (15). Based on this evidence, we hypothesized that a tapered cuff may help minimize cuff pressure increases that commonly occur during anterior cervical spine surgery.

Some investigators have reported a larger increase in tapered cuff pressures, compared with that of cylindrical cuffs, after neck extension, rotation, or a change of position in small study cohorts while others have not (16–18). To fully address the effects of cuff shape on pressure after surgical retraction during anterior cervical spine surgery, we conducted a randomized double-blind controlled study using a population sample that was calculated for power of analysis. The primary outcome was the incidence of pressure adjustment needed when the cuff pressure increased to > 25 mm Hg after surgical retraction. The secondary outcome was the incidence of postoperative sore throat and dysphonia.

MATERIALS AND METHODS

Ethics Approval

The study was approved by the Institutional Review Board (approval number: 2020-10-002C, 12 September 2020). All study participants provided written informed consent. The trial was registered before patient enrollment at clinicaltrials.gov (NCT04591769; principal investigator, Ya-Chun Chu; date of registration, 19 October 2020) and conducted in accordance with the Declaration of Helsinki. This report adheres to the Consolidated Standards of Reporting Trials guidelines. This study was designed as a randomized, double-blind, parallel-group trial and conducted at Taipei Veterans General Hospital (Taipei, Taiwan).

Patient Population

Patients eligible for the study were aged 20–80 years, who were scheduled for elective anterior cervical spine surgery via the right-sided approach (8, 19) by the same surgeon between November 2020 and September 2021. The exclusion criteria were previous trauma to the head and neck area, anticipated difficulty with mask ventilation or tracheal intubation, previous neck surgery, and a history of preoperative hoarseness or vocal cord palsy regardless of etiology, body mass index > 35, and refusal to provide informed consent.

Randomization and Blinding

Patients were randomly assigned to receive tracheal intubation with a tapered cuff (Shiley TaperGuard Tracheal Tube; Covidien, Mansfield, MA, United States) or a cylindrical cuff (i.e., the control) (Shiley Hi-Contour Tracheal Tube Cuffed; Covidien). Each tracheal tube had an internal diameter of 7.5 mm for men and 7.0 mm for women, unless otherwise specified. Randomization was performed using a computer-generated list in blocks of four in a 1:1 ratio by a statistician. Group allocation was unknown by the intubating anesthesiologist until immediately before tracheal intubation. After intubation, another

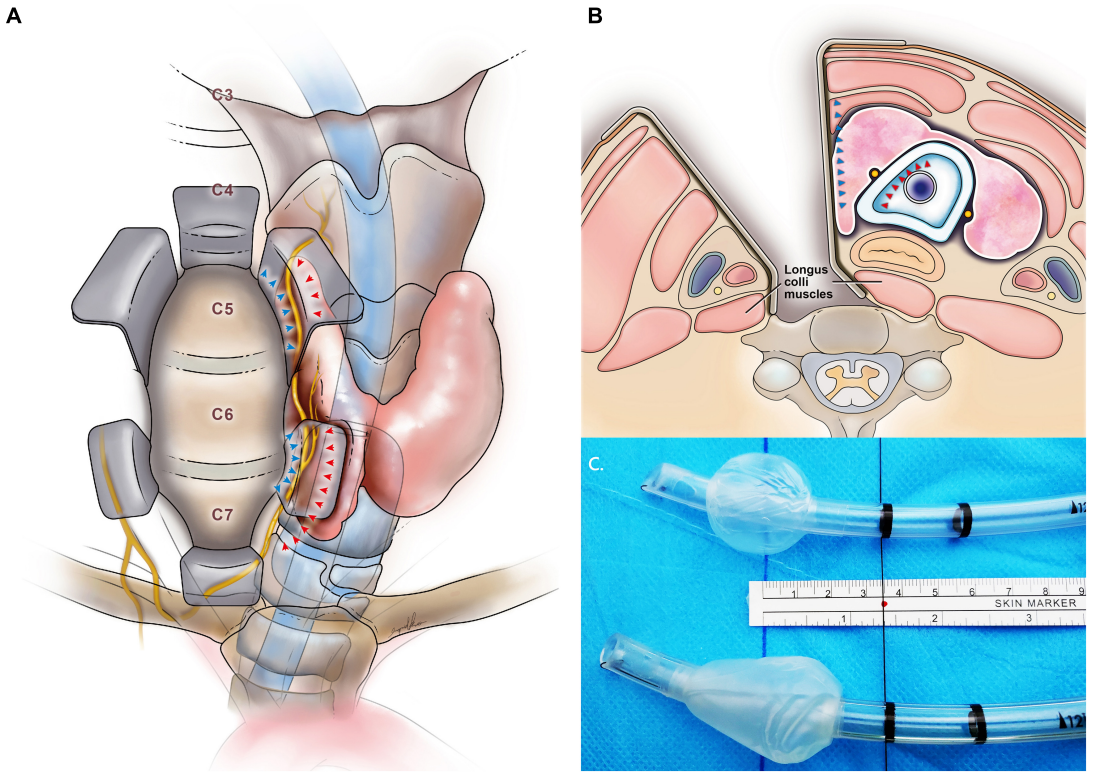

FIGURE 1 | (A) The anterior view shows surgical retraction during anterior cervical spine surgery. The retractor displaces the larynx against the unyielding tracheal tube shaft and cuff with compression on the recurrent laryngeal nerve (in yellow). The arrow indicates the force exerted by the retractor blade (blue) and tracheal tube cuff (red). **(B)** Cross-sectional neck anatomy shows the recurrent laryngeal nerve within the medial soft tissue complex between the force from the medial retractor blade (blue) and the tracheal tube cuff (red) when using the right-sided approach (seen from below). **(C)** The tracheal tube cuff shapes and the study groups: cylindrical cuff (i.e., control group, above) and tapered cuff tracheal tube (i.e., tapered group, below).

investigator, blinded to group allocation, inflated the pilot balloon with room air through a three-way stopcock attached to an extension that was accessible at the foot of the bed. The investigator that collected cuff pressure data and a speech-language pathologist who assessed voice quality were blinded to group allocation. The intubating anesthesiologist was responsible for removing the tracheal tube at the conclusion of surgery.

Conduct of the Study

Anesthesia was induced by using propofol (1.5–2.5 mg kg^{-1}), fentanyl (3 μg kg^{-1}), and cisatracurium (0.2 mg kg^{-1}). Tracheal intubation was performed using the GlideScope Titanium Reusable System with a LoPro blade (GlideScope Video Monitor; Verathon Medical, Burnaby, BC, Canada) after 5 min of mask ventilation when complete neuromuscular blockade was confirmed by a zero train of four counts. The vocal cords were visualized between two black line markings (2 cm apart) proximal to the cuff; the proximal line was 3.5 cm from the middle of the cuff (**Figure 1C**). After patient positioning, the tip of the tracheal tube was also identified and adjusted to thoracic vertebral level 2 (T2)–T4 during fluoroscopic visualization by the surgeon. The tracheal tube was then secured with tape at the left angle of the mouth. The pilot balloon of the cuff was connected to a disposable pressure transducer system (DTXPlus; Argon Medical Systems, Yishun, Singapore). The cuff pressure was continually displayed on the patient monitor (Infinity Kappa; Draeger Medical Systems, Andover, MA, United States). A three-way stopcock was used to adjust the amount of air in the cuff. The cuff was initially inflated with 2 mL of air and then, in stepwise increments of 0.5 mL, air were injected until the following three conditions were met: (1) no air leak was identified by auscultation using a stethoscope over the sternal notch; (2) the measured expired tidal volume was within the 95% limit of the predetermined setting on the ventilator; and (3) no alarm occurred indicating inadequate mechanical ventilation when the fresh gas flow was lowered to 0.5 L min^{-1} (i.e., low-flow anesthesia) for 3 min. Ventilation was set in volume-controlled auto-flow mode (Dräger Medical GmbH, Lübeck, Germany) at a flow rate of 1.2 L min^{-1}, a tidal volume of 6–8 mL kg^{-1} of ideal body weight, an inspiratory-to-expiratory ratio of 1:2, and a positive end-expiratory pressure of 5 cm H_2O to maintain an end-tidal pCO_2 of 35–40 mm Hg and a peak airway pressure of < 20 cm H_2O. The cuff pressure was checked for the presence of a leak after neck extension and recorded as the baseline pressure before surgical retraction.

The maximal cuff pressure was recorded after final positioning of the surgical retractors. If the maximal pressure was > 25 mm Hg (9, 20), then 0.5 mL of air was aspirated in a stepwise manner until reaching a pressure of ≤ 25 mm Hg. Anesthesia

was maintained using an oxygen-sevoflurane mixture and intermittent boluses of cisatracurium were given intravenously to maintain a train of four counts of ≤ 3. After removing the retractors, we recorded whether an air leak existed. At the end of surgery, the trachea and pharynx were carefully suctioned while the patient was anesthetized. Neuromuscular blockade was reversed with neostigmine (40 $\mu g\ kg^{-1}$) once the train of four count was 4. After ensuring adequate neuromuscular reversal, the inhalational anesthesia was stopped. The patient was allowed to awaken spontaneously without stimulation. The tracheal tube was then removed when the patient regained consciousness and fully recovered from the neuromuscular blockade with a train of four ratio $\geq 90\%$.

Two hours after surgery and on postoperative day 1, the patients were asked to assess throat soreness by using a 10-point numeric rating scale. The assessment was conducted by research personnel blinded to group allocation. Hoarseness was assessed using a grading system previously established in clinical studies where: "0" was no impairment; "1," was clinically detectable and "2" was severe (9, 10, 21). Five characteristics of the voice used for rating dysphonia adhered to the GRBAS scale and included the Grade of vocal impairment, Roughness, Breathiness, Asthenia (physical weakness of voice), and Strain of the voice (22–24). The speech-language pathologist, who was blinded to group allocation, calculated the GRBAS scores from the voice recordings. Each GRBAS component was rated on a four-point integer scale as previously described: "0" was normal; "1," mild impairment; "2," moderate impairment; and "3," severe impairment. The total score was recorded, as previously described (25, 26).

Primary Outcomes

Intraoperative cuff pressures were compared at five timepoints: after (1) the initial seal for tracheal intubation, (2) neck extension, (3) surgical retraction, (4) pressure adjustment, and (5) removal of the retractors. The primary outcome was the incidence of pressure adjustment needed when the cuff pressure increased to $>$ 25 mm Hg (34 cm H_2O) after surgical retraction. We chose a pressure of $>$ 25 mm Hg as a benchmark of identifying post-retraction pressures that could contribute to postoperative complications based on the findings of a previous endoscopic study (27). The study showed a normal caliber of tracheal mucosal blood vessels at cuff pressure of 22 mm Hg (30 cm H_2O). The vessel caliber was partially occluded at pressures of 29 mm Hg (39 cm H_2O). We therefore took the mean pressure between the two clinical correlates (22 and 29 mm Hg) as 3.5 and rounded down to a whole integer of 3 which resulted in a pressure of 25 mm Hg (22 + 3 mm Hg). This estimated pressure was below the threshold of 29 mm Hg where mucosal blood flow was impaired and did not result in an air leak from the tracheal cuff (9, 10, 20).

Sample Size Calculation

We estimated the risk of a cuff pressure increase of $>$ 25 mm Hg after retraction at approximately 60% for cylindrical tracheal cuffs (9, 10), and estimated that tapered cuffs would reduce this risk to 30%. We determined that a sample size of 40 patients per group would be needed at a two-sided significance level of 0.05 ($\alpha = 0.05$) and 80% power ($\beta = 0.2$). Furthermore, the estimated power of all participants ($n = 80$) and surgical level subgroups (above the C6/7 level [$n = 44$] and at the C6/7–T1 level [$n = 36$]) was > 0.8.

Statistical Analysis

Sample distributions were evaluated using the Kolmogorov–Smirnov test to evaluate the normality of the data. Continuous data derived from demographic characteristics were compared using the Mann–Whitney *U* test. Categorical data were compared using the chi square test or Fisher's exact test. Data are summarized as the median (25th–75th percentile interquartile range [IQR]) or as the number (%), as appropriate.

Factors associated with a cuff pressure $>$ 25 mm Hg after surgical retraction were analyzed using a binary logistic regression model. Risk estimates were calculated for the odds ratio and the 95% confidence interval (CI). The primary outcome, the incidence of pressure adjustment after surgical retraction, was compared using the chi square test. Absolute and relative risk reductions for pressure adjustment after surgical retraction were calculated for all study participants and subpopulations.

Cuff pressures at the five timepoints were compared between study groups by using a generalized estimating equation (GEE) model with unstructured correlation, with baseline characteristics, treatment group, time, and initial cuff pressure as the fixed effects, and study participants as the random effect. We recognized that cuff pressure data may not all fit normal distribution. The GEE approach is a marginal model commonly used for longitudinal/clustered data analysis in clinical trials. It is also robust for non-normally distributed data in the event that the distribution of cuff pressure data were non-parametric (28–30). We also analyzed the time $\times$ treatment interaction by using the difference-in-differences regression method to examine the pre–post change in cuff pressure at each observed timepoint to delineate the effect of the group on surgical intervention Data are summarized as the median (IQR) and shown as the mean (standard error of mean) (31). Postoperative outcomes were compared between groups using GEE models. All statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC, United States). Two-sided *P*-values < 0.05 were statistically significant.

RESULTS

Demographic Data

Eighty-two patients were included in the study. Eighty patients completed the study and were included in the analysis (**Figure 2**). Clinical and surgical characteristics were comparable between the groups (**Table 1**).

Intraoperative Cuff Pressure and the Need for Pressure Adjustment After Surgical Retraction

The incidence of pressure adjustment after surgical retraction was significantly lower in the tapered than the control group (13 vs. 48%, $P = 0.001$; **Table 2**). A surgical level at cervical vertebra

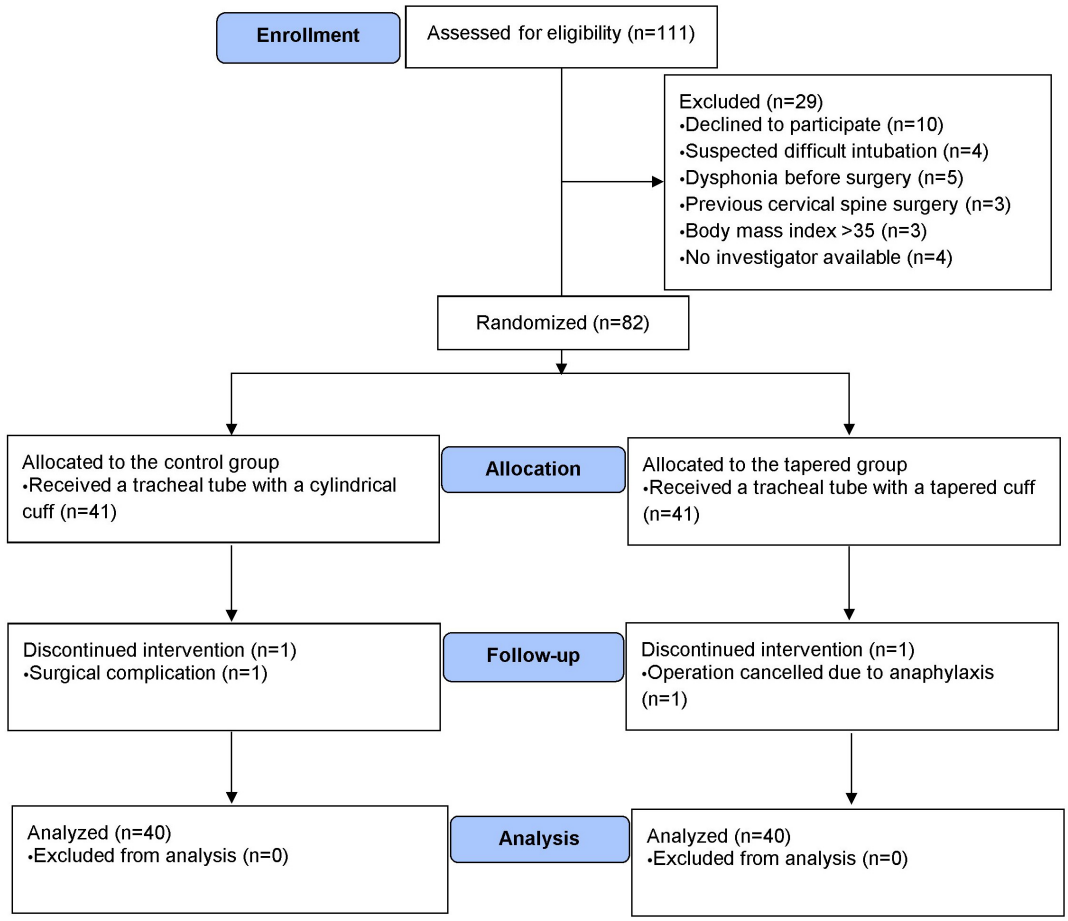

FIGURE 2 | The CONSORT diagram shows the patient recruitment process. CONSORT, Consolidated Standards of Reporting Trials.

6/7 (C6/7)–T1 was independently associated with an increased risk of pressures > 25 mm Hg after surgical retraction (adjusted odds ratio, 13.1; 95% CI, 2.4–72.7; $P = 0.003$, vs. the level above C6/7; **Table 2**). The use of the tapered cuff tube was associated with a reduced risk (adjusted odds ratio, 0.08; 95% CI, 0.02–0.4; $P = 0.002$, vs. the control; **Table 2**). The primary outcome, pressure adjustments after surgical retraction were fewer with tapered cuffs than control in all study participants, regardless of whether the surgical level was at C6/7–T1 or above C6/7 (**Table 2**). The relative risk reduction was 74% (95% CI, 36–89) for all study patients; 100% for patients with a surgical level above C6/7, and 60% (95% CI, 13–82) for patients with a surgical level at C6/7–T1 (**Table 3**).

Supplementary Table 2 shows the intraoperative cuff pressures. The median (IQR) cuff pressures (mm Hg) were significantly lower for the tapered cuff than for the control cuff after tracheal intubation [9 (7–12) vs. 11 (8–14); $P = 0.009$)], after neck extension [9 (7–12) vs. 12 (10–15); $P < 0.001$] and after retraction [18 (15–23) vs. 25 (18–31); $P = 0.007$, **Figure 3A**]. Pressure differentials (i.e., pre–post change) caused by surgical retraction and pressure adjustment were smaller in the tapered group than in the control group (**Figure 3D**).

Subpopulation Analysis According to the Surgical Level Treated

The patients were dichotomized into two groups for further analysis based on whether the surgery was at the C6/7–T1 level or above the C6/7 level. Post-retraction cuff pressures were significantly lower in the tapered group compared to the controls when the surgical level was at C6/7–T1 (**Figure 3C**), but not when the level was above C6/7 (**Figure 3B**). Cuff pressure differentials by surgical retraction and pressure adjustment were also less with the tapered cuff than with the control cuff at a surgical level of C6/7–T1 (**Figure 3F**), but not when the level was above C6/7 (**Figure 3E**).

Postoperative Outcomes

No significant differences were found between the two study groups in the severity of postoperative sore throat and self-assessed hoarseness (**Table 4**). However, the median (IQR) GRBAS dysphonia score was significantly lower in the tapered group than in the control group on postoperative day 1 [4 (3–6) vs. 5.5 (5–7); $P = 0.008$, **Table 4**].

TABLE 1 | Patients' characteristics and surgical data.

	Control group		Tapered group	
Study participants, n	40		40	
Age (y), median (IQR)	61	(48–69)	57	(46–64)
Male sex, n (%)	24	(60)	24	(60)
Body mass index, median (IQR)	26	(23.6–27.8)	26	(24.0–26.7)
Smoking habit, n (%)	5	(13)	7	(18)
ASA physical status n (%)				
I	11	(28)	11	(27)
II	28	(70)	28	(70)
III	1	(3)	1	(3)
Surgical characteristics				
Surgery, based on instrumentation, n (%)				
Cervical disc arthroplasty	20	(50)	22	(55)
Discectomy and fusion	10	(25)	10	(25)
Corpectomy and fusion	5	(13)	1	(3)
Combined	5	(13)	7	(18)
Level operated on, median (IQR)	2	(1–3)	2	(2–3)
Surgical level, n (%)				
above C6/7	21	(53)	23	(58)
at C6/7–T1	19	(48)	17	(43)
Duration (min), median (IQR)				
Surgery	155	(135–214)	155	(125–214)
Surgical retraction	100	(71–158)	97	(76–151)
Tracheal intubation	231	(186–287)	215	(188–292)
GRBAS dysphonia score, median (IQR) Total score, preoperative	4	(3–4)	4	(3–4)

ASA, American Society of Anesthesiologists. The interquartile range (IQR) is the 25th–75th percentiles.

DISCUSSION

Our study demonstrated that cuff pressures during anterior cervical spine surgery were lower with a tapered cuff than a cylindrical cuff. Lower pressures were observed for the just-seal pressure before surgical retraction and the maximal pressure after retraction. These findings were influenced by the cervical level of the surgical treatment: pressure increases were more frequent at C6/7–T1 in our surgical population. Tracheal tubes with a tapered cuff needed less pressure adjustment under all study conditions. Postoperative dysphonia scores were lower in the tapered group than in the control group, even when the cuff pressure was controlled and set at $\leq$ 25 mm Hg for both groups. We conclude that the tapered cuff design had the beneficial effect of decreasing the need for cuff pressure adjustment after surgical retraction, and of achieving a better immediate outcome of voice quality. Our results discovered the tapered cuff tracheal tube as an alternative to conventional cylindrical cuffs for neck surgery when intraoperative cuff adjustment is not feasible.

Attempts to adjust cuff pressures during surgery can cause accidental loss of occlusion pressure and increase the risk of inadvertent air leaks (32, 33). We needed fewer pressure adjustments when using tapered cuffs during anterior cervical spine surgery. This suggests that tapered cuffs may accommodate changes in compressive forces more readily than cylindrical cuffs. Overall, this appears to offer greater safety by reducing the need for pressure adjustments and the consequent complications of over and under-inflation.

An explanation for this advantage is that the tapered cuff is designed to minimize longitudinal folds, which can be the source of air leaks and aspiration of secretions (11, 34). Our findings support previous observations (35); we found that tapered cuffs had a lower sealing pressure. The sealing pressures in our study were lower than the cuff pressure of 20–30 cm H_2O (14.7–22.1 mm Hg) commonly used in clinical practice. The median occlusion cuff pressures of 9 mm Hg for tapered cuffs and 11 mm Hg for cylindrical cuffs, needed for a leak-free seal, were higher than the pressures found in a viscoelastic model of the trachea (36). The model predicted that cuffs with different designs required a pressure of only 8.8 mm Hg (12 cm H_2O) for a complete air seal (36); the findings for tapered cuffs in this study are consistent with predicted values from simulated models (36). Further, the safety of our occlusion pressures was confirmed in our human study participants.

The baseline median pressure of approximately 10 mm Hg (13.6 cm H_2O) and the maximal pressure of 25 mm Hg (34 cm H_2O) chosen for adjustment, made the allowable

TABLE 2 | Factors associated with maximal cuff pressure > 25 mmHg after the retractors splayed.

Variable	Comparison	Univariable			Multivariable		
		OR	(95% CI)	*P*-value	OR	(95% CI)	*P*-value
Tapered cuff	Control	0.16	(0.05–1.09)	0.001	0.08	(0.02–0.40)	0.002
Surgical levels: including C6/7–T1	above C6/7	8.72	(2.79–27.20)	<0.001	13.12	(2.37–72.66)	0.003
Cuff pressure before retraction	+1	1.06	(0.93–1.21)	0.367	1.01	(0.84–1.22)	0.899
Age	+1	1.04	(1.00–1.09)	0.068	1.01	(0.95–1.07)	0.790
Male sex	Female	1.16	(0.44–3.10)	0.765	0.98	(0.25–3.88)	0.979
BMI	+1	1.13	(0.97–1.33)	0.122	1.07	(0.85–1.34)	0.554
Smoking habit	none	0.18	(0.02–1.46)	0.108	0.10	(0.01–1.39)	0.086
No. of surgical levels	+1	2.05	(1.20–3.49)	0.009	1.24	(0.54–2.83)	0.618

CI, confidence interval; OR, odds ratio.

TABLE 3 | The incidence of pressure adjustment when the cuff pressure increased to > 25 mmHg after surgical retraction.

Study population n (%)	Control group	Tapered group	*P*-value	Absolute risk reduction	Relative risk reduction	Number needed to treat
				% (95% CI)	% (95% CI)	n (95% CI)
All study participants, *n* = 80 (100%)	(*n* = 40)	(*n* = 40)				
>25 mm Hg, n (%)	19 (48)	5 (13)	0.001	35 (16–54)	74 (36–89)	3 (2–7)
Surgical level above C6/7, *n* = 44 (55%)	(*n* = 21)	(*n* = 23)				
>25 mm Hg, n (%)	5 (24)	0 (0)	0.019	24 (6–42)	100	5 (3–18)
Surgical level at C6/7–T1, *n* = 36 (45%)	(*n* = 19)	(*n* = 17)				
>25 mm Hg, n (%)	14 (74)	5 (29)	0.018	44 (15–74)	60 (13–82)	3 (2–7)

CI, confidence interval.

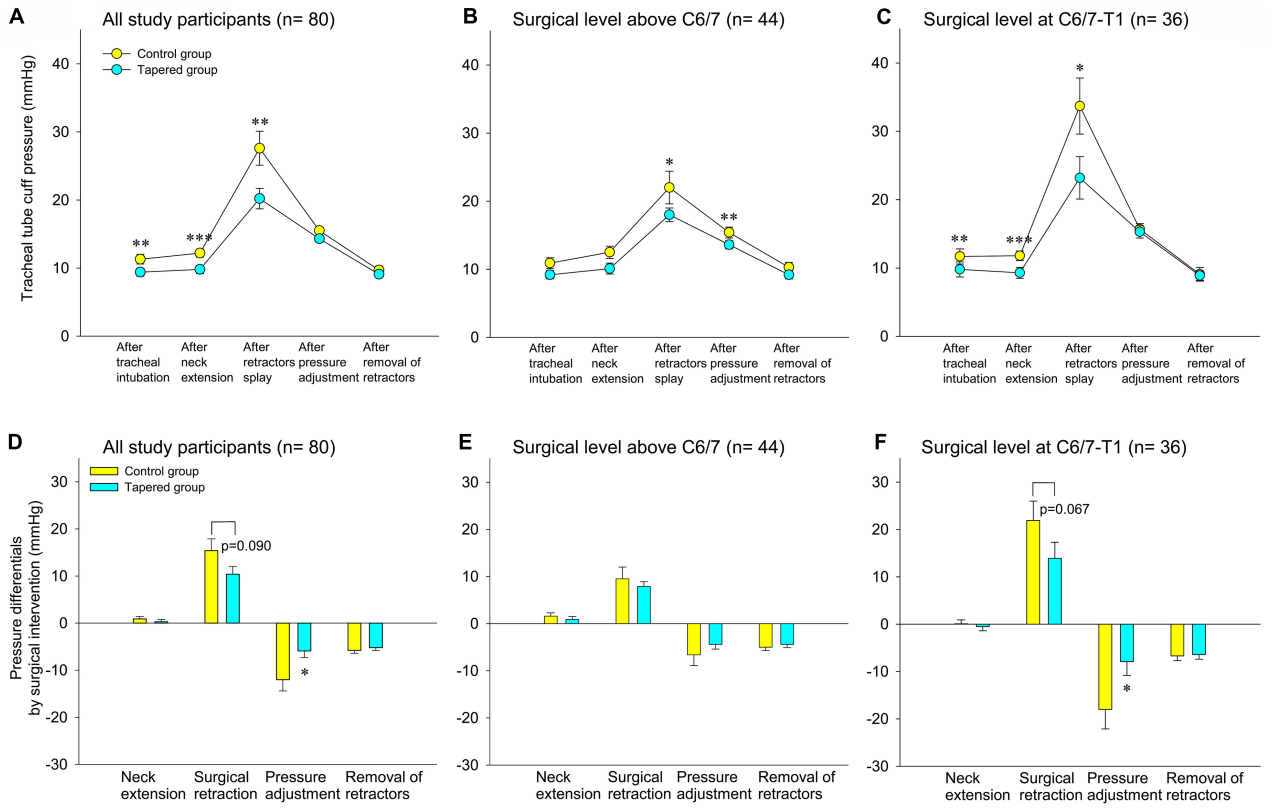

FIGURE 3 | Tracheal tube cuff pressure during surgery **(A–C)** and pressure differentials by surgical intervention **(D–F)**. **(A,C)** All study participants. **(B,D)** Surgical levels above C6/7. **(C,F)** Surgical level at C6/7–T1. Data are presented as the mean and the standard error of the mean, $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. 1 mm Hg = 1.36 cm H_2O.

pressure rangeapproximately 15 mm Hg (25 minus 10 mm Hg). The median pressure difference of 7 mm Hg after surgical retraction between our study groups accounted for one-half of the range. While continuous cuff pressure monitoring and adjustment is a recommended approach for reducing pressure-related complications (32), our data indicates that use of a tapered cuff confers additional safety. This is particularly true when continuous monitoring is not available. Further, the pilot balloon of the tube is not always easily accessible and physical impediments may delay or prevent appropriate monitoring. Our data supports the use of the just-seal pressure as the baseline for the tapered cuff tube to reach minimal occlusion pressure and potentially reduce the need for pressure adjustment.

Our observations that baseline pressures were significantly lower in the tapered than control group suggested that the use of "just-sealed" pressure is a potential safety measure that can independently reduce the risk of mucosal and nerve compression. The greater differential for pressure measurements between the baseline just-sealed pressure and the target pressure of 25 mm Hg supports our impression of the improved safety margin for tapered cuffs.

Other investigators have reported a larger increase in tapered cuff pressures than in cylindrical cuff pressures after neck

TABLE 4 | Postoperative sore throat and dysphonia.

	Control group	Tapered cuff group	*P*-value
Sore throat, median (IQR)			
NRS, 2 h after surgery	5 3–8)	5 (3–7)	0.964
NRS, postoperative day 1	3 (1–5)	3.5 (1.5–5)	0.574
Self-assessed hoarseness, postoperative day 1, n (%)			
None	9 (23)	14 (35)	0.324
Obvious	22 55)	21 (53)	
Severe	9 (23)	5 (13)	
GRBAS dysphonia score, median (IQR)			
Total score, postoperative day 1	5.5 (5–7)	4 (3–6)	0.008

The cuff pressure is controlled and set at the pressure > 25 mmHg after the retractors were set up. The interquartile range (IQR) is the 25th–75th percentiles. GRBAS, grade, roughness, breathiness, asthenia, and strain for dysphonia; NRS, numeric rating scale.

extension, rotation, or change of position (16–18). Differences in study design, including the site or type of surgery and the selection of baseline pressures, likely explain the unique findings of different studies. For example, some studies used a baseline pressure of 15 mm Hg (20 cm H_2O) for all study patients (16–18), regardless of the sealing pressure determined by clinical auscultation, whereas we used the just-seal pressure for every patient.

Previous studies reported a greater risk of postoperative vocal cord palsy in patients who have surgery at the C6/7–T1 level (6, 37, 38). The risk of postoperative vocal cord palsy can be related to the cuff pressure when surgical site levels vary. However, to date, no published reports exist on the influence of spinal level on cuff pressure after tissue retraction. In this study, we dichotomized our patient population based on the surgical level and found that the surgical level influenced the increase in cuff pressure. The risk of higher pressures (>25 mm Hg) was 13-fold higher at the C6/7–T1 level than for levels above C6/7. Our observation of cuff pressure increases by surgical level coincided with the levels with higher risk of postoperative vocal cord palsy reported in previous studies (6, 37, 38). In clinical practice, surgery may involve multiple levels, especially with instrumentation spanning the upper and lower levels of the cervical spine. Nevertheless, the benefit of the tapered cuff tube was demonstrated by significant risk reduction in both subgroups.

This study had limitations. We did not include a group with cuff pressures > 25 mm Hg after retraction because of safety concerns. Therefore, we cannot hypothesize about possible postoperative outcomes for pressures greater than our target. The study findings are specific for anterior cervical spine surgery. We did not include patients who underwent alternate surgeries to test our study design for external validity and cannot determine whether our findings could be representative of tapered cuff performance in other types of surgery that require pneumoperitoneum or in critically ill patients on long-term mechanical ventilation. The study findings are specific for anterior cervical spine surgery when using tracheal tubes with an internal diameter of 7.0 mm for females and 7.5 mm for males during general anesthesia with neuromuscular relaxation. Further, the better outcomes of using tapered cuff tube in our study cannot be generalized to other potential airway complications that have been reported after anterior cervical surgery. This study was conducted by a single surgeon at one center. Further testing is needed to determine the external validity of our findings.

In conclusion, tapered cuffs required fewer intraoperative pressure adjustments and produced better postoperative voice outcomes in our randomized double-blind study of anterior cervical spinal surgery. Tapered cuffs may confer improved patient outcomes if continuous cuff pressure monitoring is impossible or if the access for pressure adjustment is difficult.

IMPLICATION FOR PRACTICE AND RESEARCH

Surgical retraction to expose the vertebrae during anterior cervical spine surgery increases tracheal tube cuff pressure and may worsen postoperative sore throat and dysphonia. Limiting or adjusting cuff pressure after surgical retraction reduces the incidence of postoperative sore throat and dysphonia but is not always possible to routinely performed the proximity of the surgical site to the tracheal tube or pressure monitoring is unavailable. Our prospective, randomized controlled, double-blind study revealed a tapered cuff tracheal tube, compared with a conventional cylindrical high-volume low-pressure cuff tube, decreased the need for the adjustment of cuff pressure after surgical retraction during anterior cervical spine surgery, thereby avoiding intraoperative pressure increase. It also has a better outcome in terms of dysphonia.

DATA AVAILABILITY STATEMENT

The original contributions presented in this 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 Institutional Review Board of Taipei Veterans General Hospital (approval number: 2020-10-002C, 12 September 2020). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Y-SL helped recruit the patients, conduct the trial, collect the data, and draft the manuscript. EC-HT helped design the study, analyze and interpret the data, and draft the manuscript.

Y-JT helped conduct the trial and collect and analyze the data. MSM helped interpret the data and draft the manuscript. S-SH helped study design and analyze and interpret the data. T-YC helped recruit the patients, conduct the trial, and collect the data. W-CH helped study design, recruit the patients, conduct the trial, and interpret the data. W-KC helped study, conduct the trial, and interpret the data. Y-CC helped design the study, recruit the patients, conduct the trial, collect and analyze the data, and draft. All authors edited the draft, revised, and approved the manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

1. Joaquim AF, Murar J, Savage JW, Patel AA. Dysphagia after anterior cervical spine surgery: a systematic review of potential preventative measures. *Spine J.* (2014) 14:2246–60. doi: 10.1016/j.spinee.2014.03.030
2. Tan TP, Govindarajulu AP, Massicotte EM, Venkatraghavan L. Vocal cord palsy after anterior cervical spine surgery: a qualitative systematic review. *Spine J.* (2014) 14:1332–42. doi: 10.1016/j.spinee.2014.02.017
3. Tetreault L, Ibrahim A, Cote P, Singh A, Fehlings MG. A systematic review of clinical and surgical predictors of complications following surgery for degenerative cervical myelopathy. *J Neurosurg Spine.* (2016) 24:77–99. doi: 10.3171/2015.3.SPINE14971
4. Huang WC, Tan EC, Huang SS, Chou CJ, Chang WK, Chu YC. Postoperative sore throat helps predict swallowing disturbance on postoperative day 30 of anterior cervical spine surgery: a secondary exploratory analysis of a randomized clinical trial of tracheal intubation modes. *Dysphagia.* (2022) 37:37–47. doi: 10.1007/s00455-021-10247-x
5. Sperry RJ, Johnson JO, Apfelbaum RI. Endotracheal tube cuff pressure increases significantly during anterior cervical fusion with the Caspar instrumentation system. *Anesth Analg.* (1993) 76:1318–21. doi: 10.1213/00000539-199376060-00023
6. Apfelbaum RI, Kriskovich MD, Haller JR. On the incidence, cause, and prevention of recurrent laryngeal nerve palsies during anterior cervical spine surgery. *Spine (Phila Pa 1976).* (2000) 25:2906–12. doi: 10.1097/00007632-200011150-00012
7. Fassett DR, Apfelbaum RI. Vocal cord paralysis after anterior cervical spine surgery. 1st ed. In: An HS, Jenis LG editors. *Complications of Spine Surgery: Treatment and Prevention*. Philadelphia, PA: Lippincott Williams & Wilkins (2006). 23 p.
8. Jung A, Schramm J. How to reduce recurrent laryngeal nerve palsy in anterior cervical spine surgery: a prospective observational study. *Neurosurgery.* (2010) 67:10–5. doi: 10.1227/01.neu.0000370203.26164.24
9. Huang WC, Tan EC, Chang CC, Kuo YH, Hsu XTJ, Chang WK, et al. Effect of tracheal intubation mode on cuff pressure during retractor splay and dysphonia recovery after anterior cervical spine surgery: a randomized clinical trial. *Spine (Phila Pa 1976).* (2020) 45:565–72. doi: 10.1097/brs.0000000000003339
10. Tan EC, Huang WC, Chu YC. Response: effect of tracheal intubation mode on cuff pressure during retractor splay and dysphonia recovery after anterior cervical spine surgery. *Spine (Phila Pa 1976).* (2020) 45:E1052–4. doi: 10.1097/brs.0000000000003579
11. Dave MH, Frotzler A, Spielmann N, Madjdpour C, Weiss M. Effect of tracheal tube cuff shape on fluid leakage across the cuff: an in vitro study. *Br J Anaesth.* (2010) 105:538–43. doi: 10.1093/bja/aeq202
12. Zanella A, Scaravilli V, Isgro S, Milan M, Cressoni M, Patroniti N, et al. Fluid leakage across tracheal tube cuff, effect of different cuff material, shape, and positive expiratory pressure: a bench-top study. *Intensive Care Med.* (2011) 37:343–7. doi: 10.1007/s00134-010-2106-z
13. Madjdpour C, Mauch J, Dave MH, Spielmann N, Weiss M. Comparison of air-sealing characteristics of tapered- vs. cylindrical-shaped high-volume, low-pressure tube cuffs. *Acta Anaesthesiol Scand.* (2012) 56:230–5. doi: 10.1111/j.1399-6576.2011.02542.x
14. Shin HW, Kim DH, Yoo HS, Lee DK, Yoo YD, Lim CH. Changes in cuff pressure and position of cylindrical-cuff and tapered-cuff tracheal tubes during laparoscopic abdominal surgery. *J Int Med Res.* (2015) 43:544–54. doi: 10.1177/0300060515581670
15. Chang JE, Kim H, Han SH, Lee JM, Ji S, Hwang JY. Effect of endotracheal tube cuff shape on postoperative sore throat after endotracheal intubation. *Anesth Analg.* (2017) 125:1240–5. doi: 10.1213/ane.0000000000001933
16. Park JH, Lee HJ, Lee SH, Kim JS. Changes in tapered endotracheal tube cuff pressure after changing position to hyperextension of neck: a randomized clinical trial. *Medicine (Baltimore).* (2021) 100:e26633. doi: 10.1097/md.0000000000026633
17. Choi E, Park Y, Jeon Y. Comparison of the cuff pressure of a taperguard endotracheal tube and a cylindrical endotracheal tube after lateral rotation of head during middle ear surgery: a single-blind, randomized clinical consort study. *Medicine (Baltimore).* (2017) 96:e6257. doi: 10.1097/md.0000000000006257
18. Kim HC, Lee YH, Kim E, Oh EA, Jeon YT, Park HP. Comparison of the endotracheal tube cuff pressure between a tapered- versus a cylindrical-shaped cuff after changing from the supine to the lateral flank position. *Can J Anaesth.* (2015) 62:1063–70. doi: 10.1007/s12630-015-0394-z
19. Kilburg C, Sullivan HG, Mathiason MA. Effect of approach side during anterior cervical discectomy and fusion on the incidence of recurrent laryngeal nerve injury. *J Neurosurg Spine.* (2006) 4:273–7. doi: 10.3171/spi.2006.4.4.273
20. Suzuki N, Kooguchi K, Mizobe T, Hirose M, Takano Y, Tanaka Y. Postoperative hoarseness and sore throat after tracheal intubation: effect of a low intracuff pressure of endotracheal tube and the usefulness of cuff pressure indicator. *Masui.* (1999) 48:1091–5.
21. Mehra S, Heineman TE, Cammisa FP Jr., Girardi FP, Sama AA, Kutler DI. Factors predictive of voice and swallowing outcomes after anterior approaches to the cervical spine. *Otolaryngol Head Neck Surg.* (2014) 150:259–65. doi: 10.1177/0194599813515414
22. Nemr K, Simoes-Zenari M, Cordeiro GF, Tsuji D, Ogawa AI, Ubrig MT, et al. GRBAS and Cape-V scales: high reliability and consensus when applied at different times. *J Voice.* (2012) 26:812.e17–22. doi: 10.1016/j.jvoice.2012.03.005
23. Roy N, Barkmeier-Kraemer J, Eadie T, Sivasankar MP, Mehta D, Paul D, et al. Evidence-based clinical voice assessment: a systematic review. *Am J Speech Lang Pathol.* (2013) 22:212–26. doi: 10.1044/1058-0360(2012/12-0014)

24. Webb AL, Carding PN, Deary IJ, MacKenzie K, Steen N, Wilson JA. The reliability of three perceptual evaluation scales for dysphonia. *Eur Arch Otorhinolaryngol.* (2004) 261:429–34. doi: 10.1007/s00405-003-0707-7
25. Shin YS, Chang JW, Yang SM, Wu HW, Cho MH, Kim CH. Persistent dysphonia after laryngomicrosurgery for benign vocal fold disease. *Clin Exp Otorhinolaryngol.* (2013) 6:166–70. doi: 10.3342/ceo.2013.6.3.166
26. Ma J, Fang R, Zhen R, Mao W, Wu X, He P, et al. A 532-nm KTP laser for vocal fold polyps: efficacy and relative factors. *Ear Nose Throat J.* (2021) 100:87–93S. doi: 10.1177/0145561320946153
27. Seegobin RD, van Hasselt GL. Endotracheal cuff pressure and tracheal mucosal blood flow: endoscopic study of effects of four large volume cuffs. *Br Med J (Clin Res Ed).* (1984) 288:965–8. doi: 10.1136/bmj.288.6422.965
28. Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. *Biometrics.* (1988) 44:1049–60. doi: 10.2307/2531734
29. Pekár S, Brabec M. Generalized estimating equations: a pragmatic and flexible approach to the marginal GLM modelling of correlated data in the behavioural sciences. *Ethology.* (2017) 124:86–93. doi: 10.1111/eth.12713
30. Albrecht E, Bayon V, Hirotsu C, Al Ja'bari A, Heinzer R. Intrathecal morphine and sleep apnoea severity in patients undergoing hip arthroplasty: a randomised, controlled, triple-blinded trial. *Br J Anaesth.* (2020) 125:811–7. doi: 10.1016/j.bja.2020.07.052
31. Gilbert CR, Mallow C, Wishire CL, Chang SC, Yarmus LB, Vallieres E, et al. A prospective, ex vivo trial of endobronchial blockade management utilizing 3 commonly available bronchial blockers. *Anesth Analg.* (2019) 129:1692–8. doi: 10.1213/ANE.0000000000004397
32. Maertens B, Blot S. Endotracheal tube cuff pressure changes during manual cuff pressure control manoeuvres: a call for continuous cuff pressure regulation? *Acta Anaesthesiol Scand.* (2019) 63:700–1. doi: 10.1111/aas.13325
33. Aeppli N, Lindauer B, Steurer MP, Weiss M, Dullenkopf A. Endotracheal tube cuff pressure changes during manual cuff pressure control manoeuvres: an in-vitro assessment. *Acta Anaesthesiol Scand.* (2019) 63:55–60. doi: 10.1111/aas.13249
34. Li Bassi G, Ranzani OT, Marti JD, Giunta V, Luque N, Isetta V, et al. An in vitro study to assess determinant features associated with fluid sealing in the design of endotracheal tube cuffs and exerted tracheal pressures. *Crit Care Med.* (2013) 41:518–26. doi: 10.1097/ccm.0b013e31826a4804
35. Tsuboi S, Miyashita T, Yamaguchi Y, Yamamoto Y, Sakamaki K, Goto T. The TaperGuard endotracheal tube intracuff pressure increase is less than that of the Hi-Lo tube during nitrous oxide exposure: a model trachea study. *Anesth Analg.* (2013) 116:609–12. doi: 10.1213/ane.0b013e318279b399
36. Rozycki SK, Dixon FP, Yopp MA, Maxvold NJ, Rubin BK. Endotracheal tube seal and suction performance in a novel biorealistic tracheal model. *Respir Care.* (2015) 60:1113–9. doi: 10.4187/respcare.03799
37. Chen CC, Huang YC, Lee ST, Chen JF, Wu CT, Tu PH. Long-term result of vocal cord paralysis after anterior cervical disectomy. *Eur Spine J.* (2014) 23:622–6. doi: 10.1007/s00586-013-3084-y
38. Razfar A, Sadr-Hosseini SM, Rosen CA, Snyderman CH, Gooding W, Abla AA, et al. Prevention and management of dysphonia during anterior cervical spine surgery. *Laryngoscope.* (2012) 122:2179–83. doi: 10.1002/lary.23284

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A multicenter prospective cohort study of cardiac ultrasound phenotypes in patients with sepsis: Study protocol for a multicenter prospective cohort trial

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Background: Sepsis-induced cardiomyopathy significantly increased the mortality of patients with sepsis. The diagnostic criteria for septic cardiomyopathy has not been unified, which brings serious difficulties to clinical treatment. This study aimed to provide evidence for the early identification and intervention in patients with sepsis by clarifying the relationship between the ultrasound phenotype of septic cardiomyopathy and the prognosis of patients with sepsis.

Methods: This was a multicenter, prospective cohort study. The study population will consist of all eligible consecutive patients with sepsis or septic shock who meet the Sepsis 3.0 diagnostic criteria and were aged ≥18 years. Clinical data and echocardiographic measurements will be recorded within 2 h, at the 24th hour, at the 72nd hour, and on the 7th day after admission. The prevalence of each phenotype will be described as well, and their association with prognosis will be analyzed statistically.

Discussion: To achieve early recognition, prevent reinjury, achieve precise treatment, and reduce mortality in patients with sepsis, it is important to

identify septic cardiac alterations and classify the phenotypes at all stages of sepsis. First, there is a lack of studies on the prevalence of each phenotype in Chinese populations. Second, each phenotype and its corresponding prognosis are not clear. In addition, the prognosis of patients with normal cardiac ultrasound phenotypes vs. those with suppressed or hyperdynamic cardiac phenotypes is unclear. Finally, this study was designed to collect data at four specific timing, then the timing of occurrence, duration, changes over time, impact to outcomes of each phenotype will probably be found. This study is expected to establish a standard and objective method to assess the ultrasound phenotype of septic cardiomyopathy due to its advantages of visualization, non-invasiveness and reproducibility, and to provide more precise information for the hemodynamic management of septic patients. In addition, this research will promote the clinical application of critical care ultrasound, which will play an important role in medical education and make ultrasound the best method to assess cardiac changes in sepsis.

Trial registration: https://clinicaltrials.gov/ct2/show/NCT05161104, identifier NCT05161104.

KEYWORDS

sepsis, septic cardiomyopathy, ultrasound, cardiac phenotype, prognosis

Introduction

Sepsis is a life-threatening organ dysfunction resulting from a dysregulated host response to infection (1). The heart is one of the most important organs for oxygen supply and consumption and is frequently involved in sepsis. Septic myocardial suppression increases mortality in patients (2). Recent studies have found that a hyperdynamic state of the left ventricle (left ventricular ejection fraction [LVEF] >70%) is associated with mortality in intensive care unit (ICU) patients with sepsis, possibly because it reflects unresolved vascular paralysis from sepsis (2). For septic myocardial suppression, there is still a lack of uniform criteria for diagnosis; however, it is well established that the cardiac ultrasound phenotype of septic myocardial suppression can be left ventricular systolic dysfunction (LVSD), left ventricular diastolic dysfunction (LVDD), right ventricular dysfunction (RVD), diffuse ventricular dysfunction, and mixed ventricular dysfunction. According to available literature statistics, the prevalence of LVSD ranges from 12 to 60%, the prevalence of LVDD is higher at 20% to 79%, and the prevalence of RVD varies from 30 to 55% (3). However, based on the current understanding of septic myocardial suppression, the relationship between each stage and its prognosis is unclear. Echocardiography can rapidly identify septic myocardial suppression and guide its classification, thus further optimizing the diagnosis and treatment process of sepsis, particularly to avoid over-resuscitation during fluid resuscitation and perform reverse resuscitation in a timely manner to improve patient prognosis and reduce hospitalization time. This study aimed to classify and evaluate the prognosis of patients with different septic cardiac ultrasound phenotypes in multiple centers across China by measuring the right and left heart systolic and diastolic indices through echocardiography, recording the baseline conditions and clinical indices of patients, and combining them with their prognosis. Thus, in this study, a standardized evaluation system was established to evaluate the cardiac ultrasound phenotype of sepsis patients for the early identification of septic cardiac changes and classification of cardiac phenotypes in various stages of sepsis and to further alleviate sepsis treatment problems caused by the disease. This study also demonstrates the benefits of ultrasound in clinical dynamics and individualized assessment, with medical students gaining not only a convenient tool in their education, but also the clinical thinking skills needed to match it.

Methods

Inclusion criteria

The present study will be conducted in several medical centers in China, including Fujian Provincial Hospital, West China Hospital of Sichuan University, Peking Union Medical College Hospital, Fourth Hospital of Hebei Medical University, Chinese PLA General Hospital, First People's Hospital of Hangzhou City Affiliated to Zhejiang University, First Affiliated Hospital of Xiamen University, Shandong Provincial Hospital Affiliated to Shandong First Medical University, the Affiliated Hospital of Qingdao University, Quanzhou First Hospital

affiliated to Fujian Medical University, the First Affiliated Hospital of Anhui Medical University, between April 2022 to April 2025. Informed consent will be obtained from all patients or their legal guardians. All patients with sepsis or septic shock who diagnosed using the Sepsis 3.0 diagnostic criteria (1) and were ≥18 years of age who admitted or hospitalized to each center will be included. Sepsis is defined as an increasing of ≥2 points from baseline in the Sequential Organ Failure Assessment (SOFA) score due to infection, and septic shock is defined as persistent hypotension on top of sepsis, requiring vasoactive drugs to maintain a mean arterial pressure ≥65 mmHg and a blood lactate level >2 mmol/L despite adequate fluid resuscitation. Patients will be admitted to the ICU, and transthoracic echocardiograms will be performed by relevant qualified personnel and interpreted by two qualified personnel. Two senior sonographers (A and B) will independently examine the patients and compare them to identify the true positives as accurately as possible. The agreement rate between the two specialists is as high as 100%, and the reconfirmation of the individual set with doubts reach a unified conclusion. In case of diagnostic disagreement, we will ask an expert panel for a resolution, and as a quality control, all ultrasound images and measurements of each enrolled patient will be recorded. In addition, the results will be compared with the latest guidelines before building the dataset. Patients eligible for inclusion will have their first echocardiogram examination completed within 2 h of admission. If eligible, informed consent will be required prior to formal study entry.

Exclusion criteria

The exclusion criteria included patients with the following situations:

- Preexisting chronic heart disease, such as cardiomyopathy, chronic pulmonary heart disease, severe cardiac valve disease, coronary heart disease, congenital heart disease, and pericardial disease, and with cardiac function of grade ≥III (NYHA classification) prior to sepsis
- End-stage malignancies
- Severe trauma
- Pregnancy
- Patients for whom transthoracic echocardiography data are not available.

Data acquisition

This study has been approved by the local ethics committee of every participated center. The continuous inpatient electronic medical records will be reviewed for sepsis between April 2022 to April 2025. The prevalence of septic myocardial suppression has been reported in previous literature as 10–70% (4), taking the middle value of 40%. With a 95% confidence level, the results were required to fall within 10% of the overall truth rate, and the required sample size was estimated to be at least 1,152 cases. Detailed demographic and clinical characteristics will be collected and recorded, including age, sex, height, weight, primary diagnosis, site of infection, etiology (if known), underlying disease (hypertension, diabetes, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, oncologic disease, autoimmune disease, etc.), and medication history (beta-blockers, digitalis analogs, hormones, immunosuppressive agents, antineoplastic drugs, etc.).

Clinical and laboratory data will be collected included temperature, heart rate, respiratory rate, peripheral oxygen saturation, blood pressure (systolic/diastolic), pH, partial pressure of oxygen, inspired oxygen concentration, Glasgow Coma Scale score, white blood cell count, neutrophil count, lymphocyte count, hematocrit level, platelet count, calcitonin level, G-test scores, serum albumin level, total bilirubin level, serum creatinine level, troponin I level, NT-proBNP level, maximum dose of vasoactive drugs (norepinephrine, dopamine, vasopressin) or cardiac drugs (dobutamine, levosimendan, desacetyl trichothecene), SOFA score, and APACHE II score.

The ultrasound parameters are as follows:

- Indicators of left ventricular systolic function: mitral annular plane systolic excursion (MAPSE), LVEF, and left ventricular outflow tract flow velocity time integral
- Indicators of left ventricular diastolic function: E, A, and *e*'
- Right ventricular function indicators: tricuspid annular plane systolic excursion (TAPSE), inferior vena cava end-expiratory and end-inspiratory internal diameters, and right/left heart diastolic basal segment transverse diameter ratio (apical four-chamber heart view)
- Basal status indicators: right ventricular free wall thickness (subxiphoid four-chamber cardiac section) and septal thickness (apical four-chamber cardiac section).

The hemodynamic parameters will be collected included the central venous pressure, central venous–arterial blood carbon dioxide partial pressure difference, central venous oxygen saturation, and arterial blood lactate concentration.

All parameters mentioned above will be recorded within 2 h after sepsis diagnosis in the ICU, followed by recording of the ultrasound parameters and hemodynamic parameters once at 24, 72 h, and 7 days.

The prevalence of each phenotype will be described firstly. The primary outcomes are in-hospital and 28-day mortality rates. The secondary outcomes are the degree of echocardiographic improvement on day 7, length of stay in the ICU, and number of days on mechanical ventilation. Severe and irreversible disease will be determined by the supervising physician, and the patient's family chose

automatic discharge due to local customary conditions indicating death.

If a respondent is absent at a point in time when access is required, resulting in missing data at that point in time, or if an ending visit is missed, data from other points in time can be included in the analysis for that point in time without affecting the integrity and accuracy of the data at other points in time. We will ensure that the data collection was standardized and controllable, with the advantages of complete information, consistent structure, and no redundant information. In the process of data collection, we use the case report form to extract the clinical information required for the study from the research subjects, convert it into a standardized data form, and construct a reasonable database.

Data statistical analysis

SPSS (version 23.0; SPSS Inc., Chicago, IL, USA) will be used for the analysis. Continuous variables will be defined as the mean ± standard deviation, and categorical variables will be presented as percentages. The Kolmogorov–Smirnov test will be used to verify the normality of the distribution of the continuous variables. One-way ANOVA will be used for comparison of means between groups; two independent samples *t*-test will be used for comparison between two groups; χ^2 test will be used for counting data; and multifactor logistic regression and Cox survival analysis will be used to determine the factors of prognosis. P-values < 0.05 will be considered statistically significant.

The participants will be divided into a modeling cohort and a validation cohort in a 7:3 ratio. In the modeling cohort, variables with $P < 0.05$ in the univariate Cox analysis will be included in the multivariate Cox analysis, and nomogram plots will be constructed. Finally, the validation cohort will be used to evaluate the discrimination ability of the model based on the area under the ROC curve.

Discussion

Several studies have confirmed the high mortality rate in patients with sepsis, ranging from 34 to 56% (5) and 33.5% (6) in foreign and domestic countries, respectively, and even higher in patients with combined hyperdynamic left ventricular function or myocardial depression (3, 7). Standardizing the staging of myocardial depression in sepsis and realizing the early identification of patients with sepsis are of great significance for clarifying the cardiac changes in sepsis at various stages, adjusting and guiding treatment in a timely manner, and optimizing hemodynamics.

The study will obtained the systolic and diastolic function indices of the left and right hearts through ultrasound, filling the gap of cardiac ultrasound indices for sepsis in China in the existing guidelines or expert consensus. Some studies have shown that EF <52% in men or EF <54% in women suggests abnormal left ventricular systolic function (8), and EF >70% suggests a hyperdynamic state of left ventricular function (9). Systolic function can also be assessed by obtaining the MAPSE using M-mode echocardiography. There are no consensus recommendations for abnormal MAPSE values; however, MAPSE <1 cm can indicate abnormal left ventricular systolic function (10). Diastolic function is a major determinant of left ventricular compliance, and diastolic dysfunction is common in septic myocardial suppression and a major predictor of mortality in patients with sepsis and septic shock (11). This can lead to a further increase in left ventricular end-diastolic pressure (LVEDP) by increasing left ventricular end-diastolic volume (12), subsequently increasing the pressure in the pulmonary, right heart, and body circulations, leading to increased extravascular lung water and tissue edema. The preferred method to evaluate diastolic function is the early diastolic mitral annular velocity (*e*') measured by TDI; the lower the value, the worse the diastolic function. The ratio of early diastolic transdiastolic inflow velocity (*E*) to early diastolic mitral annular velocity (*E*/*e*') correlates with left heart pressure and better reflects the increase in pressure (13). *e*' (at the septum) <7 cm/s or *e*' (at the lateral wall of the ventricle) <10 cm/s suggests abnormal left ventricular diastolic function, *E*/*e*' >14 cm/s suggests abnormal left ventricular diastolic function, and *E*/*e*' <8 cm/s suggests normal left ventricular diastolic function (14). The occurrence of acute respiratory distress syndrome and mechanical ventilation in patients with sepsis impacts right ventricular function, as right ventricular function is associated with afterload, which increases with hypoxemia, hypercapnia, elevated inspiratory pressure, and elevated positive end-expiratory pressure (15). The TAPSE is the simplest and most reproducible measure of right ventricular function, and a TAPSE <17 mm suggests abnormal right ventricular systolic function (16). A decrease in TAPSE is associated with increased mortality in critical illness (17).

In addition, septic cardiac changes exist in both directions, and there are currently no studies that consider both changes together in the same study. A previous radionuclide angiography study showed a reduced LVEF in a subgroup of patients with sepsis because the left ventricle, which undergoes dilatation in sepsis, can maintain beat volume if fluid resuscitation is adequate (18); however, more surprisingly, a study showed that patients with a reversible decrease in EF have a better prognosis than those without a decrease in EF (19), probably because septic myocardial suppression is a protective event that prevents the activation of cell death pathways by reducing energy expenditure in the presence of limited energy production and may allow the potential for full recovery of cellular function to be realized (20). Since the occurrence of "inhibition" may instead be beneficial, in line with the findings that left ventricular function in a

hyperdynamic state affects mortality, it contradicts our previous knowledge that the occurrence of septic myocardial inhibition increases mortality in patients with sepsis (2). The prognostic differences between patients with normal, suppressed, and hyperdynamic cardiac phenotypes are unclear.

Finally, owing to the temporal variability in the onset of septic cardiac changes, this study was designed to collect data at four specific time points. One of the main clinical features of septic myocardial suppression is its apparent reversibility, with several studies reporting that patients can fully recover their cardiac function to the premorbid state (18, 21, 22). The changes detected by cardiac magnetic resonance imaging suggest myocardial edema or altered metabolic status, unlike the pattern of ischemia and necrosis, which are consistent with the characteristics of reversibility (23). This "reversibility" also suggests that there may be interconversion between the three states of cardiac suppression, hyperdynamic, and normal in sepsis patients, but the ratio and time of conversion are not clear, which is also important for triggering the timing of treatment initiation and withdrawal. Therefore, the type of septic cardiac changes at occurrence, timing of occurrence, duration, and prognostic impact of subsequent phenotypic alterations are also aims and innovations of this study.

Clinically, septic cardiac changes manifest as symptoms of circulatory failure associated with systemic infections. The differences in the clinical manifestations of cardiac insufficiency in patients with nonseptic decompensated heart failure lie in the alterations of overall hemodynamic parameters (preload, afterload, microcirculation). Unlike other cardiac diseases, cardiac changes in patients with sepsis require a multimodal approach for diagnosis and treatment. Unfortunately, there are no treatment recommendations specifically for the cardiac changes associated with sepsis. Patients with impaired left ventricular diastolic function may be at greater risk of fluid over-resuscitation, whereas patients with impaired left heart systolic function require more cardiac stimulant support, as volume resuscitation alone to correct perfusion deficits may be difficult to achieve; patients with right heart insufficiency require intensive treatment for acute respiratory distress syndrome and adjustment of mechanical ventilation parameters. In contrast, patients in a hyperdynamic left ventricular state require vasoconstrictors to improve vascular paralysis or symptomatic use of cardiac depressants.

Elevated plasma levels of troponin I and troponin T in patients with sepsis have been associated with LVSD and myocardial injury (24), as well as mortality (25). The mechanism of troponin elevation in sepsis may be caused by inflammation-induced cytoplasmic leakage from cardiomyocytes rather than cell death, and myocardial ischemia does not appear to be the culprit (26). BNP and NT-proBNP are hormones secreted by the myocardium in response to pressure stretching of the ventricular wall and have been proposed as markers of fluid loading status and early indicators of myocardial depression (27). However, other organ dysfunctions may affect troponin and BNP metabolism without being fully influenced by the actual myocardial injury and volume profile. In another study on coronary arteries in patients with sepsis, blood samples from the coronary sinus showed no increase in lactate production by cardiomyocytes, excluding myocardial ischemia as a cause of left ventricular dysfunction (28). Coronary angiography or CT imaging cannot be routinely performed in patients with sepsis with elevated troponin levels. Therefore, sepsis-induced cardiac changes should be defined as functional phenomena rather than as biochemical elevations. Echocardiography, which is widely used in clinical practice, has the advantage of being noninvasive and reproducible, making it the best way to assess cardiac changes in patients with sepsis.

The results of this study will enable medical students to understand the important value of ultrasound as a means of non-invasive hemodynamic monitoring in screening for etiology and dynamic assessment of disease in critically ill patients. In addition, this study was conducted under the guidance of the China Critical Ultrasound Study Group (CCUSG), and its research results are expected to become the organization's ultrasound training content to be applied and promoted in China and even around the world, which will help promote ultrasound in the promotion and application of residency and specialist physician training to improve the quality of medical teaching and residency training.

In conclusion, this study aimed to obtain data on patients with sepsis from multiple centers across the country, analyze each echocardiographic phenotype of sepsis, and investigate its incidence, duration, and prognosis. The prognosis of various patients can be compared as a predictor of future clinical prognosis, especially in those with "suppressed" and "hyperdynamic" phenotypes. This will be a novel predictor of clinical outcomes in patients with sepsis and the establishment of cardiac ultrasound phenotypes can also serve to guide and educate young physicians.

A limitation of this study may be that patients for whom transthoracic echocardiography data were not available did not undergo further transesophageal ultrasound due to medical constraints at each center and to avoid additional risks and lack of benefit to the patient. It is promising to study subgroups of sepsis patients with other underlying diseases, such as chronic hepatic and renal diseases, autoimmune diseases, and immunosuppressive states, as their underlying diseases may affect the prognosis by influencing the infection status. More specific and sensitive biomarkers for cardiac alterations in sepsis will also be an important area of future research and should be further explored in other studies.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Fujian Provincial Hospital.

The patients/participants provided their written informed consent to participate in this study.

Author contributions

HongxZ: conceptualization, methodology, data curation, and writing—original draft. XW: validation and writing—review and editing. WY, HongmZ, LL, and PP: validation and data curation. YZ, WH, ZX, BY, CW, and TL: data curation. RY and XS: validation, writing—review and editing, and supervision. 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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References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA*. (2016) 315:801–10. doi: 10.1001/jama.2016.0287

2. Havaldar AA. Evaluation of sepsis induced cardiac dysfunction as a predictor of mortality. *Cardiovasc Ultrasound*. (2018) 16:31. doi: 10.1186/s12947-018-0149-4

3. Wang J, Wang XT, Liu DW, Zhang HM. Su LX.Induction and deduction in sepsis-induced cardiomyopathy: five typical categories. *Chin. Med. J.* (2020) 133:2205–11. doi: 10.1097/CM9.0000000000000929

4. Beesley SJ, Weber G, Sarge T, Nikravan S, Grissom CK, Lanspa MJ, et al. Septic Cardiomyopathy. *Crit Care Med*. (2018) 46:625–34. doi: 10.1097/CCM.0000000000002851

5. Liu V, Escobar GJ, Greene JD, Soule J, Whippy A, Angus DC, et al. Hospital deaths in patients with sepsis from 2 independent cohorts. *JAMA*. (2014) 312:90–2. doi: 10.1001/jama.2014.5804

6. Zhou JF, Qian CY, Zhao MY Yu XY, Kang Y, Ma XC, et al. Epidemiology and outcome of severe sepsis and septic shock in intensive care units in mainland China. *PLoS ONE*. (2014) 9:e107181. doi: 10.1371/journal.pone.0107181

7. Chotalia M, Ali M, Hebballi R, Singh H, Parekh D, Bangash MN. et al.Hyperdynamic left ventricular ejection fraction in ICU patients with sepsis. *Crit Care Med*. (2021) 50:770–9. doi: 10.1097/CCM.0000000000005315

8. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. (2015) 16:233–70. doi: 10.1093/ehjci/jev014

9. Paonessa JR, Brennan T, Pimentel M, Steinhaus D, Feng ML. Celi LA. Hyperdynamic left ventricular ejection fraction in the intensive care unit. *Critical Care*. (2015) 19:288. doi: 10.1186/s13054-015-1012-8

10. Ehrman RR, Sullivan AN, Favot MJ, Sherwin RL, Reynolds CA, Abidov A, et al. Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardiomyopathy: a review of the literature. *BioMed Central*. (2018) 22:112. doi: 10.1186/s13054-018-2043-8

11. Landesberg G, Gilon D, Meroz Y, Georgieva M, Levin PD, Goodman S, et al. Diastolic dysfunction and mortality in severe sepsis and septic shock. *Eur Heart J*. (2012) 33:895–903. doi: 10.1093/eurheartj/ehr351

12. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the european association of cardiovascular imaging. *Eur Heart J Cardiovasc Imaging*. (2016) 17:1321–60. doi: 10.1093/ehjci/jew082

13. Pittman SM, Hirshberg EL, Jones JP, Lanspa MJ, Kuttler KG, Kuttler KG, et al. Diastolic dysfunction and mortality in early severe sepsis and septic shock: a prospective, observational echocardiography study. *Crit. Ultrasound J.* (2012) 4:8. doi: 10.1186/2036-7902-4-8

14. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF III, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American society of echocardiography and the European association of cardiovascular imaging. *Eur Heart J CardiovascImaging*. (2016) 29:277–314. doi: 10.1016/j.echo.2016.01.011

15. Gordo-Vidal F, Enciso-Calderón V. Acute respiratory distress syndrome, mechanical ventilation and right ventricular function. *Medicina Intensiva*. (2012) 36:138–142. doi: 10.1016/j.medine.2012.03.003

16. Lahham S, Lee C, Ali Q, Moeller J, Fischetti C, Thompson M, et al. Tricuspid Annular Plane of Systolic Excursion (TAPSE) for the Evaluation of Patients with Severe Sepsis and Septic Shock. *West J Emerg Med*. (2020) 21:348–52. doi: 10.5811/westjem.2019.11.44968

17. Demirkol S, Ozturk C, Unlu M, Arslan Z, Celik T. Tricuspid annular plane systolic excursion and its association with mortality in critically Ill patients: right ventricular function in critically Ill patients. *Echocardiography*. (2015) 32:1330. doi: 10.1111/echo.12974

18. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, et al. Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med*. (1984) 100:483. doi: 10.7326/0003-4819-100-4-483

19. Parker MM, Suffredini AF, Natanson C, Ognibene FP, Shelhamer JH, Parrillo JE. Responses of left ventricular function in survivors and nonsurvivors of septic shock. *J Crit Care*. (1989) 4:19–25. doi: 10.1016/0883-9441(89)90087-7

20. Rudiger A, Singer M. Mechanisms of sepsis-induced cardiac dysfunction. *Crit Care Med*. (2007) 35:1599–608. doi: 10.1097/01.CCM.0000266683.64081.02

21. Kakihana Y, Ito T, Nakahara M, Yamaguchi K, Yasuda T. Sepsis-induced myocardial dysfunction: pathophysiology and management. *J Intens Care*. (2016) 4:22. doi: 10.1186/s40560-016-0148-1

22. Jardin F, Fourme T, Page B, Loubières Y, Vieillard-Baron A, Beauchet A, et al. Persistent preload defect in severe sepsis despite fluid loading: a longitudinal echocardiographic study in patients with septic shock. *Chest*. (1999) 116:1354–9. doi: 10.1378/chest.116.5.1354

23. Siddiqui Y, Crouser ED, Raman SV. Nonischemic myocardial changes detected by cardiac magnetic resonance in critical care patients with sepsis. *Am J Respir Crit Care Med.* (2013) 188:1037–9. doi: 10.1164/rccm.201304-0744LE

24. Turner A, Tsamitros M. Bellomo R. Myocardial cell injury in septic shock. *Crit Care Med.* (1999) 27:1775–80. doi: 10.1097/00003246-199909000-00012

25. Ammann P, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oechslin E, et al. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. *J Am Coll Cardiol.* (2003) 41:2004–9. doi: 10.1016/S0735-1097(03)00421-2

26. Ostermann M, Ayis S, Tuddenham E, Lo J, Lei K, Smith J, et al. Cardiac troponin release is associated with biomarkers of inflammation and ventricular dilatation during critical illness. *Shock.* (2017) 47:702–8. doi: 10.1097/SHK.0000000000000811

27. Maeder M, Fehr T, Rickli H, Ammann P. Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. *Chest.* (2006) 129:1349–66. doi: 10.1378/chest.129.5.1349

28. Cunnion RE, Schaer GL, Parker MM, Natanson C, Parrillo JE. The coronary circulation in human septic shock. *Circulation.* (1986) 73:637–44. doi: 10.1161/01.CIR.73.4.637

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Prognostic value of National Early Warning Score and Modified Early Warning Score on intensive care unit readmission and mortality: A prospective observational study

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Background: Modified Early Warning Score (MEWS) and National Early Warning Score (NEWS) are widely used in predicting the mortality and intensive care unit (ICU) admission of critically ill patients. This study was conducted to evaluate and compare the prognostic value of NEWS and MEWS for predicting ICU readmission, mortality, and related outcomes in critically ill patients at the time of ICU discharge.

Methods: This multicenter, prospective, observational study was conducted over a year, from April 2019 to March 2020, in the general ICUs of two university-affiliated hospitals in Northwest Iran. MEWS and NEWS were compared based on the patients' outcomes (including mortality, ICU readmission, time to readmission, discharge type, mechanical ventilation (MV), MV duration, and multiple organ failure after readmission) using the univariable and multivariable binary logistic regression. The receiver operating characteristic (ROC) curve was used to determine the outcome predictability of MEWS and NEWS.

Results: A total of 410 ICU patients were enrolled in this study. According to multivariable logistic regression analysis, both MEWS and NEWS were predictors of ICU readmission, time to readmission, MV status after readmission, MV duration, and multiple organ failure after readmission. The area under the ROC curve (AUC) for predicting mortality was 0.91 (95% CI = 0.88–0.94, $P < 0.0001$) for the NEWS and 0.88 (95% CI = 0.84–0.91,

$P < 0.0001$) for the MEWS. There was no significant difference between the AUC of the NEWS and the MEWS for predicting mortality ($P = 0.082$). However, for ICU readmission (0.84 vs. 0.71), time to readmission (0.82 vs. 0.67), MV after readmission (0.83 vs. 0.72), MV duration (0.81 vs. 0.67), and multiple organ failure (0.833 vs. 0.710), the AUCs of MEWS were significantly greater ($P < 0.001$).

Conclusion: National Early Warning Score and MEWS values of >4 demonstrated high sensitivity and specificity in identifying the risk of mortality for the patients' discharge from ICU. However, we found that the MEWS showed superiority over the NEWS score in predicting other outcomes. Eventually, MEWS could be considered an efficient prediction score for morbidity and mortality of critically ill patients.

KEYWORDS

intensive care unit, National Early Warning Score, Modified Early Warning Score, readmission, mortality, prognosis

Introduction

Readmission to the intensive care units (ICUs) is associated with poor patient outcomes, including higher mortality, a longer length of stay, and higher adverse event rates (1–3). In addition, ICU readmissions bring financial burden and wastefulness to the patient flow of the healthcare system (4, 5). Readmitted patients reduce ICU bed availability and, probably, the efficiency of the ICU facilities (6, 7). The intensivist usually decides to discharge patients from the ICU based on clinical evaluations (8, 9). However, several other non-clinical factors contribute to such decisions – including the high demand and need for ICU beds by emergency and surgical departments – making the discharge decision a complex, challenging, and risky care transfer process (10, 11). These factors may lead to an early and inadequate discharge of patients, which increases the risk of readmission, as up to 42% of patients discharged early are eventually readmitted to the ICU (12). Hence, several attempts have been made to optimize and prioritize ICU discharges, either by identifying risk factors associated with ICU readmission (9, 13) or developing readmission prediction models (14, 15). These models for mortality and readmission after ICU discharge have shown diverse accuracy. Although prospective validation is warranted for these scoring systems, they speculate that these models could be valuable assistance to clinicians for ICU discharge planning.

Several Early Warning Scores (EWSs) with different designs have been developed to diagnose early signs of deterioration in a patient's conditions and initiate further medical care and possible ICU admission (16–18). Since a critical state usually follows specific deteriorations in the patient's physiological signs, monitoring these signs could help the physicians predict the patient's outcomes (19–21). One of the common EWSs is the Modified Early Warning Score (MEWS), validated in 2001 in the United Kingdom as a bedside tool to identify patients at risk for catastrophic events, including death or readmission to ICU (22). National Early Warning Score (NEWS) is another EWS introduced in 2012 by the Royal College of Physicians (23). The NEWS score identifies the patients at risk of deterioration and facilitates prompt critical care intervention. Also, many studies have shown the capability of NEWS in predicting the degree of illness (18, 24). Several studies have explored the association between these risk scores and hospital admission. The findings suggest that these risk scores could also be used as triage tools to identify patients requiring hospital admission (22, 25, 26).

Due to the lack of studies comparing NEWS and MEWS risk-scoring systems in ICU settings, it is still unclear which risk-scoring system is superior as a triage tool for ICU readmission and predicting mortality of critically ill patients. Considering the lack of information and the inconsistency in the cut-off values, this study was conducted to evaluate and compare the prognostic value of NEWS and MEWS for predicting ICU readmission, mortality, and related outcomes in critically ill patients at the time of ICU discharge.

Materials and methods

Study design and population

This multicenter, prospective, observational study was conducted over a year, from April 2019 to March 2020, in the general intensive care units (ICUs) of two university-affiliated hospitals in Northwest Iran, to evaluate and compare the prognostic value of NEWS and MEWS scores for predicting ICU readmission, mortality and related outcomes in critically ill patients at the time of discharge from the ICU. All adult

(over 18 years old) patients alive at the time of ICU discharge were eligible to enroll in this study, regardless of the medical diagnoses and underlying comorbidities. However, patients were excluded if they were: (a) stayed in the ICU for less than 48 h (such as postoperative patients), (b) patients directly discharged home or transferred to other medical centers, (c) patients discharged for palliative care, and (d) patients readmitted to the ICU for the second time. Patients who no longer needed mechanical ventilation (MV), vasopressor support, and renal replacement therapies were discharged from the ICU with appropriate levels of consciousness and transferred to general wards. Subsequently, all patients were followed up for 2 weeks to identify readmitted patients.

Ethical considerations

The protocol study was reviewed and approved by the Research Ethics Committees of Islamic Azad University-Tabriz Branch (IR.TBZMED.REC.1397.994), following the Declaration of Helsinki of the World Medical Association (27). Written informed consent was obtained from the patients or their legally accepted representatives. In addition, the study was conducted and reported in accordance with the recommendations of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (28).

Data collection

Demographic characteristics and clinical data, including comorbidities, reasons for admission (medical, surgical, or emergency), the severity of illness [based on Acute Physiology and Chronic Health Evaluation IV (APACHE-IV) and Sequential Organ Failure Assessment (SOFA) scores], consciousness state, and vital signs (respiratory rate, peripheral oxygen saturation (SpO_2), systolic/diastolic blood pressure, heart rate, pulse rate, and body temperature) upon ICU admission were recorded for all patients. Additionally, we collected the information, including the status and type of multiple organ failure, mechanical ventilation (MV) status, MV duration, length of stay (LOS) in the ICU, and the NEWS and MEWS scores at the time of ICU discharge. All data were collected and analyzed by researchers completely independent of the clinical decision-makers.

Calculation of National Early Warning Score and Modified Early Warning Score scores

A trained nurse calculated the NEWS and MEWS scores for all patients who were alive at the time of ICU discharge using physiological parameters. NEWS scores were obtained by nursing staff at the ICUs, including the following seven common vital signs parameters: Respiratory rate (RR), peripheral oxygen saturation (SpO_2) measured by pulse oximetry, supplementary oxygen, systolic arterial blood pressure (SBP), pulse rate (PR), body temperature (T), and AVPU (Alert, responds to Voice, responds to Pain, Unresponsive) score based on the Glasgow Coma Scale (GCS) [The AVPU score was derived from the GCS as follows: $A = 14–15$, $V = 9–13$, $P = 4–8$, $U = 3$] (29). Patients with a score between 0 and 4 are considered low risk, those with a score of 5 or 6 are considered medium risk, and patients with a score ≥ 7 are considered high risk (29). The MEWS consists of five physiological variables, including systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), body temperature (T), and AVPU score based on the GCS. Determining a MEWS score involves assigning a number between 0 and 3 to each of the six vital signs. Patients with scores between 2 and 4 are considered at medium risk and should remain under specialized care and be assessed again in 2 to 8 h. Those with a score ≥ 5 are considered at high risk for mortality and being moved to ICU (22).

Outcomes

The primary outcomes were mortality and readmission to the ICU. The secondary outcomes were the type of discharge from ICU and subgroups of consequences related to the readmission, such as mechanical ventilation, duration of mechanical ventilation, and multiple organ failure.

Statistical analysis

Data were expressed as mean ± standard division (SD) or median with interquartile range (IQR) for continuous variables, and frequencies with percentages (%) for categorical characteristics. The Shapiro-Wilk test was used to determine whether data were normally distributed. To compare the NEWS and MEWS scores according to the outcomes and subgroups of outcomes, we used Mann–Whitney as a non-parametric test for non-normal distributions. Univariate and multivariate binary logistic regression analyses were performed to evaluate associations of NEWS and MEWS scores with the outcomes. Each variable was first tested by univariate analysis with odds ratios (OR) and 95% confidence intervals (95% CI). In multivariate analysis, based on conditional logistic regression, variables with a p-value < 0.05 in the univariate analyses were proposed for entry into the model. To assess the predictive prognostic efficacy of the NEWS and MEWS scores, we performed receiver operating characteristic (ROC) curves and calculated the area under the curves (AUC). AUC figures were calculated alongside sensitivity (SN), specificity (SP), positive likelihood ratio (LR +), negative likelihood ratio (LR-), positive predictive value (PPV), negative predictive value (NPV), and

Youden index to find appropriate cut-offs. In addition, we compared the ROC of NEWS and MEWS scores using the DeLong test. According to the general guide, AUC between (0.9–1.0), (0.8–0.9), (0.7–0.8), and (0.6–0.7) was considered as excellent, good, fair, and poor, respectively. Statistical analysis was performed using SPSS Statistics 21.0 (SPSS Inc., Chicago, IL, United States) and MedCalc.[1] In all analyses, *p*-values less than 0.05 were considered significant.

Results

Characteristics of patients

In total, 410 patients were selected for this study. The basic information and clinical characteristics of the patient population are listed in Table 1. The median age (IQR) of the patients was 59 (49.75–69) years, and 223 (56.8%) patients were male. Nearly half of the patients (n = 185, 45.1%) had comorbidities, and 25 (6.1%) had more than two underlying diseases. The most common reason of admission was surgical (n = 272, 66.3%) followed by medical (n = 102, 24.9%) and emergency (n = 36, 8.8%). The median (IQR) of APACHE IV and SOFA scores of the patients were 23.5 (21–26) and 9 (6–13.25), respectively. More than half of patients had multiple organ failure (n = 286, 69.8%) and underwent MV (n = 273, 66.6%). The median (IQR) length of stay in the ICU and MV duration were 9 (6–13.25) and 8 (5–12) days, respectively.

TABLE 1 Demographic and clinical characteristics data of all patients (n = 410).

Variables		Frequency
Age (years)	**Median (IQR)**	**59 (49.75–69)**
Gender	Male (%)	223 (56.8)
	Female (%)	177 (43.2)
Comorbidities	Yes (only one disease,%)	160 (39)
	Yes (more than two diseases,%)	25 (6.1)
	No (%)	225 (54.9)
Types of comorbidities	CVA (%)	26 (6.3)
	Malignancy (%)	14 (3.4)
	IHD (%)	51 (12.4)
	HTN (%)	43 (10.5)
	DM (%)	32 (7.8)
	CHF (%)	33 (8)
	HLP (%)	7 (1.7)
	MI (%)	3 (0.7)
	ESRD (%)	1 (0.2)
Reasons of admission	Medical (%)	102 (24.9)
	Surgical (%)	272 (66.3)
	Emergency (%)	36 (8.8)
APACHE IV	Median (IQR)	23.5 (21–26)
SOFA	Median (IQR)	9 (6–13.25)
Multiple organ failure	Yes (%)	286 (69.8)
	No (%)	124 (30.2)
Type of multiple organ failure	Respiratory (%)	173 (42.2)
	Cardiovascular (%)	57 (13.9)
	Neurologic (%)	92 (22.4)
	Renal (%)	67 (16.3)
ICU length of stay (LOS)	Median (IQR)	9 (6–13.25)
Mechanical ventilation	Yes (%)	273 (66.6)
(MV)	No (%)	137 (33.4)
MV duration (days)	Median (IQR)	8 (5–12)
NEWS score	Median (IQR)	4 (3–4)
MEWS score	Median (IQR)	3 (3–3)

Cerebrovascular accident (CVA), Ischemic heart disease (IHD), Hypertension (HTN), Diabetes mellitus (DM), Congestive heart failure (CHF), Hyperlipidemia (HLP), Myocardial infarction (MI), End-stage renal disease (ESRD), Acute Physiology and Chronic Health Evaluation IV (APACHE-IV), Sequential Organ Failure Assessment (SOFA), National Early Warning Score (NEWS), Modified Early Warning Score (MEWS).

Characteristics of readmitted patients

A total of 50 (12.2%) ICU patients discharged to the general ward were readmitted within 2 to 12 days, with a median (IQR) time of 4 (3–4) days. Clinical characteristics of readmitted patients and the main reasons for readmission are presented in Table 2. Of 50 patients readmitted to the ICU, 39 (78%) underwent MV. The median (IQR) MV duration in readmitted patients was 6 (5–6) days. Organ failure was present in 48 (96%) readmitted patients.

Comparison of National Early Warning Score and Modified Early Warning Score scores according to outcomes

Table 3 presents the detailed comparison of NEWS and MEWS scores among the patients regarding mortality, type of discharge, readmission, time to readmission, MV status, MV duration, and organ failure after readmission. Comparing NEWS and MEWS scores between outcomes showed statistically significant differences, as the median scores of NEWS and MEWS were significantly higher in non-survivors, readmitted patients, patients with lower (<4) days to readmission, those who underwent MV, patients with higher (≥6) days of MV, and patients with multiple organ failure. However, no significant differences were observed between median scores of NEWS (p-value = 0.332) and MEWS (p-value = 0.447) in the patients with planned and unplanned types of discharge.

1 https://www.medcalc.org/calc/diagnostic_test.php

TABLE 2 Clinical characteristics of patients readmitted to the ICU (n = 50).

Variables		Frequency
Reasons of readmission	Embolism (%)	1 (2)
	Consciousness disorder (%)	9 (18)
	Cardiovascular (%)	6 (12)
	Renal (%)	4 (8)
	Brain (%)	3 (6)
	Pneumonia (%)	3 (6)
	Respiratory failure (%)	24 (48)
Time to readmission	Median (IQR) days	4 (3–6)
Re-mechanical ventilation	Yes (%)	39 (78)
	No (%)	11 (22)
MV duration readmission	Median (IQR) days	6 (5–6)
Multiple organ failure readmission	Yes (%)	48 (96)
	No (%)	2 (4)
Type of multiple organ failure	Respiratory (%)	20 (40)
	Cardiovascular (%)	9 (18)
	Neurologic (%)	12 (24)
	Renal (%)	9 (18)

Logistic regression findings

Tables 4, 5 present the univariable and multivariable binary logistic regression analyses to evaluate associations of NEWS and MEWS scores to predict outcomes. In univariable analysis, an increase in mortality risk was observed in a higher NEWS score (OR: 18.58, 95% CI: 8.45–40.86, p-value < 0.001) and MEWS score (OR: 12.19, 95% CI: 6.43–23.11, p-value < 0.001). However, multivariable analysis showed that the higher NEWS was only associated with mortality (OR: 6.51, 95% CI: 1.81–23.43, p-value = 0.004). In addition, the multivariable binary logistic regression model identified that the higher NEWS and MEWS scores upon discharge were associated with readmission, lower time to readmission, the risk of undergoing MV after readmission, higher MV duration, and the risk of multiple organ failure after readmission.

Predicting outcomes by National Early Warning Score and Modified Early Warning Score scores

Table 6 shows the performance of NEWS and MEWS scores to predict outcomes with cut-off points. Excellent predictive performance of the NEWS score was found regarding mortality, with an AUC of 0.91 (95% CI: 0.88–0.94, p-value < 0.0001). The best cut-off value (>4) had a sensitivity of 71.87%, specificity of 95.5%, LR + of 15.98, LR- of 0.29, PPV of 57.5%, NPV of 97.6%, and 0.67% of Yuden index. The AUC values of the NEWS scores for ICU readmission, MV status, and multiple organ failure after readmission were considered fair. However, the poor predictive performance of the NEWS score was observed regarding the time to readmission and MV duration after readmission (Supplementary Figure 1).

According to the results, the MEWS score had a good predictive performance for all outcomes, except for the type of discharge, which was insignificant. Best performing predictive value of MEWS score was related to the mortality with AUC of 0.88 (95% CI: 0.84–0.91, p-value < 0.0001), and the best

TABLE 3 Comparison of NEWS and MEWS scores according to the outcomes and subgroups of outcomes.

Outcomes		Frequency (%)	NEWS score			MEWS score		
			Median (IQR)	Mean Rank	*P*-value	Median (IQR)	Mean Rank	*P*-value
Mortality (n = 410)	Yes	32 (7.8)	5 (4–6)	362.7	<**0.0001**	5 (4–5)	193.3	<**0.0001**
	No	378 (92.2)	4 (3–4)	192.2		3 (3–3)	349.5	
Discharge type of ICU (n = 410)	Planned	392 (95.6)	3 (3–4)	206.6	0.332	3 (3–3)	204.7	0.447
	Unplanned	18 (4.4)	4 (3–4)	181.5		3 (2–4)	222.9	
ICU Readmission	Yes	50 (12.2)	4 (4–4.25)	281.5	<**0.0001**	4 (4–4)	327.4	<**0.0001**
	No	360 (87.8)	3.5 (3–4)	194.9		3 (3–3)	188.5	
Time to readmission (n = 50)	≥4 days	37 (76)	4 (3–4)	198.9	<**0.0001**	3 (3–3)	193.4	<**0.0001**
	<4 day	13 (24)	4 (4–4)	271.2		4 (4–4)	327.2	
MVReadmission (n = 50)	Yes	39 (78)	4 (4–5)	287.1	<**0.0001**	4 (4–4)	327.4	<**0.0001**
	No	11 (22)	4 (3–4)	196.9		3 (3–3)	192.6	
MVreadmission duration (n = 50)	≥6 days	22 (44)	4 (4–5)	273.5	**0.002**	4 (3.7–4)	326.8	<**0.0001**
	<6 days	28 (56)	4 (3–4)	201.6		3 (3–3)	198.6	
Multiple organ failure readmission (n = 50)	Yes	48 (96)	4 (4–4.75)	281.6	<**0.0001**	4 (4–4)	326.2	<**0.0001**
	No	2 (4)	4 (3–4)	195.4		3 (3–3)	189.5	

P-value < 0.05 considered significant. The p-value was evaluated based on the Mann–Whitney test.

TABLE 4 Univariable and multivariable binary logistic regression analysis to evaluate associations of NEWS and MEWS scores to predict mortality, readmission, discharge type, and time to readmission.

Variables	Univariate		Multivariate	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
Mortality (Yes vs. No)				
Age	1.01 (0.97–1.03)	0.741	–	–
Gender (Male vs. Female)	1.17 (0.57–2.426)	0.66	–	–
Comorbidities (Yes vs. No)	2.90 (1.33–6.29)	**0.007***	3.23 (0.82–12.6)	0.092
Comorbidities (≥2 vs. 1)	5.60 (2.14–14.66)	<**0.001***	2.19 (0.37–12.8)	0.385
SOFA	2.05 (1.67–2.52)	<**0.001***	0.64 (0.23–1.74)	0.385
APACHE IV	1.48 (1.32–1.65)	<**0.001***	1.50 (0.87–2.58)	0.137
NEWS score	18.58 (8.45–40.86)	<**0.001***	6.51 (1.81–23.4)	**0.004***
MEWS score	12.19 (6.43–23.12)	<**0.001***	2.62 (0.86–7.95)	0.089
ICU Readmission (Yes vs. No)				
Age	1.01 (0.98–1.03)	0.382	–	–
Gender (Male vs. Female)	2.17 (1.18–3.97)	**0.012***	2.36 (1.18–4.70)	**0.015***
Comorbidities (Yes vs. No)	1.50 (0.82–2.71)	0.18	–	–
Comorbidities (≥2 vs. 1)	1.88 (0.67–5.28)	0.225	–	–
SOFA	1.30 (1.13–1.49)	<**0.001***	1.02 (0.54–1.93)	0.935
APACHE IV	1.14 (1.06–1.22)	<**0.001***	0.95 (0.68–1.33)	0.798
NEWS score	2.17 (1.52–3.10)	<**0.001***	2.24 (1.11–5.54)	<**0.001***
MEWS score	3.43 (2.36–4.99)	<**0.001***	8.12 (3.71–17.80)	<**0.001***
Discharge type (Unplanned vs. Planned)				
Age	0.93 (0.91–0.97)	**0.001***	0.93 (0.90–0.97)	**0.002***
Gender (Male vs. Female)	1.05 (0.41–2.73)	0.911	–	–
Comorbidities (Yes vs. No)	0.76 (0.29–2.01)	0.588	–	–
Comorbidities (≥2 vs. 1)	0.87 (0.35–3.54)	0.998	–	–
SOFA	0.66 (0.49–0.88)	**0.006***	0.67 (0.27–1.65)	0.392
APACHE IV	0.82 (0.71–0.96)	**0.013***	1.03 (0.64–1.65)	0.884
NEWS score	0.67 (0.32–1.41)	0.299	–	–
MEWS score	1.16 (0.65–2.09)	0.604	–	–
Time to readmission (< 4 days vs. ≥4 days)				
Age	1.01 (0.97–1.03)	0.862	–	–
Gender (Male vs. Female)	1.62 (0.82–3.19)	0.164	–	–
Comorbidities (Yes vs. No)	1.03 (0.52–2.04)	0.916	–	–
Comorbidities (≥2 vs. 1)	0.87 (0.19–3.84)	0.854	–	–
SOFA	1.32 (1.14–1.54)	<**0.001***	1.15 (0.58–2.27)	0.672
APACHE IV	1.15 (1.06–1.25)	<**0.001***	0.93 (0.65–1.33)	0.709
NEWS score	1.87 (1.26–2.78)	**0.002***	3.21 (1.08–6.51)	**0.001***
MEWS score	2.84 (1.94–4.17)	<**0.001***	7.04 (2.95–16.77)	<**0.001***

**P-value* < 0.05 considered significant, Abbreviations: Odds ratio (OR), Confidence Interval (CI), Acute Physiology and Chronic Health Evaluation IV (APACHE-IV), Sequential Organ Failure Assessment (SOFA), National Early Warning Score (NEWS), Modified Early Warning Score (MEWS).

cut-off value (>4) had a value sensitivity of 68.75%, specificity of 98.94%, LR + of 64.97, LR- of 0.32, PPV of 84.6%, NPV of 97.4%, and 0.67% of Yuden index. The AUCs for predicting readmission, time to readmission, MV status, MV duration, and multiple organ failure varied between 0.81 and 0.83 (**Supplementary Figure 2**). The cut-off values for predicting readmission, time to readmission, MV status, MV duration, and multiple organ failure were three or more scores.

Comparison of the outcome prediction ability between National Early Warning Score and Modified Early Warning Score

A comparison of NEWS and MEWS AUCs was performed to predict the outcomes using the DeLong test, and the results are presented in **Table 7**. To predict mortality, the

TABLE 5 Univariable and multivariable binary logistic regression analysis to evaluate associations of NEWS and MEWS scores to predict MV status, MV duration, and organ failure after readmission.

Variables	Univariate		Multivariate	
	OR (95% CI)	*P-value*	OR (95% CI)	*P-value*
MV after Readmission (Yes vs. No)				
Age	1.01 (0.98–1.03)	0.493	–	–
Gender (Male vs. Female)	2.02 (1.03–3.96)	0.039	–	–
Comorbidities (Yes vs. No)	1.47 (0.76–2.85)	0.252	–	–
Comorbidities (≥2 vs. 1)	2.58 (0.91–7.31)	0.074	–	–
SOFA	1.32 (1.14–1.54)	<**0.001***	0.98 (0.51–1.90)	0.967
APACHE IV	1.16 (1.07–1.25)	<**0.001***	0.98 (0.69–1.38)	0.917
NEWS score	2.28 (1.55–3.35)	<**0.001***	1.35 (1.10–4.78)	**0.011***
MEWS score	3.15 (2.15–4.64)	<**0.001***	5.38 (2.42–11.96)	<**0.001***
MVduration after readmission (≥6 days vs. <6 days)				
Age	1.00 (0.97–1.04)	0.771	–	–
Gender (Male vs. Female)	2.98 (1.19–7.49)	**0.020***	3.01 (1.14–7.95)	**0.026***
Comorbidities (Yes vs. No)	1.23 (0.52–2.90)	0.637	–	–
Comorbidities (≥2 vs. 1)	2.62 (0.72–9.55)	0.143	–	–
SOFA	1.25 (1.03–1.51)	**0.020***	0.67 (0.29–1.53)	0.350
APACHE IV	1.12 (1.02–1.24)	**0.016***	1.25 (0.81–1.95)	0.313
NEWS score	1.90 (1.17–3.08)	**0.009***	2.18 (1.10–4.78)	**0.011***
MEWS score	2.92 (1.87–4.56)	<**0.001***	12.39 (3.36–45.67)	<**0.001***
Multiple organ failure after readmission (Yes vs. No)				
Age	1.01 (0.98–0.03)	0.485	–	–
Gender (Male vs. Female)	2.43 (1.31–4.53)	**0.0058**	2.67 (1.32–5.40)	**0.006***
Comorbidities (Yes vs. No)	1.37 (0.75–2.51)	0.304	–	–
Comorbidities (≥2 vs. 1)	1.98 (0.71–5.57)	0.191	–	–
SOFA	1.29 (1.12–1.48)	<**0.001***	1.09 (0.57–2.06)	0.784
APACHE IV	1.13 (1.05–1.22)	<**0.001***	0.91 (0.65–1.27)	0.594
NEWS score	2.17 (1.51–3.11)	<**0.001***	3.27 (1.12–8.59)	**0.001***
MEWS score	3.33 (2.29–4.84)	<**0.001***	7.44 (3.39–16.36)	<**0.001***

**P-value* < 0.05 considered significant. Odds ratio (OR), Confidence Interval (CI), Acute Physiology and Chronic Health Evaluation IV (APACHE-IV), Sequential Organ Failure Assessment (SOFA), National Early Warning Score (NEWS), Modified Early Warning Score (MEWS).

AUCs of NEWS and MEWS scores were 0.916 and 0.881, respectively, but this difference was not statistically significant (p-value = 0.082) (Figure 1A). However, the AUCs of the MEWS were significantly greater than NEWS for readmission (0.83 vs. 0.71, p-value < 0.0001) (Figure 1B), no significant difference for unplanned discharge types (Figure 1C), time to readmission (0.82 vs. 0.67, p-value < 0.0001) (Figure 1D), MV status, (0.82 vs. 0.72, p-value < 0.0001) (Figure 1E), MV duration (0.81 vs. 0.67, p-value < 0.0001) (Figure 1F), and multiple organ failure (0.83 vs. 0.71, p-value < 0.0001) (Figure 1G).

Discussion

The MEWS and NEWS are relatively new scoring systems capable of predicting the prognosis of ICU patients. Few studies employ and compare the MEWS or NEWS as outcome predictors in ICU patients. In this multicenter, prospective, observational study, we compared the NEWS and MEWS scores to predict the outcomes in critically ill patients at the time of ICU discharge. The analysis from the multivariable logistic model showed that high MEWS and NEWS were the risk factors for readmission occurrences, time to readmission, mortality, MV status, MV duration, and multiple organ failure after readmission. By comparing these two scoring systems, we identified that there was no significant difference between the AUCs of the NEWS and the MEWS for predicting mortality (P-value = 0.082). In contrast, the prognostic accuracy of MEWS in other outcomes such as readmission occurrence, time to readmission, MV status, MV duration, and multiple organ failure excels the prognostic accuracy of NEWS score (P-value < 0.001). Such a result can be due to the fact that most problems that directly or indirectly affect the readmission of critically ill patients are related to respiratory dysfunction. The

TABLE 6 Receiver operating characteristic curve results of NEWS and MEWS scores to predicting outcomes.

	Outcomes	AUC (95% CI)	*p*-value	SN (95% CI)	SP (95% CI)	LR + (95% CI)	LR- (95% CI)	PPV (95% CI)	NPV (95% CI)	Youden Index	Cut-point
NEWS score	**Mortality** (Yes vs. No)	0.916 (0.885–0.941)	<0.0001*	71.87 (53.3–86.3)	95.50 (92.9–97.4)	15.98 (9.57–26.68)	0.29 (0.17–0.51)	57.5 (44.7–69.3)	97.6 (95.8–98.6)	0.673	>4
	ICU Readmission (Yes vs. No)	0.711 (0.665–0.755)	<0.0001*	88.00 (75.7–95.5)	50.00 (44.7–55.3)	1.76 (1.52–2.04)	0.24 (0.11–0.51)	19.7 (17.5–22.0)	96.8 (93.4–98.5)	0.380	>3
	Discharge type (Unplanned vs. Planned)	0.561 (0.512–0.610)	0.318	55.56 (30.8–78.5)	55.10 (50.0–60.1)	1.24 (0.81–1.90)	0.81 (0.48–1.36)	5.4 (3.6–8.0)	96.4 (94.1–97.8)	0.106	≤3
	Time to readmission (≥4 days vs. < 4 days)	0.676 (0.628–0.721)	<0.0001*	83.78 (68.0–93.8)	48.26 (43.1–53.5)	1.62 (1.36–1.92)	0.34 (0.16–0.70)	13.8 (11.9–16.0)	96.8 (93.5–98.4)	0.320	>3
	MV Readmission (Yes vs. No)	0.720 (0.674–0.763)	<0.0001*	87.18 (72.6–95.7)	48.79 (43.6–54.0)	1.70 (1.46–1.99)	0.26 (0.12–0.60)	15.2 (13.3 –17.3)	97.3 (94.1–98.8)	0.359	>3
	Duration of MV readmission (≥6 days vs. < 6 days)	0.675 (0.628–0.720)	0.0008*	81.82 (59.7–94.8)	46.91 (41.9–52.0)	1.54 (1.24–1.92)	0.39 (0.16–0.95)	8.1 (6.6–9.9)	97.8 (94.9–99.1)	0.287	>3
	Multiple organ failure readmission (Yes vs. No)	0.710 (0.664–0.754)	<0.0001*	87.50 (74.8–95.3)	49.72 (44.5–55.0)	1.74 (1.50–2.02)	0.25 (0.12–0.54)	18.7 (16.6–21.1)	96.8 (93.4–98.5)	0.372	>3
MEWS score	**Mortality** (Yes vs. No)	0.881 (0.846–0.911)	<0.0001*	68.75 (50.0–83.9)	98.94 (97.3–99.7)	64.97 (23.84–177.1)	0.32 (0.19–0.53)	84.6 (66.9–93.7)	97.4 (95.7–98.4)	0.676	>4
	ICU Readmission (Yes vs. No)	0.839 (0.799–0.873)	<0.0001*	80.00 (66.3–90.0)	88.61 (84.9–91.7)	7.02 (5.10–9.67)	0.23 (0.13–0.39)	49.4 (41.5–57.3)	97.0 (94.8–98.2)	0.686	>3
	Discharge type (Unplanned vs. Planned)	0.545 (0.495–0.593)	0.561	38.89 (17.3–64.3)	81.12 (76.9–84.9)	2.06 (1.11–3.81)	0.75 (0.52–1.09)	8.7 (4.9–14.9)	96.6 (95.2–97.7)	0.200	>3
	Time to readmission (≥4 days vs. <4 days)	0.826 (0.786–0.862)	<0.0001*	81.08 (64.8–92.0)	86.33 (82.4–89.6)	5.93 (4.40–7.99)	0.22 (0.11–0.43)	37.0 (30.3–44.2)	97.9 (95.9–98.9)	0.674	>3
	MV Readmission (Yes vs. No)	0.829 (0.789–0.864)	<0.0001*	79.49 (63.5–90.7)	86.52 (82.6–89.8)	5.90 (4.36–7.99)	0.24 (0.13–0.44)	38.2 (31.4–45.6)	97.6 (95.6–98.7)	0.660	>3
	Duration of MV readmission (≥6 days vs. <6 days)	0.813 (0.772–0.849)	<0.0001*	77.27 (54.6–92.2)	83.51 (79.4–87.1)	4.68 (3.41–6.44)	0.27 (0.13–0.59)	21.1 (16.3–26.9)	98.5 (96.7–99.3)	0.607	>3
	Multiple organ failure readmission (Yes vs. No)	0.833 (0.794–0.868)	<0.0001*	79.17 (65.0–89.5)	88.12 (84.3–91.3)	6.66 (4.86–9.14)	0.24 (0.14–0.41)	46.9 (39.2–54.8)	97.0 (94.8–98.2)	0.672	>3

LOS: Length of stay, MV: Mechanical ventilation, CI: Confidence interval, SN: Sensitivity; SP: Specificity; LR + : Positive likelihood ratio; LR-: Negative likelihood ratio; PPV: positive predictive value; NPV: Negative predictive value, *p-value < 0.05 considered significant.

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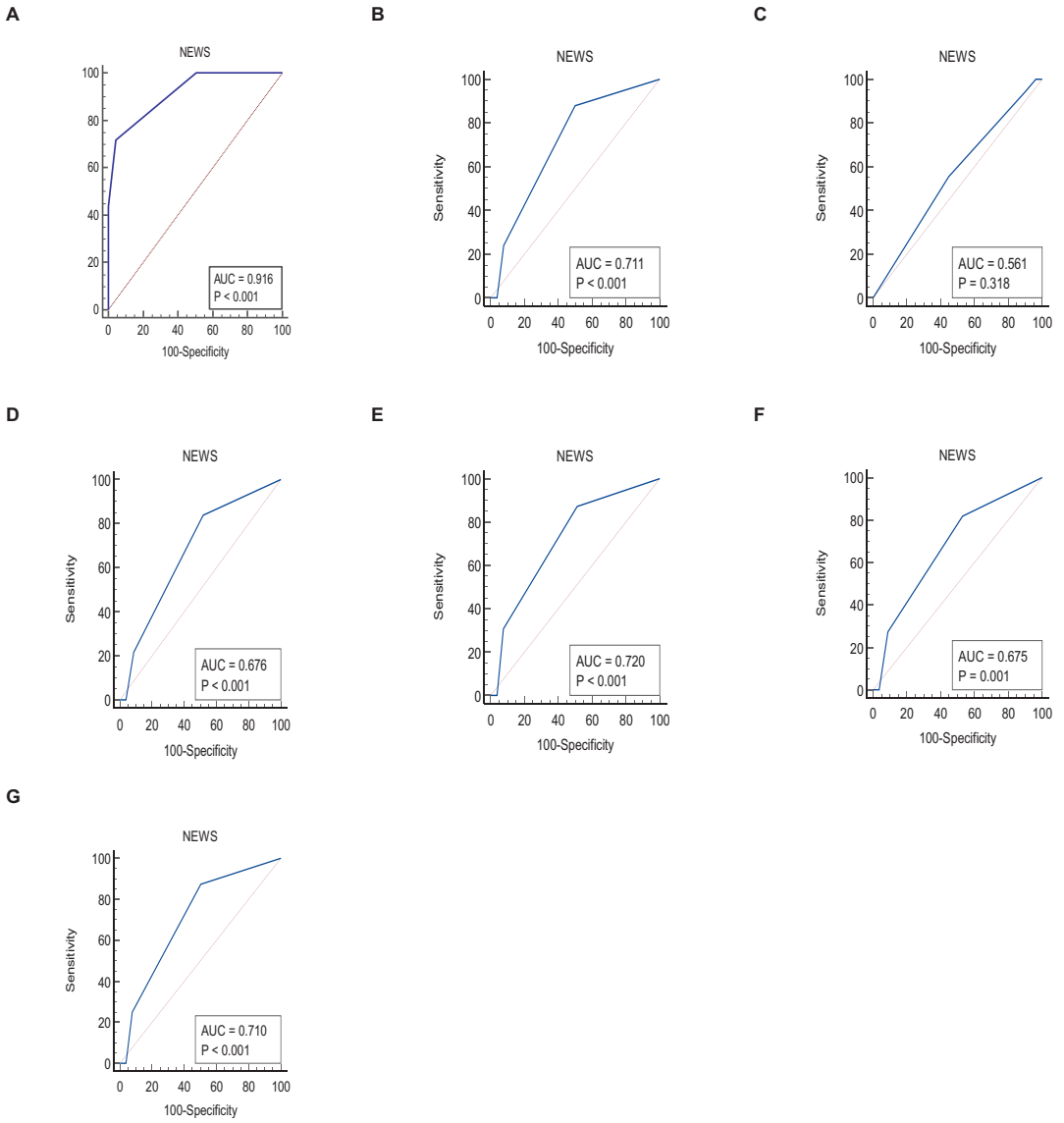

FIGURE 1
Comparison of ROC curves between NEWS and MEWS scores to predict **(A)** mortality, **(B)** ICU readmission, **(C)** unplanned discharge type, **(D)** time to readmission ≥ 4 days, **(E)** MV after readmission, **(F)** duration of MV ≥ 6 days, and **(G)** multiple organ failure after readmission.

TABLE 7 Comparison of ROC curves between NEWS and MEWS scores to predict outcomes.

Outcomes	NEWS score			MEWS score			*P-value**
	AUC	95% CI	*p*-value	AUC	95% CI	*p*-value	
Mortality	0.916	0.885–0.941	<0.0001	0.881	0.846–0.911	<0.0001	0.082
ICU Readmission	0.711	0.665–0.755	<0.0001	0.839	0.799–0.873	<0.0001	<**0.0001**
Discharge type	0.561	0.512–0.610	0.318	0.545	0.495–0.593	0.561	0.899
Time to readmission	0.676	0.628–0.721	<0.0001	0.826	0.786–0.862	<0.0001	<**0.0001**
MV Readmission	0.720	0.674–0.763	<0.0001	0.829	0.789–0.864	<0.0001	<**0.0001**
MV readmission duration	0.675	0.628–0.720	0.0008	0.813	0.772–0.849	<0.0001	<**0.0001**
Multiple organ failure	0.710	0.664–0.754	<0.0001	0.833	0.794–0.868	<0.0001	<**0.0001**

**P-value* based on DeLong test to compare AUCs between NEWS and MEWS score for each outcome.

rate of readmission due to respiratory dysfunction in this study was almost 50%. In addition, our results show that male patients are more likely to be readmitted, have multiple organ failures, and have a longer MV duration. From a clinical perspective, these findings suggest that gender may also be an important consideration in discharge planning in addition to the use of NEWS and MEWS. However, further studies are needed to confirm this finding. Based on the findings of this study, we conclude that MEWS can be considered an effective prognostic tool for predicting all outcomes, and the NEWS score is a good predictor of mortality and ICU readmission in critically ill patients at the time of ICU discharge. Hence, we advocate for determining the MEWS and NEWS at ICU discharge as an assistive tool to make a better-informed decision.

Scoring systems can be used to measure the performance of one ICU over a time period, or used to compare the performance of different ICUs which allows ICUs to understand more about the quality of delivered care, audit themselves and assist them in decision-making, resource allocation, quality assessment programs and teaching. Each physician should consider that the decision regarding to whether the patients should or should not be admitted to the ICU is dependent on some other factors. These include the risk and complications of ICU admission/readmission, patients' wishes, and the time lag when scores are calculated (usually 24 h after admission to the ICU), which means that clinical intervention may precede the calculation of the score. As the MEWS and NEWS scores includes all qSOFA variables, so they can serve as an accurate score in prediction of outcome even in patients with infection. Using a scores that includes a points-based risk score, such as the NEWS/MEWS, may improve teaching, the integration, and incorporation of early warning scores into clinical practice focused on identifying and managing patients at risk for poor outcome (30, 31). Our findings coincide with many similar studies. Consistent with this study, many previous studies have shown the NEWS and MEWS scores to be a decisive tool for the early identification of patients with a high risk of poor outcomes, including mortality and ICU readmission (32–34). Balshi et al. reported that the MEWS is associated with ICU readmission, and a score > 6 has an excellent accuracy as a prognostic predictor (32). A prospective observational study by Xie et al. showed good performance of MEWS for in-hospital mortality prediction, with AUC values at 0.83 in patients presenting to the emergency department (35). MEWS also helps predict the mortality of COVID-19 patients, with AUC values of 0.913 and 0.833 (36, 37). Lv et al. found that MEWS shows superiority over the quick Sequential Organ Function Assessment (qSOFA), Combination of Confusion, Urea, Respiratory Rate, Blood Pressure, and Age ≥ 65 (CURB-65), and NEWS scores in predicting hospital mortality, and NEWS showed superiority over the other scores in predicting ICU admission in patients with community-acquired pneumonia (CAP) (38). Klepstad et al. showed that the higher NEWS in gastrointestinal surgical patients at ICU discharge was the predictive factor of ICU readmission (33). Moreover, the study by Doðu et al. demonstrated that a NEWS value of >7.5 at the time of discharge from ICU estimates a high probability of ICU readmission within the first 48 h after discharge (34). However, in contrast to these findings, a study by Reini et al. showed that the MEWS at ICU discharge is not a predictor of ICU readmission (39). On the other hand, this finding might be influenced (as acknowledged by the authors) by the decision to withhold ICU readmission for 10 out of 15 patients discharged with a MEWS of 5 or more. MEWS and NEWS are widely used scoring systems in many countries, but differences between these studies, including study setting, population, and disease type, have led to differences in the predictive ability of these scoring systems.

The most important advantage of MEWS and NEWS scores compared with other scoring systems, such as APACHE IV, SOFA, and Simplified Acute Physiology Score (SAPS), are their simplicity. They consist of basic physiological measurements in contrast to APACHE IV, SOFA, and SAPS, which, for instance, need documentation of laboratory results, making them a simpler tool with facilitated assessment procedures (38, 39). The advantage of these simple scoring systems could be the early identification of patients who were becoming increasingly unstable. In addition, they could facilitate the discharge decision by the intensivist. Early identification of critically ill patients with poor outcomes at the time of discharge from the ICU can enable the appropriate allocation of limited resources, such as intensive care beds.

The strengths of this study were the multicenter prospective design with heterogeneous patients from the general ICUs of two hospitals, which adjusted the confounding variables and made the findings more generalizable. However, our study has several limitations. First, the patient selection criteria were inclusive (all patients aged 18 years and above admitted to general ICU); this creates a rather heterogeneous cohort, and due to the wide range of ICU admission causes, we could not see the reason for admission evaluated as a variable. Second, we have not presented the individual physiological parameters included in the MEWS and NEWS; identifying whether any of these parameters had a better predictive value than the others would be interesting. Third, we could not use multiple parametric models like MANOVA to adjust the potential correlation among outcomes due to the lack of normal distribution of outcomes as the pre-assumption required for multiple testing. Fourth, to deal with multiple outcomes, we considered mortality and ICU readmission as primary outcomes. However, secondary outcomes are then subsidiary, and the results concerning them can only have an exploratory rather than a confirmatory interpretation. In addition, the frequency of readmission in the ICU was low (50 from 410), so interpreting results related to secondary outcomes such as readmission time, MV readmission, and duration of MV

readmission should be interpreted with caution. Nevertheless, due to the varied performance of MEWS and NEWS in other studies, future disease-specific studies are required to improve the accuracy and applicability of MEWS and NEWS.

Conclusion

The MEWS and NEWS at the time of ICU discharge are independent predictors of ICU readmission and mortality. NEWS and MEWS scores greater than 4 have excellent and good accuracy in predicting mortality with 91 and 82% AUCs, respectively. In addition, scores greater than 3 have good and fair accuracy in predicting ICU readmission with AUCs of 83 and 71%, respectively. We found that the MEWS showed superiority over the NEWS score in predicting ICU readmission, time to readmission, MV readmission, MV duration, and multiple organ failure.

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 Ethics Committees of Islamic Azad University-Tabriz Branch (IR.TBZMED.REC.1397.994). The patients/participants provided their written informed consent to participate in this study.

Author contributions

FR-B, AM, SS, NS, and AV-A: study concept and design. SHS, ZO, M-SH, and SS: analysis and interpretation of data. SHS and AS: acquisition of data and drafting of the manuscript. FR-B, ZO, and SS: critical revision of the manuscript for important intellectual content. FR-B and AM: statistical analysis. 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.938005/full#supplementary-material

References

1. Brown SE, Ratcliffe SJ, Kahn JM, Halpern SD. The epidemiology of intensive care unit readmissions in the United States. *Am J Respir Crit Care Med.* (2012) 185:955–64. doi: 10.1164/rccm.201109-1720OC

2. Ponzoni CR, Corrêa TD, Filho RR, Serpa Neto A, Assunção MSC, Pardini A, et al. Readmission to the intensive care unit: incidence, risk factors, resource use, and outcomes. a retrospective cohort study. *Ann Am Thoracic Soc.* (2017) 14:1312–9. doi: 10.1513/AnnalsATS.201611-851OC

3. Grochla M, Saucha W, Borkowski J, Knapik P. [Readmission to the intensive care unit - epidemiology, prediction and clinical consequences]. *Wiadomosci Lekarskie.* (2019) 72:1387–96.

4. Jo YS, Lee YJ, Park JS, Yoon HI, Lee JH, Lee CT, et al. Readmission to medical intensive care units: risk factors and prediction. *Yonsei Med J.* (2015) 56:543–9. doi: 10.3349/ymj.2015.56.2.543

5. van Sluisveld N, Bakhshi-Raiez F, de Keizer N, Holman R, Wester G, Wollersheim H, et al. Variation in rates of ICU readmissions and post-ICU in-hospital mortality and their association with ICU discharge practices. *BMC Health Serv Res*. (2017) 17:281. doi: 10.1186/s12913-017-2234-z

6. Kramer AA, Higgins TL, Zimmerman JE. The association between ICU readmission rate and patient outcomes. *Crit Care Med*. (2013) 41:24–33. doi: 10.1097/CCM.0b013e3182657b8a

7. Marquet K, Claes N, De Troy E, Kox G, Droogmans M, Schrooten W, et al. One fourth of unplanned transfers to a higher level of care are associated with a highly preventable adverse event: a patient record review in six Belgian hospitals. *Crit Care Med*. (2015) 43:1053–61. doi: 10.1097/ccm.0000000000000932

8. Hosein FS, Bobrovitz N, Berthelot S, Zygun D, Ghali WA, Stelfox HT. A systematic review of tools for predicting severe adverse events following patient discharge from intensive care units. *Crit Care*. (2013) 17:R102. doi: 10.1186/cc12747

9. Elliott M, Worrall-Carter L, Page K. Intensive care readmission: a contemporary review of the literature. *Intensive Crit Care Nurs*. (2014) 30:121–37. doi: 10.1016/j.iccn.2013.10.005

10. Tanaka Gutiez M, Ramaiah R. Demand versus supply in intensive care: an ever-growing problem. *Crit Care*. (2014) 18:P9. doi: 10.1186/cc13199

11. Mathews KS, Long EFA. Conceptual framework for improving critical care patient flow and bed use. *Ann Am Thoracic Soc*. (2015) 12:886–94. doi: 10.1513/AnnalsATS.201409-419OC

12. van Sluisveld N, Zegers M, Westert G, van der Hoeven JG, Wollersheim H. A strategy to enhance the safety and efficiency of handovers of ICU patients: study protocol of the pICUp study. *Implement Sci*. (2013) 8:67. doi: 10.1186/1748-5908-8-67

13. Kareliusson F, De Geer L, Tibblin AO. Risk prediction of ICU readmission in a mixed surgical and medical population. *J Intensive Care*. (2015) 3:30. doi: 10.1186/s40560-015-0096-1

14. Badawi O, Breslow MJ. Readmissions and death after ICU discharge: development and validation of two predictive models. *PLoS One*. (2012) 7:e48758. doi: 10.1371/journal.pone.0048758

15. Ouanes I, Schwebel C, Français A, Bruel C, Philippart F, Vesin A, et al. A model to predict short-term death or readmission after intensive care unit discharge. *J Crit Care*. (2012) 27:422.e1–9. doi: 10.1016/j.jcrc.2011.08.003

16. Alam N, Hobbelink EL, van Tienhoven AJ, van de Ven PM, Jansma EP, Nanayakkara PW. The impact of the use of the Early Warning Score (EWS) on patient outcomes: a systematic review. *Resuscitation*. (2014) 85:587–94. doi: 10.1016/j.resuscitation.2014.01.013

17. Chapman SM, Maconochie IK. Early warning scores in paediatrics: an overview. *Arch Dis. Child*. (2019) 104:395–9. doi: 10.1136/archdischild-2018-314807

18. Kramer AA, Sebat F, Lissauer M. A review of early warning systems for prompt detection of patients at risk for clinical decline. *J Trauma Acute Care Surg*. (2019) 87:S67–73. doi: 10.1097/ta.0000000000002197

19. Petersen JA. Early warning score challenges and opportunities in the care of deteriorating patients. *Danish Med J*. (2018) 65:B5439.

20. Nannan Panday RS, Minderhoud TC, Alam N, Nanayakkara PWB. Prognostic value of early warning scores in the emergency department (ED) and acute medical unit (AMU): a narrative review. *Eur J Internal Med*. (2017) 45:20–31. doi: 10.1016/j.ejim.2017.09.027

21. Padilla RM, Mayo AM. Clinical deterioration: a concept analysis. *J Clin Nurs*. (2018) 27:1360–8. doi: 10.1111/jocn.14238

22. Subbe CP, Kruger M, Rutherford P, Gemmel L. Validation of a modified early warning score in medical admissions. *Qjm*. (2001) 94:521–6. doi: 10.1093/qjmed/94.10.521

23. Royal College of Physicians. *National Early Warning Score (NEWS): Standardising the Assessment of Acute-Illness Severity in the NHS. Report of Working Party*. London: Royal College of Physicians (2012).

24. Pirneskoski J, Kuisma M, Olkkola KT, Nurmi J. Prehospital national early warning score predicts early mortality. *Acta Anaesthesiol Scand*. (2019) 63:676–83. doi: 10.1111/aas.13310

25. Burch VC, Tarr G, Morroni C. Modified early warning score predicts the need for hospital admission and inhospital mortality. *Emerg Med J*. (2008) 25:674–8. doi: 10.1136/emj.2007.057661

26. Cei M, Bartolomei C, Mumoli N. In-hospital mortality and morbidity of elderly medical patients can be predicted at admission by the Modified Early Warning Score: a prospective study. *Int J Clin Pract*. (2009) 63:591–5. doi: 10.1111/j.1742-1241.2008.01986.x

27. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. (2013) 310:2191–4. doi: 10.1001/jama.2013.281053

28. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. (2008) 61:344–9. doi: 10.1016/j.jclinepi.2007.11.008

29. Jones M. NEWSDIG: the national early warning score development and implementation group. *Clin Med*. (2012) 12:501–3. doi: 10.7861/clinmedicine.12-6-501

30. Liu VX, Lu Y, Carey KA, Gilbert ER, Afshar M, Akel M, et al. Comparison of early warning scoring systems for hospitalized patients with and without infection at risk for in-hospital mortality and transfer to the intensive care unit. *JAMA Netw Open*. (2020) 3:e205191. doi: 10.1001/jamanetworkopen.2020.5191

31. Desai N, Gross J. Scoring systems in the critically ill: uses, cautions, and future directions. *BJA Educ*. (2019) 19:212–8. doi: 10.1016/j.bjae.2019.03.002

32. Balshi AN, Huwait BM, Noor ASN, Alharthy AM, Madi AF, Ramadan OE, et al. Modified Early Warning Score as a predictor of intensive care unit readmission within 48 hours: a retrospective observational study. *Rev Bras Terapia Intensiva*. (2020) 32:301–7. doi: 10.5935/0103-507x.20200047

33. Klepstad PK, Nordseth T, Sikora N, Klepstad P. Use of national early warning score for observation for increased risk for clinical deterioration during post-ICU care at a surgical ward. *Therapeut Clin Risk Manag*. (2019) 15:315–22. doi: 10.2147/tcrm.s192630

34. Doğu C, Doğan G, Kayir S, Yağan Ö. Importance of the National Early Warning Score (NEWS) at the time of discharge from the intensive care unit. *Turk J Med Sci*. (2020) 50:1203–9. doi: 10.3906/sag-1906-78

35. Xie X, Huang W, Liu Q, Tan W, Pan L, Wang L, et al. Prognostic value of Modified Early Warning Score generated in a Chinese emergency department: a prospective cohort study. *BMJ Open*. (2018) 8:e024120. doi: 10.1136/bmjopen-2018-024120

36. Wang L, Lv Q, Zhang X, Jiang B, Liu E, Xiao C, et al. The utility of MEWS for predicting the mortality in the elderly adults with COVID-19: a retrospective cohort study with comparison to other predictive clinical scores. *PeerJ*. (2020) 8:e10018. doi: 10.7717/peerj.10018

37. Aygun H, Eraybar S. The role of emergency department triage early warning score (TREWS) and modified early warning score (MEWS) to predict in-hospital mortality in COVID-19 patients. *Ir J Med Sci*. (2021) 191:997–1003. doi: 10.1007/s11845-021-02696-y

38. Lv C, Chen Y, Shi W, Pan T, Deng J, Xu J. Comparison of different scoring systems for prediction of mortality and ICU admission in elderly CAP population. *Clin Intervent Aging*. (2021) 16:1917–29. doi: 10.2147/cia.s335315

39. Reini K, Fredrikson M, Oscarsson A. The prognostic value of the Modified Early Warning Score in critically ill patients: a prospective, observational study. *Eur J Anaesthesiol*. (2012) 29:152–7. doi: 10.1097/EJA.0b013e32835032d8

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Comparison of clinical safety and efficacy of dexmedetomidine, remifentanil, and propofol in patients who cannot tolerate non-invasive mechanical ventilation: A prospective, randomized, cohort study

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Background and objectives: Non-invasive ventilation (NIV) is used in intensive care units (ICUs) to treat of respiratory failure. Sedation and analgesia are effective and safe for improving compliance in patients intolerant to NIV. Our study aimed to evaluate the effects of dexmedetomidine, remifentanil, and propofol on the clinical outcomes in NIV intolerant patients.

Methods: This prospective randomized cohort study was conducted in a tertiary ICU, between December 2018 and December 2019. We divided a total of 120 patients into five groups (DEX_L, DEX_H, REM_L, REM_H, PRO). IBM SPSS Statistics 20 (IBM Corporation, Armonk, New York, USA) was used to conduct the statistical analyses.

Results: The DEX_L, DEX_H, REM_L, and REM_H groups consisted of 23 patients each while the PRO group consisted of 28 patients. Seventy-five patients (62.5%) became tolerant of NIV after starting the drugs. The NIV time, IMV time, ICU LOS, hospital LOS, intubation rate, side effects, and mortality were significantly different among the five groups ($P = 0.05$). In the groups that were given dexmedetomidine (DEX_L, and DEX_H), NIV failure, mortality, ICU LOS, and hospital LOS were lower than in the other groups.

Conclusion: In this prospective study, we compared the results of three drugs (propofol, dexmedetomidine, and remifentanil) in patients with NIV intolerance. The use of sedation increased NIV success in patients with NIV intolerance. NIV failure, mortality, ICU LOS, IMV time, and hospital LOS were found to be lower with dexmedetomidine.

KEYWORDS

non-invasive ventilation, chronic obstructive pulmonary disease, dexmedetomidine, remifenthanyl, propofol, intensive care

Introduction

Non-invasive ventilation (NIV) is frequently used in intensive care units (ICUs) to treat of acute exacerbations of chronic obstructive pulmonary disease (COPD). This supportive treatment reduces both the need for invasive ventilation (IV) and mortality in patients (1, 2).

Despite many advantages of NIV are many when used in critically ill patients, NIV has a 40% failure rate due to patient non-compliance (3). Many studies have shown that sedation and analgesia are effective and safe for improving compliance in patients intolerant to NIV (4–7).

There are a limited number of studies on sedation protocols applied during NIV, and there is no recommended drug and no common protocol regarding sedation and analgesia in NIV (8). It has been stated that sedation, when used appropriately and with precautions, increases patient comfort and reduces the possibility of failure in patients using NIV (8, 9).

Dexmedetomidine is a potent selective α2-agonist with sedative, analgesic and anxiolytic properties (10). Many studies have shown that dexmedetomidine is useful for sedation in the ICU (11–13). In placebo-controlled studies, it has been reported that low doses of dexmedetomidine also provide sedation and analgesia, which can easily be aroused (14, 15). Remifentanil is an ultra- short -acting opioid that rapidly reaches a steady state, with an onset of action of <1 min and μ selectivity (16). Remifentanil is a safe and effective opioid that reduces NIV failure (17). Propofol is frequently used for sedation due to its short duration of action and clear awakening profile (18). Propofol is an appropriate sedative agent for NIV owing to its pharmacokinetic rate (19).

To our knowledge, no previous study has compared dexmedetomidine, remifentanil, and propofol used to provide sedation and/or analgesia, in NIV management. Our study aimed to evaluate the effects of dexmedetomidine, remifentanil, and propofol on the clinical outcomes in NIV intolerant patients.

Materials and methods

Patient population and design

Ethics statement

Ethical approval for this prospective randomized study was obtained from the Clinical Research Ethics Committee of University of Health Sciences, Yüksek Ihtisas Training and Research Hospital, Ankara, Turkey (dated 12.11.2018 and numbered 12079).

Patients

This prospective randomized cohort study was conducted in a tertiary ICU, between December 2018 and December 2019.

TABLE 1 Ramsay sedation scale (20).

Clinical evaluation	Score
Patient is anxious and agitated or restless, or both	1
Patient is cooperative, oriented and tranquil	2
Patient responds to commands only	3
Patient exhibits brisk response to light glabellar tap or loud auditory stimulus	4
Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus	5
Patient exhibits no response	6

Written informed consent was obtained from all patients. The patients included in the study were over 18 years of age, and had NIV intolerance, admission to the ICU, acute respiratory acidosis [partial pressure of carbon dioxide (PCO_2) ≥ 45 mmHg], a diagnosis of COPD, respiratory rate (RR) ≥ 24 per minute, and respiratory distress, with the use of auxiliary respiratory muscles. Patients with congestive heart failure, neurologic disease, muscular disease, treatment rejection, hepatic failure, gastrointestinal bleeding, severe hypotension [mean arterial pressure (MAP) < 60 mmHg], acute cardiac ischemia, and dexmedetomidine, remifentanil, and propofol allergy were excluded from the study.

We divided patients into five groups besed on the type and dose of drugs administered dexmedetomidine low (DEX_L), dexmedetomidine high (DEX_H), remifentanil low (REM_L), remifentanil high (REM_H), and propofol (PRO). Patients underwent simple randomization using a total of 120 (23 each for DEX_L, DEX_H, REM_L, REM_H groups, and 28 for the PRO group) closed envelopes, which declared group assignment and described the sedation protocol.

Data collection

Gender, age (years), body mass index (BMI, kg/m^2), ejection fraction (EF,%), Acute Physiology and Chronic Health Evaluation (APACHE) II score, comorbidities, NIV time (hours), invasive mechanical ventilation (IMV) time (days), length of intensive care unit stay (ICU LOS) (days), length of hospital stay (hospital LOS) (days), NIV complications, intubation (endotracheal intubation recordings), 30-day mortality, side effects, pH, partial pressure of carbon dioxide (PCO_2), partial pressure of oxygen (PO_2), Ramsay Sedation Scale (RSS) (Table 1) (20), peripheral oxygen saturation (SpO_2),respiratory rate (RR), heart rate (HR), and mean arterial pressure (MAP) were recorded. All data were recorded at the start of the NIV, at the first, second, fourth, sixth, ninth, and twelfth hours of the NIV; and at the first hour after the end of the NIV.

Non-invasive mechanical ventilation

NIV was performed using a Servo-S ICU mechanical ventilator (Maquet Critical Care AB; Rontgenvagen, Sweden), administered intermittently through a nose-mouth mask in the pressure support ventilation (PSV) mode. The patients were ventilated with 6 cmH_2O positive end expiratory pressure (PEEP), 12 cmH_2O pressure support, and an inspiratory oxygen fraction (FiO_2) of 50%. The NIV settings were meticulously adjusted during therapy based on each patient's condition after therapy began. Mechanical ventilation parameters were increased or decreased according to the patient's needs and the target saturation was at least 90%. We recorded the number of hours NIV was administered in 24 h as the "NIV time".

In the first hour of NIV administration, NIV intolerance was assessed using the NIV intolerance score (NIS). The NIS included four points; 1, a comfortable patient tolerating NIV; 2, a mildly intolerant patient who felt some degree of discomfort and occasionally grabbed at the NIV mask; 3, moderate intolerance and discomfort (sometimes pulling), most often with NIV mask, with frequent grabbing at the mask; 4, severe NIV intolerance with an agitation unable to keep the NIV mask on the face (21). According to this scoring, patients who scored 3 and 4 were considered to have NIV intolerance.

We stopped NIV treatment in patients without acute respiratory acidosis who did not show signs of respiratory distress (such as an RR of $\geq$ 24 per minute and increased use of the accessory respiratory muscle), and had an SpO_2 of 90% or more (with the inhaled oxygen flow through the oxygen mask $\leq$ 10 L/min). Invasive mechanical ventilation after endotracheal intubation was applied to patients who met at least two criteria; RR $\geq$ 45 per minute, increased amount of secretions in the trachea, acidosis with a pH value $\leq$ 7.25, SpO2 values $\leq$ 90% for at least 5 min, hemodynamic instability (HR: $\leq$ 60 beats/min/$\geq$200 beats/min, MAP: $\leq$60 mmHg), impaired consciousness, and persistent/worsening respiratory failure symptoms.

Sedatives

The first measurements were recorded when NIV treatment was initiated. A loading dose of dexmedetomidine 1 μg/kg was administered as an infusion within 10 min, after which regular infusion was started. Regular dexmedetomidine infusion was started 0.2 μg/kg/h in the DEXL group and at 0.6 μg/kg/h in the DEXH group. Any increases and/or decreases during the infusion were made at the dose rate of 0.1 μg/kg/h, according to the RSS 2–3 target. A loading dose of remifenthanyl 1 μg/kg was administered as an infusion within 30–60 s, after which regular infusion was started. Regular remifenthanyl infusion was started at 0.03 μg/kg/h in the REML group, and at 0.06 μg/kg/h in the REMH group. Any increases and/or decreases during the infusion were made at the rate of 0.025 μg/kg/h, according to the RSS 2–3 target. A loading dose of 1 mg/kg was administered as an infusion within 10 min, after which regular infusion was started. Regular propofol infusion was initiated at 0.3 mg/kg/h, and any increases and/or decreases were made at the rate of 0.1 mg/kg/h, according to the RSS 2–3 target. Hemodynamics and side effects were recorded (Table 2). Medication infusions were administered continuously for 24 h. Data were recorded at the start of NIV; at the first, second, fourth, sixth, ninth, and twelfth hours of NIV; and at the first hour after the end of the NIV.

TABLE 2 Initial dose and increasing and decreasing dose of each sedative drug.

Drug	Initial dose	Increasing and decreasing dose
Dexmedetomidine	0.2–0.7 μg/kg/h by continuous intravenous infusion	0.1 μg/kg/h
L (low)	0.2 μg/kg/h by continuous intravenous infusion	
H (High)	0.6 μg/kg/h by continuous intravenous infusion	
Remifentanyl	0.03–0.1 μg/kg/h by continuous intravenous infusion	0.025 μg/kg/h
L (low)	0.03 μg/kg/h by continuous intravenous infusion	
H (High)	0.06 μg/kg/h by continuous intravenous infusion	
Propofol	0.3 mg/kg/h by continuous intravenous infusion	0.1 mg/kg/h

Statistical analysis

G*Power 3.1.9.4 program was used to calculate the sample size. In the priori analysis, it was planned to include at least 16 participants in each group, with medium effect size (0.3), 80% power, 5% type 1 error, and 20% type 2 error. At the end of the study, the power of the study was found to be 91% in the *post-hoc* analysis.

Histograms, q-q plots, and Shapiro-Wilk's test were used to assess data normality. The Levene's test was used to test variance homogeneity. Various tests were used to compare demographic and clinical parameters among the study groups; one-way analysis of variance (ANOVA) or Kruskal-Wallis H tests were use for continuous variables, whereas Pearson chi-square analysis or Fisher-Freeman-Halton test were used for categorical variables. Bonferroni- adjusted Dunn's test and Bonferroni-adjusted *z*- tests were performed for multiple comparison analysis. In descriptive statistics, continuous numerical variables

are presented as medians [interquartile range (IQR)], and categorical variables are presented as the number of samples (%). IBM SPSS Statistics 20 (IBM Corporation, Armonk, New York, USA) was used to conduct the statistical analyses. A p-value of <5% was considered statistically significant.

Results

Between December 2018 and December 2019, 548 patients who received niv support were followed. Four hundred and twenty-eight patients were excluded from the study [Not meeting inclusion criteria (n = 69), declined to participate (n = 38), patients with NIV tolerance (n = 321)]. Total NIV intolerance was found to be 41.4% (n: 227). One hundred and twenty patients with NIV intolerance were included in the study. The DEX_L, DEX_H, REM_L, and REM_H groups consisted of 23 patients each while the PRO group consisted of 28 patients (Figure 1). There was no difference in baseline variables other than gender distribution between the groups ($P = 0.031$). Female gender was dominant in the DEX_L group, while male gender was dominant in the DEX_H, REM_L, REM_H, and PRO groups. The baseline characteristics of the patients were similar among the five groups. There were no differences between the groups with respect to age, BMI, EF, APACHE II score, and comorbidities (P = 0.993, 0.546, 0.953, 0.293, 0.783, respectively). However, diabetes mellitus (DM) differed between the groups with the highest rate observed in the PRO group. The NIV time, IMV time, ICU LOS, hospital LOS, intubation rate, and mortality were significantly different among the five groups (P = 0.045, 0.001, 0.001, 0.010, 0.001 and 0.041, respectively). Based on the intubation numbers, NIV failure in each group was: 2 (8.7%) in the DEX_L group, 3 (13%) in the DEX_H group, 7 (30.4%) in the REM_L group, 13 (56.5%) in the REM_H group, and 20 (71.4%) in the PRO group ($P = 0.001$). The side effects showed a significant difference among the five groups; apnea was higher in the PRO group (25%) than in the other groups (0% in the DEX_L group, 0% in the DEX_H group, 0% in the REM_L group, 4.3% in the REM_H group) ($P = 0.001$) (Table 3).

During continuous intravenous infusion in all groups except the PRO group, the pH level gradually good compared to the baseline values. There were significant differences between the groups at the sixth, ninth, twelfth, and first hour after NIV. There was a statistically significant difference between the REM_H/DEX_H groups at the sixth hour (P = 0.015), and between the REM_H/DEX_H groups and the PRO/DEX_H groups at both the ninth (P = 0.02, 0.012, respectively) and twelfth (P = 0.004 and 0.028, respectively) hours. There was a difference between the PRO/DEX_L groups, PRO/DEX_H groups, REM_L/DEX_L groups, and REM_L/DEX_H groups at the first hour after NIV (P = 0.001, 0.001, 0.04, 0.039, respectively).

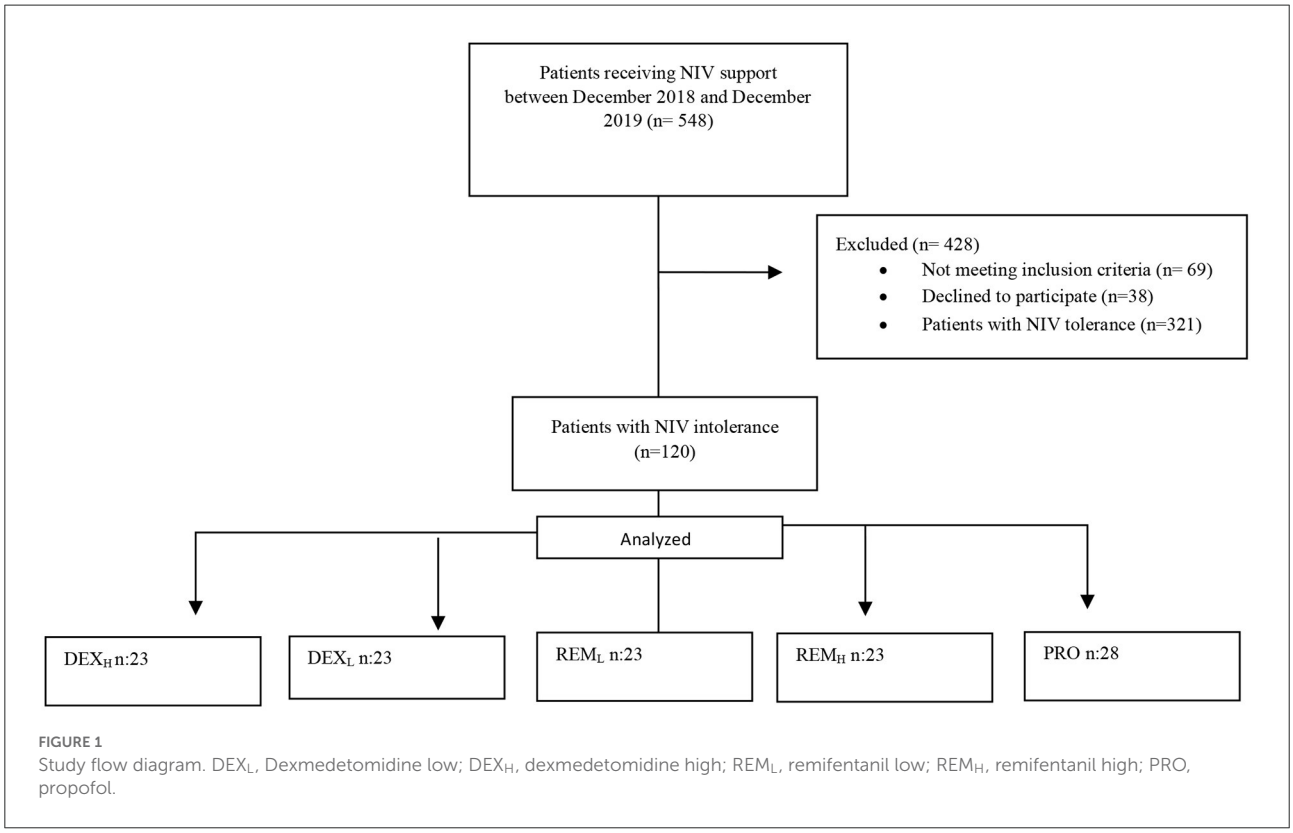

FIGURE 1
Study flow diagram. DEX_L, Dexmedetomidine low; DEX_H, dexmedetomidine high; REM_L, remifentanil low; REM_H, remifentanil high; PRO, propofol.

TABLE 3 Baseline characteristics of the groups and data on clinical follow-up.

	DEX_L *n*: 23	DEX_H *n*: 23	DEX_H *n*: 23	REM_H *n*: 23	PRO *n*: 28	*p*-value
Gender F/M (*n*)	14/9[a]	9/14[b]	4/19[b]	6/17[b]	10/18[b]	**0.031***
Age (year)[#]	66 (60–82)	74 (59–80)	71 (67–77)	72 (62–76)	71.5 (64.5–76)	0.993
BMI (kg/m^2)[#]	26.4 (24.6–34.3)	26.4 (25.6–29.3)	27.5 (25–29.4)	28.4 (26.3–31.2)	30 (26.1–34.3)	0.546
EF%[#]	60 (57–67)	60 (58–66)	60 (55–66)	60 (58–67)	60 (55.75–65.75)	0.953
APACHE II score[#]	12 (10–18)	12 (8–16)	11 (10–15)	10 (8–13)	13.5 (8.25–19)	0.293
Comorbidity[¤]	10 (43.5)	12 (52.2)	10 (43.5)	13 (56.5)	16 (57.1)	0.783
DM	1 (4.3)[a]	2 (8.7)[a]	0 (0.0)[a]	0 (0.0)[a]	9 (32.1)[b]	**0.001***
HT	1 (4.3)	3 (13)	4 (17.3)	3 (13)	4 (14.3)	0.740
CAD	1 (4.3)	3 (13)	1 (4.3)	3 (13)	1 (3.6)	0.510
AF	3 (13)	5 (21.7)	5 (21.7)	7 (30.4)	6 (21.4)	0.730
Obesity 30 ≤ BMI	8 (34.8)	5 (21.7)	5 (21.7)	6 (26)	10 (35.7)	0.691
NIV time (hour)[#]	12 (10–14)[a]	12 (8–16)[a]	14 (10–18)[a]	12 (9–16)[a]	15 (12–17.75)[a]	**0.045*[§]**
IMV time (day)[#]	0 (0–0)[a]	0 (0–5)[a]	0 (0–10)[ab]	0 (0–5)[ab]	3.5 (0–8.5)[b]	**0.001***
ICU LOS (day)[#]	5 (4–8)[ab]	3 (2–9)[a]	6 (2–8)[abc]	10 (6–13)[bc]	9 (6.25–15.75)[c]	**0.001***
Hospital LOS (day)[#]	9 (7.5–12)[a]	9 (7–16)[a]	11 (9–14.5)[a]	13 (10–19)[a]	15 (10–18.5)[a]	**0.010*[§]**
NIV comp[¤]	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	0 (0.0)	0.479
Intubation[¤]	2 (8.7)[a]	3 (13)[a]	7 (30.4)[ab]	13 (56.5)[bc]	20 (71.4)[c]	**0.001***
Mortality[¤]	1 (4.3)[a]	2 (8.7)[a]	5 (21.7)[ab]	5 (21.7)[ab]	10 (35.7)[b]	**0.041***
Side effect[¤]	1 (4.3)[a]	3 (13)[b]	1 (4.3)[a]	8 (34.8)[c]	8 (28.6)[c]	**0.012***
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.6)	0.507
Bradycardia	1 (4.3)	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.215
Apnea	0 (0.0)[a]	0 (0.0)[a]	0 (0.0)[a]	1 (4.3)[a]	7 (25)[b]	**0.001***
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	0 (0.0)	0.075
Thorax rigidity	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	0 (0.0)	0.075
Mouth dry	0 (0.0)	0 (0.0)	1 (4.3)	1 (4.3)	0 (0.0)	0.518
Hypotension + bradycardia	0 (0.0)	1 (4.3)	0 (0.0)	2 (8.7)	0 (0.0)	0.215

F, female; M, male; BMI, body mass index (kg/m^2); EF, ejection fraction (%); APACHE II score, Acute Physiology and Chronic Health Evaluation II score; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HT, hypertension; AF, atrial fibrillation; NIV time, noninvaziv ventilasyon time (hours); IMV time, invasive mechanical ventilation time (days); ICU LOS, length of intensive care unit stay (days); Hospital LOS length of hospital stay (days);NIV comp, noninvaziv ventilasyon complication; IQR, interquartile range; SD, standard deviation ($^*P < 0.05$, $^§P > 0.005$).

Different superscripts among groups indicate a statistically significant difference between groups. Significant results are shown in bold.

[¤]Results are expressed as *n* (%).

[#]Results are expressed as median (IQR).

There were significant differences in the PaO_2 between the groups at the second (REM_H/DEX_L), fourth (REM_L/REM_H), and sixth (REM_H/DEX_L) hours ($P < 0.05$). Significant differences were also found in the SpO_2 between the groups at the twelfth hour (PRO/DEX_L), and the first hour after NIV (PRO/DEX_L) ($P < 0.05$). There were no significant differences in the $PaCO_2$, HR, RR, and MAP between the groups. The Ramsay Sedation Scale (RSS) differed significantly between the groups at all times other than baseline values ($P < 0.05$). The highest RSS values were recorded in the PRO group at the second, fourth, sixth, ninth, and twelfth hours, and the first hour after NIV. The lowest values were observed in the REM_L group at all times except the baseline. Except for the REML group, the target sedation was reached at the second hour in the other groups (Figure 2).

Discussion

We frequently use NIV therapy in patients hospitalized in the ICU due to type 2 respiratory failure, as is the trend worldwide. Although NIV has many advantages when used in critically ill patients, a 40% failure rate is observed due to patient non-compliance. The lack of tolerance to NIV makes its application difficult (3). In this study, we included 120 patients with NIV intolerance in tertiary ICU and evaluated three drugs (dexmedetomidine, remifentanil, and propofol) used for sedation and/or analgesia, based on their clinical results in five groups. In the groups that were given dexmedetomidine (DEX_L, and DEX_H), NIV failure, mortality, ICU LOS, and hospital LOS were lower than in the other groups.

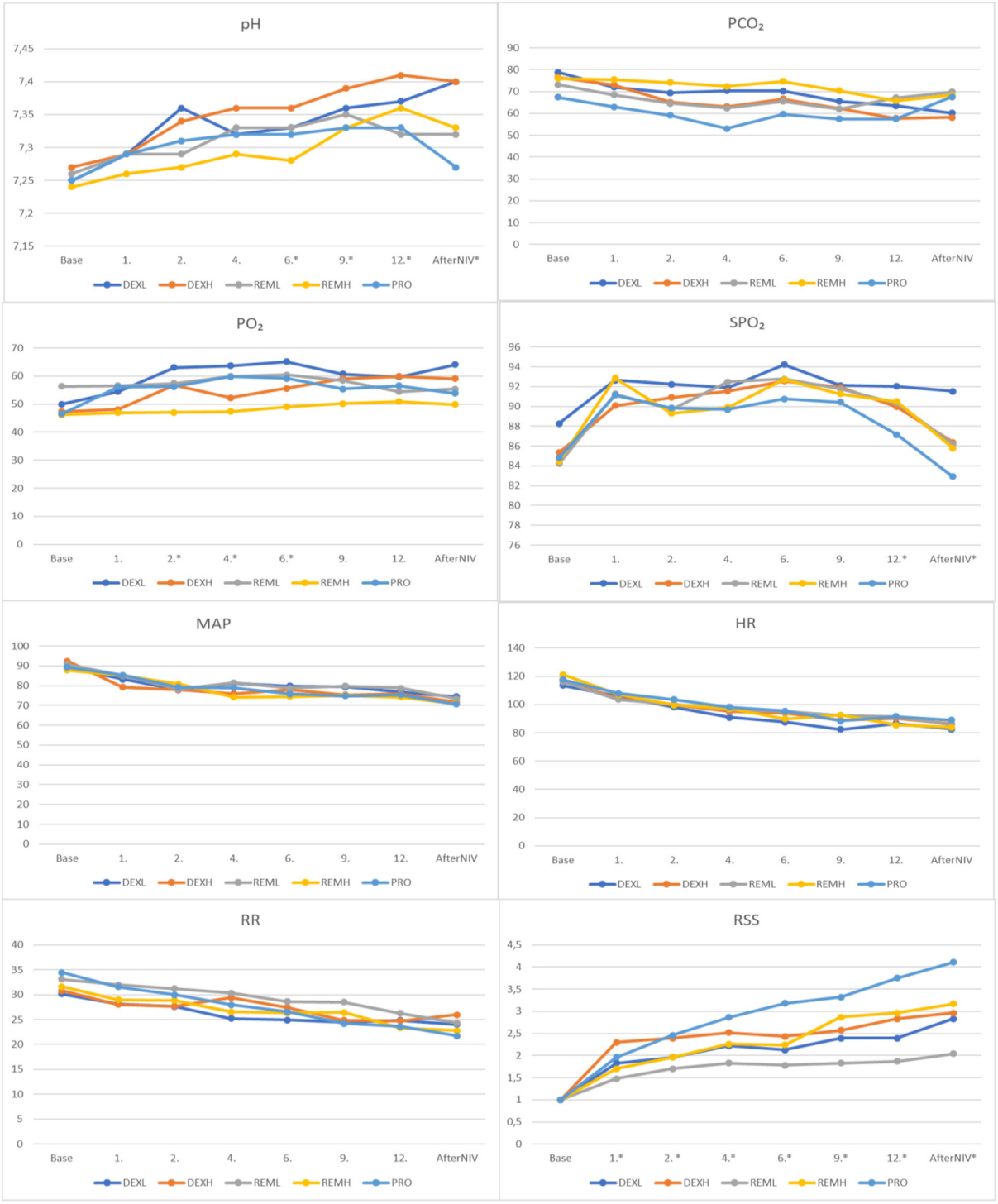

FIGURE 2
Comparison of study groups according to blood gas results, RSS and monitoring records. RSS, Ramsay Sedation Scale; SpO_2, peripheral oxygen saturation; RR, respiratory rate; HR, heart rate; MAP, mean arterial pressure; pH, potential of hydrogen; PCO_2, partial pressure of carbon dioxide; PO_2, partial pressure of oxygen. $^*P < 0.05$.

The "ISCCM (Indian Society of Critical Care Medicine) Guidelines" were published in 2020, but did not recommend any drug specifically. They suggested that sedation in patients undergoing NIV can be used in an ICU setting, with very close monitoring, and paying attention to the signs of NIV failure (8). It has been stated that sedation, when used appropriately and

with precautions, reduces the possibility of failure in patients and increases patient comfort using NIV (8, 9).

Agitation during NIV may be caused by various factors such as fear, pain, fever, anxiety, sleep deprivation, and hypoxia (22). The sedation applied during NIV facilitates and calms ventilation and improves patient compliance. It also regulates autonomic system responses to stress such as hypertension and tachycardia and can also reduce the rate of NIV failure (5, 23, 24). In this prospective study, when we examined the groups based on the number of intubations, NIV failure in the dexmedetomidine groups was low compared to that in the other groups. Many studies have shown that sedation provided by dexmedetomidine, midazolam, propofol, and remifentanil during NIV is effective and safe (8, 25). We consider that the safest drug is dexmedetomidine, since NIV failure was lowest in patients receiving this drug.

Dexmedetomidine provides sedo-analgesia without causing respiratory depression (10). It does not cause respiratory depression even when deep sedation levels are achieved (26). Consistent with these studies, we also did not observe apnea at low or high doses of dexmedetomidine.

Propofol negatively affects the respiratory drive and gas Exchange, in proportion to the infusion rate of the sedation dose (19). Clinicians use drugs, which may impair the respiratory and cough reflexes, carefully (27). We did not study propofol at high doses due to the high possibility of this side effect. Despite its risk, it has been shown that propofol can be used effectively with target-controlled infusion (28). In our study, apnea developed in 25% patients in propofol.

It is well-known that the use of opioids for sedation causes respiratory depression (29, 30). However, it has been reported that remifentanyl infusion can be administered safely at doses of 0.05–0.1 μg/kg/min in patients with spontaneous ventilation (31). However, Cavaliere et al. concluded that remifentanyl infusion at a dose higher than 0.05 μg/kg/min may inhibit the respiratory impulse (30). In our study, apnea was observed in only one (4.3%) patient in the REM_H group (0.06 μg/kg/min), while no case of apnea was observed in the REM_L group (0.03 μg/kg/min).

Bradycardia may occur when remifentanil is administered rapidly and in high doses. Low doses of remifentanil do not cause significant changes in blood pressure (32). In this study, coexistence of hypotension and bradycardia (HR: <60 beats/min, MAP: < 60 mmHg) was recorded in two (8.7%) patients in the REM_H group. Similar to the studies showing that dexmedetomidine is associated with a high incidence of bradycardia and hypotension (33, 34), we also found a higher incidence of bradycardia in the DEX_L (4.3%) and DEX_H (8.7%) groups than in the other groups (0%), but this difference was not statistically significant ($P = 0.215$).

Opioids, are frequently added to the treatment regimens in the ICU for cardiovascular diseases, because of their protective effect on the heart tissue (35). Remifentanil is an ultra- short - acting opioid that rapidly reaches a steady state, with an onset of action of <1 min and μ selectivity (34). The elimination half life of remifentanil is <10 min, independent of kidney function, liver function, and infusion time (36). Remifentanil is a safe and effective opioid that reduces NIV failure (17). According to a recent study, there was no significant difference between dexmedetomidine and remifentanil in terms of NIV failure and other clinical outcomes (tracheostomy, length of ICU stay, length of hospital stay, and in hospital mortality). The side effects of both drugs were rare (chest wall rigidity in one patient with remifentanil, and severe hemodynamic instability requiring intubation with dexmedetomidine). In addition, NIV failure was avoided in more than 80% of the patients enrolled in this study (21). We also did not find any differences between the groups in terms of the incidence of side effects ($P > 0.05$). However, we observed better clinical results in the DEX_L and DEX_H groups. IMV time, ICU LOS, hospital LOS were significantly reduced in these groups compared with the other groups ($P < 0.05$). Mortality and NIV failure were also lower in these groups compared to the other groups ($P < 0.05$).

In summary, NIV has become increasingly important in the treatment of both hypercapnic and hypoxemic acute respiratory failure. NIV reduces the need for IMV. NIV failure defined as the need for endotracheal intubation, is one of the biggest problems in NIV patients. Patient rejection and discomfort are among the reasons for failure. Therefore, patient comfort must be monitored. Non-pharmacological methods and analgo-sedative drug schemes are used to manage agitation during NIV. In the case of agitation, the addition of sedatives to therapy should be considered. There is evidence that sedation reduces the NIV failure rate. In the selection of the drug, clinical and side effects should be considered. Sedative drugs should be administered in ICU, in the presence of well-trained personnel in airway emergency management, with monitoring of vital signs and depth of sedation (37).

One limitation of this study was that it was conducted in a single center and with a limited number of participants. In this study, in which we evaluated the sedative effects of the drugs used with the target RSS 2–3, we did not add analgesic drugs in addition to propofol, which has no analgesic effect. Using drugs in different doses, we aimed to establish the best safe and effective evidence-based dosing recommendation for sedatives used in NIV intolerance. We did not study propofol at high doses due to the high possibility of side effect.

In conclusion, in this prospective study, we compared the results of three drugs (propofol, dexmedetomidine, and remifentanil) in patients with NIV intolerance. Seventy-five patients (62.5%) in total become tolerant of NIV after starting the drugs. Sedation used in patients with NIV intolerance increased the success of NIV. NIV failure, mortality, ICU LOS, IMV time, and hospital LOS were found to be lower with dexmedetomidine. With the use of low doses, the incidence of

side effects decreased, the target sedation level was reached, and NIV intolerance decreased.

We believe that this study, supported by multicenter studies with larger sample sizes in the future, will help improve outcomes, in patients with NIV intolerance, who are hospitalized in the ICU due to respiratory failure.

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

Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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References

1. Keenan SP, Sinuff T, Cook DJ, Hill NS. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med.* (2003) 138:861–70. doi: 10.7326/0003-4819-138-11-200306030-00007

2. Lightowler JV, Wedzicha JA, Elliott MW, Ram FS. Non-invasive positive pressure ventilation to treat respiratory failure resulting from exacerbations of chronic obstructive pulmonary disease: cochrane systematic review and meta-analysis. *BMJ.* (2003) 326:185. doi: 10.1136/bmj.326.7382.185

3. Carron M, Freo U, BaHammam AS, Dellweg D, Guarracino F, Cosentini R, et al. Complications of non-invasive ventilation techniques: a comprehensive qualitative review of randomized trials. *Br J Anaesth.* (2013) 110:896–914. doi: 10.1093/bja/aet070

4. Constantin JM, Schneider E, Cayot-Constantin S, Guerin R, Bannier F, Futier E, et al. Remifentanil-based sedation to treat noninvasive ventilation failure: a preliminary study. *Intens Care Med.* (2007) 33:82–7. doi: 10.1007/s00134-006-0447-4

5. Ni YN, Wang T, Yu H, Liang BM, Liang ZA. The effect of sedation and/ or analgesia as rescue treatment during noninvasive positive pressure ventilation in the patients with Interface intolerance after Extubation. *BMC Pulm Med.* (2017) 17:125. doi: 10.1186/s12890-017-0469-4

6. Hilbert G, Navalesi P, Girault C. Is sedation safe and beneficial in patients receiving NIV? *Yes Intensive Care Med.* (2015) 41:1688–91. doi: 10.1007/s00134-015-3935-6

7. Piastra M, Pizza A, Gaddi S, Luca E, Genovese O, Picconi E, et al. Dexmedetomidine is effective and safe during NIV in infants and young children with acute respiratory failure. *BMC Pediatr.* (2018) 18:282. doi: 10.1186/s12887-018-1256-y

8. Chawla R, Dixit SB, Zirpe KG, Chaudhry D, Khilnani GC, Mehta Y, et al. ISCCM guidelines for the use of non-invasive ventilation in acute respiratory failure in adult ICUs. *Indian J Crit Care Med.* (2020) 24:61–81. doi: 10.5005/jp-journals-10071-G23186

9. Matsumoto T, Tomii K, Tachikawa R, Otsuka K, Nagata K, Otsuka K, et al. Role of sedation for agitated patients undergoing noninvasive ventilation: clinical practice in a tertiary referral hospital. *BMC Pulm Med.* (2015) 15:71. doi: 10.1186/s12890-015-0072-5

10. Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care. *Br J Anaesth.* (2002) 88:669–75. doi: 10.1093/bja/88.5.669

11. Pasero D, Sangalli F, Baiocchi M, Blangetti I, Cattaneo S, Paternoster G, et al. Experienced use of dexmedetomidine in the intensive care unit: a report of a structured consensus. *Turk J Anaesthesiol Reanim.* (2018) 46:176–83. doi: 10.5152/TJAR.2018.08058

12. Flükiger J, Hollinger A, Speich B, Meier V, Tontsch J, Zehnder T, et al. Dexmedetomidine in prevention and treatment of postoperative and intensive care unit delirium: a systematic review and meta-analysis. *Ann Intens Care.* (2018) 8:92. doi: 10.1186/s13613-018-0437-z

13. Dalfino L, Brienza N, Bruno F. Patient-targeted light sedation in the Intensive Care Unit: are we ready for precision medicine with dexmedetomidine? *Minerva Anestesiol.* (2018) 84:661–3. doi: 10.23736/S0375-9393.18.12892-6

14. Hall JE, Uhrich TD, Barney JA, Arain SR, Ebert TJ. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. *Anesth Analg.* (2000) 90:699–705. doi: 10.1097/00000539-200003000-00035

15. Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. *Anesthesiology.* (2000) 93:1345–9. doi: 10.1097/00000542-200011000-00030

16. Jo YY, Kwak HJ. Sedation strategies for procedures outside the operating room. *Yonsei Med J.* (2019) 60:491–9. doi: 10.3349/ymj.2019.60.6.491

17. Rocco M, Conti G, Alessandri E, Morelli A, Spadetta G, Laderchi A, et al. Rescue treatment for noninvasive ventilation failure due to interface intolerance with remifentanil analgosedation: a pilot study. *Intens Care Med.* (2010) 36:2060–5. doi: 10.1007/s00134-010-2026-y

18. Rao GP, Wong D, Groenewald C, McGalliard JN, Jones A, Ridges PJ. Local anesthesia for vitreoretinal surgery: a case control study of 200 cases. *Eye.* (1998) 12:407–11. doi: 10.1038/eye.1998.96

19. Vaschetto R, Cammarota G, Colombo D, Longhini F, Grossi F, Giovanniello A, et al. Effects of propofol on patient-ventilator synchrony and interaction during pressure support ventilation and neurally adjusted ventilatory assist. *Crit Care Med.* (2014) 42:74–82. doi: 10.1097/CCM.0b013e31829e53dc

20. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J.* (1974) 2:656–9. doi: 10.1136/bmj.2.5920.656

21. Hao GW, Luo JC, Xue Y, Ma GG, Su Y, Hou JY, et al. Remifentanil versus dexmedetomidine for treatment of cardiac surgery patients with moderate to severe noninvasive ventilation intolerance (REDNIVIN): a prospective, cohort study. *J Thorac Dis.* (2020) 12:5857–68. doi: 10.21037/jtd-20-1678

22. Nava S, Ceriana P. Patient-ventilator interaction during noninvasive positive pressure ventilation. *Respir Care Clin N Am.* (2005) 11:281–93. doi: 10.1016/j.rcc.2005.02.003

23. Hilbert G, Clouzeau B, Nam Bui H, Vargas F. Sedation during non-invasive ventilation. *Minerva Anestesiol.* (2012) 78:842—6.

24. Senoglu N, Oksuz H, Dogan Z, Yildiz H, Demirkiran H, Ekerbicer H. Sedation during noninvasive mechanical ventilation with dexmedetomidine or midazolam: a randomized, double-blind, prospective study. *Curr Ther Res Clin Exp.* (2010) 71:141–53. doi: 10.1016/j.curtheres.2010.06.003

25. Longrois D, Conti G, Mantz J, Faltlhauser A, Aantaa R, Tonner P. Sedation in noninvasive ventilation: do we know what to do (and why)? *Multidiscip Respir Med.* (2014) 9:56. doi: 10.4081/mrm.2014.391

26. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care.* (2000) 4:302–8. doi: 10.1186/cc712

27. Devlin JW, Mallow-Corbett S, Riker RR. Adverse drug events associated with the use of analgesics, sedatives, and antipsychotics in the intensive care unit. *Crit Care Med.* (2010) 38:231–43. doi: 10.1097/CCM.0b013e3181de125a

28. Clouzeau B, Bui HN, Vargas F, Grenouillet-Delacre M, Guilhon E, Gruson D, et al. Target-controlled infusion of propofol for sedation in patients with non-invasive ventilation failure due to low tolerance: a preliminary study. *Intensive Care Med.* (2010) 36:1675–80. doi: 10.1007/s00134-010-1904-7

29. Servin FS, Raeder JC, Merle JC, Wattwil M, Hanson AL, Lauwers MH, et al. Remifentanil sedation compared with propofol during regional anaesthesia. *Acta Anaesthesiol Scand.* (2002) 46:309–15. doi: 10.1034/j.1399-6576.2002.t01-1-460314.x

30. Cavaliere F, Antonelli M, Arcangeli A, Conti G, Costa R, Pennisi MA, et al. A lowdose remifentanil infusion is well tolerated for sedation in mechanically ventilated, critically-ill patients. *Can J Anaesth.* (2002) 49:1088–94. doi: 10.1007/BF03017909

31. Mingus ML, Monk TG, Gold MI, Jenkins W, Roland C. Remifentanil versus propofol as adjuncts to regional anesthesia. *J Clin Anesth.* (1998) 10:46–53. doi: 10.1016/S0952-8180(97)00220-1

32. Glass PS, Hardman D, Kamiyama Y, Quill TJ, Marton G, Donn KH, et al. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B). *Anesth Analg.* (1993) 77:1031–40. doi: 10.1213/00000539-199311000-00028

33. Liu H, Ji F, Peng K, Applegate RL 2nd, Fleming N. Sedation after cardiac surgery: is one drug better than another? *Anesth Analg.* (2017) 124:1061–70. doi: 10.1213/ANE.0000000000001588

34. Shehabi Y, Ruettimann U, Adamson H, Innes R, Ickeringill M. Dexmedetomidine infusion for more than 24 hours in critically ill patients: sedative and cardiovascular effects. *Intens Care Med.* (2004) 30:2188–96. doi: 10.1007/s00134-004-2417-z

35. Rawal H, Patel BM. Opioids in cardiovascular disease: therapeutic options. *J Cardiovasc Pharmacol Ther.* (2018) 23:279–91. doi: 10.1177/1074248418757009

36. Conti G, Costa R, Pellegrini A, Craba A, Cavaliere F. Analgesia in PACU: intravenous opioids. *Curr Drug Targets.* (2005) 6:767–71. doi: 10.2174/138945005774574407

37. Cammarota G, Simonte R, De Robertis E. Comfort during non-invasive ventilation. *Front Med.* (2022) 9:874250. doi: 10.3389/fmed.2022.874250

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Electrical impedance tomography to aid in the identification of hypoxemia etiology: Massive atelectasis or pneumothorax? A case report

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Background: Bedside ultrasound is often used to determine the etiology of hypoxaemia, but not always with definitive results. This case reports the application of electrical impedance tomography (EIT) and saline injection to determine the etiology of hypoxaemia in a complex case that could not be identified by bedside ultrasound. The determination of the etiology of hypoxaemia by EIT and saline injection, regional ventilation and perfusion information can be used as a new clinical diagnostic method.

Case presentation: A post-cardiac surgery patient under prolonged mechanical ventilation for lung emphysema developed sudden hypoxemia in the intensive care unit (ICU). A line pattern and lung sliding sign abolishment were found in the left lung, but there was no evidence of a lung point sign on bedside ultrasound. Hence, the initial diagnosis was considered to be a massive pneumothorax. To further define the etiology, EIT and saline bolus were used to assess regional ventilation and perfusion. A massive ventilation defect was found in the left lung, in which regional perfusion was maintained, resulting in an intrapulmonary shunt in the left lung. Finally, the conjecture of a pneumothorax was ruled out considering the massive atelectasis. After the diagnosis was clarified, hypoxaemia was corrected by restorative ventilation of the left lung after changing the patient's posture and enhancing sputum drainage with chest physiotherapy.

Conclusions: This was the clinical case involving EIT and saline bolus to establish the differential diagnosis and guide clinical decisions for patients with acute hypoxemia. This study highlighted that combination regional ventilation, EIT perfusion, and saline bolus provided helpful information for determining the etiology of hypoxemia. The results of this study contribute to the development of emergency patient management.

KEYWORDS

EIT, lung perfusion and ventilation, massive atelectasis or pneumothorax, case report, electrical impedance tomography

Background

Interpreting ventilation-perfusion matching is essential in the differential diagnosis of acute hypoxemia. Electrical impedance tomography (EIT) is a new, non-invasive, radiation-free, bedside lung imaging method, that has gained attention in the diagnosis of acute respiratory failure (ARF), such as pleural effusion and pneumothorax (1, 2). Moreover, the saline bolus-based EIT method has been validated against electron beam computed tomography (CT) imaging for assessing regional lung perfusions (3). Hence, combination regional ventilation with perfusion data derived from EIT and saline bolus significantly aids in the bedside diagnosis of ARF etiology. We report a case involving the application of EIT and saline bolus to determine the etiology of an acute hypoxemia patient with a suspected pneumothorax on bedside ultrasound. This case had been enrolled in a previous study (4).

Case presentation

A 58-year-old post-cardiac surgery patient, who underwent prolonged mechanical ventilation [pressure support (PS) mode: PS 12 cmH_2O, positive end-expiratory pressure 5 cmH_2O, fraction of inspired oxygen 40%] for lung emphysema, developed sudden dyspnea and severe hypoxemia [peripheral oxygen saturation (SpO_2) decreased from 99 to 76%] in the ICU. The patient had a heart rate of 110-120 bp/min and blood pressure of 120-130/75-90 mmHg. A previous CT scan showed emphysema and a pulmonary bulla in the left lung (Figure 1). The medical team immediately performed an emergency bedside ultrasound on the patient. A line pattern and lung sliding sign abolishment were found in the left lung (Figure 2), but there was no evidence of a lung point sign on emergency bedside ultrasound. A massive pneumothorax was suspected. Immediately afterwards, the doctor called the radiology department for a bedside chest X-ray scan. In the meantime, the EIT and saline bolus were used to assess the regional ventilation and perfusion. A massive ventilation defect was found in the left lung, which had normal perfusion (Figure 2). This suggested an intrapulmonary shunt in the left lung. Massive atelectasis, rather than pneumothorax, was considered. After enhancing sputum drainage by changing the patient's posture and chest physical therapy, the SpO_2 improved, and the left lung ventilation recovered (Figure 3). The radiology staff arrived at the ICU unit to perform the scan later than the EIT assessment was completed. The bedside chest X-ray excluded pneumothorax (Figure 4). When the patient was successfully weaned from the ventilator, he was transferred to the regular ward 19 days after ICU admission.

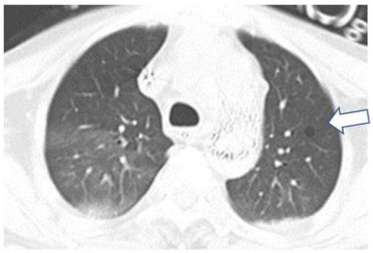

FIGURE 1
The computed tomography (CT) scans of the patient (baseline). A baseline lung CT scan noted emphysema and pulmonary bulla in the left lung. The arrow in this figure points to the pulmonary bulla of lung.

EIT methods

Electrical impedance tomography measurements were performed using PulmoVista (Dräger Medical, Lübeck, Germany). During the protocol, a silicone EIT belt with 16 surface electrodes was placed around the patient's thorax in one transverse plane corresponding to the fourth intercostal parasternal space, and then connected to the EIT monitor. A bolus of 10 ml 10% NaCl was injected through the central venous catheter during an 8s respiratory pause. The ventilation maps were derived from a previous publication, where the impedance changes reliably tracked local changes in the air content within the lung, pixel by pixel (1). The perfusion maps were obtained by injecting a bolus of 10 ml hypertonic solution (NaCl 10%) through a central venous catheter during an expiratory breath-hold for at least 8 s. Due to its high conductivity, NaCl 10% acted as an EIT contrast agent, which passed through the pulmonary circulation after being injected into the right atrium, thereby producing a dilution curve following the typical first-pass kinetics. The resulting regional time impedance curves were then analyzed to quantitatively assess regional perfusion (3, 5).

Discussion and conclusions

This case demonstrated the application of combined ventilation with perfusion data from EIT and saline bolus to establish the differential diagnosis of acute hypoxemia. EIT has been used in several animal studies and clinical cases to identify pneumothorax by regional ventilation defection (6, 7).

However, regional ventilation defection results from various intrathoracic pathologies, such as atelectasis, hemothorax, and pneumothorax. Without additional imaging data, it is difficult

Abbreviations: ARF, acute respiratory failure; CT, computerized tomography; EIT, electrical impedance tomography; ICU, intensive care unit; PS, pressure support; SPO_2, peripheral oxygen saturation.

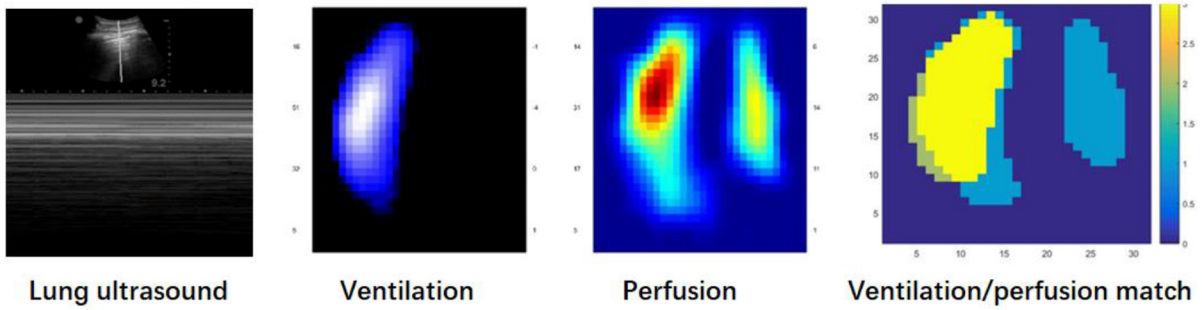

FIGURE 2
The lung ultrasound and EIT monitoring (hypoxemia occurs). 1. Lung ultrasound imaging with a convex probe (5 MHz) showed the absence of gliding sign, confirmed by the Barcode sign in M-mode at the onset of hypoxemia. 2. Functional electrical impedance tomography (EIT) images of ventilation and perfusion distribution at the onset of hypoxemia. Low-ventilated regions are marked in dark blue and high-ventilated regions in white. Regions with high perfusion are marked in red and low perfusion in blue. A massive ventilation defect was found in the left lung in which perfusion was maintained, and perfusion and ventilation matched the image at the onset of hypoxemia. Regions with high ventilation and low perfusion (indicate dead space) are marked in light green; low ventilation and high perfusion regions (indicate intrapulmonary shunt) in light blue; good ventilation-perfusion matching in yellow.

to establish the differential diagnoses clinically. EIT has been used as a diagnostic tool for atelectasis. EIT is currently used in clinical practice to monitor the patient's lung ventilation, which can indirectly assist the clinician in determining the patient's lung condition. In this case the patient was in a unique situation and we administered saline as soon as the patient's condition allowed, which helped us to further determine the patient's condition and identify the patient as having pulmonary asplenia. The combined regional ventilation and perfusion enhances EIT performance in determining lung pathology. Tingay et al. reported the use of EIT to measure perfusion and ventilation patterns in a newborn with impaired perfusion and ventilation in a single lung (8).

In the present case, we auscultated the patient's lungs and found a reduced breath sound, but no positive signs on percussion. We immediately performed a bedside lung ultrasound and EIT. A massive pneumothorax was suspected based on a "regional ventilation defection," and "A line pattern and lung sliding sign abolishment" on bedside EIT and ultrasound examination. However, pneumothorax could not be determined without findings of the lung point sign. The presence of the lung sliding sign excluded pneumothorax, but the absence of lung sliding sign can be related to other conditions, such as phrenic nerve paralysis, pleural adhesions, pulmonary contusion, emphysema, and obesity (8). Moreover, the patient had emphysema in the related lung region. Anna Del Colle et al. reported that the lack of the "gliding sign" mimicked pneumothorax in patients with severe asthmatic patients (9). Boccatonda et al. found that lung sliding sign was abolished by lung atelectasis, but not pneumothorax (10). That was due to adhesions caused by solid lung lesions and the lung sliding sign may disappear.

The present case supported the utility of the combination of regional ventilation and perfusion, assessed by saline

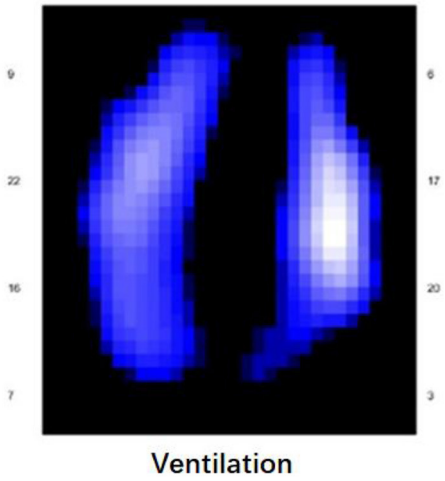

FIGURE 3
The results of the EIT assessment of the patient's lungs (post-treatment).

injection, in differentiating between pneumothorax and atelectasis, and making an accurate clinical decision. The lung regional perfusion and saline bolus helped identify massive intrapulmonary and extrapulmonary lesions. A similar change in regional ventilation defection with normal perfusion was observed in the one-lung ventilation animal model with capnothorax (5). Moreover, several animal studies have found that the indicator-based EIT method determined the regional lung perfusion defect after a pulmonary embolism-like event (3).

This patient was enrolled in a clinical study of using lung perfusion and ventilation by EIT for respiratory failure

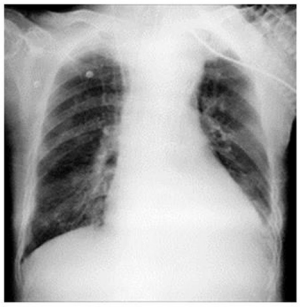

FIGURE 4
The chest X-ray of patient. Chest radiography did not show signs of pneumothorax. Functional EIT images of ventilation showed that the defect of the left lung had been restored after treatment.

etiology. The related examinations for massive atelectasis or pneumothorax were performed based on clinical regulations, and the EIT examination did not affect the clinical therapy in this case. Because the lung point sign was not observed, the bedside ultrasound could not make a definitive diagnose of pneumothorax. Moreover, the chest X-ray examination usually takes about 30-60min since there was no mobile X-ray machine at the bedside in our department. Hence, the EIT examination was a reasonable option, which has potential advantages for early diagnoses. We found that the EIT examination was helpful for the differential diagnoses of massive atelectasis or pneumothorax in this case. The diagnosis of EIT corresponded with the result of the following Chest-X ray examination. The patient's atelectasis improved after physiotherapy of the lungs and therefore no definite atelectasis images were found on chest X-ray. This case suggested that saline bolus EIT examination might be an early and alternative method for respiratory failure etiology during the waiting period for Chest-ray under some difficult conditions. Caio et al. found that EIT Monitoring could early identify pneumothorax appearance during recruitment maneuvers in ARDS patients (11). Moreover, the influence of the 10 mL 10% NaCl on hydro electrolyte balance was minimal. Several clinical studies have validated the safety of the method (12).

At last, we acknowledge that monitoring and judgment of pulmonary circulation using EIT is still not well established. The case, as a proof concept, will significantly contribute to the development of emergency patient management by saline bolus EIT examination.

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

This study was approved by the institutional review board of PUMCH (approval number: JS-1896). The patients/participants' family provided written informed consent to participate in this study.

Author contributions

YL and HH conceived the original idea. RZ carried out the research and wrote the manuscript with support from HH, CH, and YC. QL verified the numerical results of RZ. SY, BT, and ZL supervised the findings of this work and provided support in writing the manuscript. All authors have discussed the results and contributed to the final manuscript.

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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.

Publisher's note

References

1. Frerichs I, Amato MBP, Van Kaam AH, Tingay DG, Zhao Z, Grychtol B, et al. Chest electrical impedance tomography examination, data analysis, terminology, clinical use and recommendations: consensus statement of the translational EIT development study group. *Thorax*. (2017) 72:83–93. doi: 10.1136/thoraxjnl-2016-208357

2. Becher T, Bußmeyer M, Lautenschläger I, Schädler D, Weiler N, Frerichs I. Characteristic pattern of pleural effusion in electrical impedance tomography images of critically ill patients. *Br J Anaesth*. (2018) 120:1219–28. doi: 10.1016/j.bja.2018.02.030

3. Frerichs I, Hinz J, Herrmann P, Weisser G, Hahn G, Quintel M, et al. Regional lung perfusion as determined by electrical impedance tomography in comparison with electron beam CT imaging. *IEEE Trans Med Imaging*. (2002) 21:646–52. doi: 10.1109/TMI.2002.800585

4. He H, Chi Y, Long Y, Yuan S, Zhao Z. Bedside evaluation of pulmonary embolism by saline contrast electrical impedance tomography method: a prospective observational study. *Am J Respir Crit Care Med*. (2020) 202:1464–8. doi: 10.1164/rccm.202005-1780LE

5. Reinius H, Borges JB, Fredén F, et al. Real-time ventilation and perfusion distributions by electrical impedance tomography during one-lung ventilation with capnothorax. *Acta Anaesthesiol Scand*. (2015) 59:354–68. doi: 10.1111/aas.12455

6. Reinius H, Borges JB, Fredén F, Jideus L, Camargo EDLB, Amato MBP, et al. Pneumothorax in a preterm infant monitored by electrical impedance tomography: a case report. *Neonatology*. (2011) 99:10–3. doi: 10.1159/000292626

7. Girrbach F, Landeck T, Schneider D, Reske US. Detection of posttraumatic pneumothorax using electrical impedance tomography-an observer-blinded study in pigs with blunt chest trauma. *PLoS One*. (2020) 15:e0227518. doi: 10.1371/journal.pone.0227518

8. Tingay DG. Waldmann, AD, Frerichs I, Ranganathan S, Adler A, et al. Electrical impedance tomography can identify ventilation and perfusion defects: a neonatal case. *Am J Respir Crit Care Med*. (2019) 199:384–5. doi: 10.1164/rccm.201808-1551LE

9. Quarato CMI. Sperandeo, M, Pianella VVD. Lung ultrasound for pneumothorax in children: relevant limits. *Pediatr Radiol*. (2020) 50:451–2. doi: 10.1007/s00247-020-04621-4

10. Boccatonda A, Primomo G, Cocco G, D'Ardes D, Schiavon C. Not all abolished lung sliding sign are pneumothorax: the case of a particular lung atelectasis. *J Ultrasound*. (2021) 24:519–23. doi: 10.1007/s40477-020-00427-0

11. Morais CC, De Santis Santiago RR, Filho JR, Hirota AS, Pacce PH, Ferreira JC, et al. Monitoring of pneumothorax appearance with electrical impedance tomography during recruitment maneuvers. *Am J Respir Crit Care Med*. (2017) 195:1070–3. doi: 10.1164/rccm.201609-1780LE

12. Xu M, He H, Long Y. Lung perfusion assessment by bedside electrical impedance tomography in critically ill patients. *Front Physiol*. (2021) 12:748724. doi: 10.3389/fphys.2021.748724

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Construction and efficacy evaluation of an early warning scoring system for septic shock in patients with digestive tract perforation: A retrospective cohort study

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Objective: To establish an early warning scoring system for septic shock in patients with digestive tract perforation (DTP) and evaluate its diagnostic efficacy.

Methods: Patients with surgically confirmed or clinically diagnosed DTP admitted to the Department of Intensive Care Medicine of Fujian Provincial Hospital from June 2012 to October 2021 were retrospectively analyzed. General demographic characteristics, perforation-related information, vital signs, common laboratory indicators, and common ICU scores (Glasgow Coma Scale score, Acute Physiology and Chronic Health Evaluation-II score,Sequential Organ Failure Assessment score) were collected. The patients were divided into shock group and non-shock group according to whether the patients had septic shock during hospitalization. The risk factors of septic shock were screened by basic statistical analysis and multivariate Logistic regression analysis. The receiver operating characteristic curve was drawn to determine the cut-off value of the continuous indicators and discretized with reference to clinic, and the corresponding score was set according to the β regression coefficient of each variable.

Results: A total of 176 patients with DTP were included. The average age of the patients was 64.13 ± 14.67 years old, and 74.40% were males. The incidence of septic shock was 30.11% (53/176). Multivariate Logistic regression analysis showed that the highest heart rate≥105 beats/min, Glasgow Coma

Scale score≤14 points, lactic acid≥5.75 mmol/L, procalcitonin≥41.47 ug/L, C-reactive protein≥222.5 mg/L were independent risk factors for septic shock in patients with DTP. The total score of clinical diagnostic scoring system of septic shock in patients with DTP was 6 points, including the highest heart rate≥105 beats/min (1 point), lactic acid≥5.75 mmol/L (two points), procalcitonin≥41.47 ug/L (one point), C-reactive protein≥222.5 mg/L (1 point), and Glasgow Coma Scale score ≤14 points (1 point). The area under ROC curve (AUC) of this scoring system was 0.789 and the 95% confidence interval was 0.717–0.860 ($P < 0.001$); when the optimal cut-off value was 2.5, the sensitivity and specificity were 54.70 and 87.80%, respectively.

Conclusion: This new score system has its certain clinical value and has important guiding significance for clinicians to judge the prognosis of patients with DTP in time.

KEYWORDS

septic shock, gastrointestinal tract, perforation, risk factors, early warning score

Background

Digestive tract perforation (DTP) is a potentially devastating complication that may result from various disease processes and is an important indication of emergency surgery. The most common conditions that cause gastrointestinal perforation are peptic ulcer, gastrointestinal tumor, trauma, and inflammatory bowel disease. If left untreated, it leads to death. Although the incidence of DTP has decreased significantly over the past 30 years, especially due to the development of intensive care technology, the advancement of treatment concepts, and the development of various new drugs, the mortality rate is still high (1, 2). According to statistics, the average 30-day mortality rate of peptic ulcer perforation is 23.75% (3). Another report pointed out that gastrointestinal perforation accounted for 40% of peptic ulcer-related deaths, and its 90-day mortality rate was as high as 30% (4–6). Multiple factors, including advanced age, use of non-steroidal anti-inflammatory drugs, diabetes, and use of glucocorticoids, have been associated with increased mortality in patients with DTP (7–10).

Septic shock is a major risk factor for increased mortality in patients with DTP (2, 4). Five studies in Europe, Asia, and Africa reported a significant increase in shock-related mortality in patients with DTP (11–15). Also, septic shock after DTP is a common critical illness in intensive care units (ICU) (16). It is estimated that 30–35% of patients with DTP have sepsis before they arrive in the operating room, and 25% of patients develop septic shock within 30 days of surgery (17).

Recent studies indicated that early recognition and appropriate management of the first few hours after septic shock could significantly improve the prognosis of patients (18). However, so far, no early identification methods have been proposed for screening patients with DTP. Therefore, based on quantitative clinical data, in this study, we analyzed risk factors of septic shock in the patients with DTP and established an early warning scoring system for septic shock in patients with gastrointestinal perforation, aiming to assist clinicians in early identification and intervention of patients with DTP, so as to reduce the occurrence of adverse outcomes.

Materials and methods

Study design

Patients with surgically confirmed or clinically diagnosed DTP admitted to the Department of Intensive Care Medicine of Fujian Provincial Hospital from June 2012 to October 2021 were retrospectively analyzed. DTP was defined as the destruction of the integrity of the digestive tract, i.e., complete non-invasive penetration of the wall of the esophagus, stomach, small intestine, or large intestine (19). The clinical diagnostic criteria were the presence of free gas under the diaphragm by the plain abdominal film in a vertical position, or the presence of gas-liquid coexistence by abdominal ultrasound, or the presence of free gas in the abdominal cavity by abdominal computed tomography (CT) (20, 21). The diagnostic criteria for septic shock were in line with sepsis-3.0 (22), i.e., patients with sepsis had persistent hypotension after adequate volume resuscitation and needed vasoconstrictor drugs to maintain mean arterial pressure (MAP) ≥ 65 mmHg and serum lactate level > 2 mmol/L.

Patients were divided into shock group and non-shock group according to whether septic shock occurred during hospitalization. Clinical data, including demographic characteristics, perforation-related information, vital signs, common laboratory indicators, ICU common scores (Glasgow

Coma Scale score, GCS score;Acute Physiology and Chronic Health Evaluation-II score,APACHE-II score;Sequential Organ Failure Assessment score,SOFA score), and mortality rate within 28 days were collected and compared.

The study protocol was approved by the ethics committee (K2021-09-043), and since it was a retrospective study, the informed consent of patients was exempted from ethical approval.

Research subjects

Inclusion criteria were: (1) patients admitted to the Intensive Care Unit of our Hospital from June 2012 to October 2021; (2) patient aged > 18 years at the date of admission; (3) patients with surgically confirmed or clinically diagnosed DTP based on the above criteria (see section Study design). Exclusion criteria were: (1) patients aged <18 years; (2) those with missing electronic medical records. All selected patients were routinely treated by the same associate chief physician with 10 years of experience in the field.

Data collection

The general data of patients were collected, including gender, age, past medical history, perforation area, and perforation-operation time interval. Within 24 h of admission to ICU, the heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), oxygenation index (PaO2/FiO2), 24-h urine volume, serum sodium (Na^+), serum potassium (K^+), total bilirubin (TBIL), serum creatinine (SCr), platelet count (PLT), albumin (Alb), procalcitonin (PCT), C-reactive protein (CRP), the potential of hydrogen (pH), lactic acid (Lac), GCS score, APACHE-II score, SOFA score and the mortality rate within 28 days were collected and analyzed.

Statistical analysis

Data were analyzed using SPSS 25.0 statistical software. Quantitative data conforming to a normal distribution were expressed as mean ± standard deviation ($\bar{x}\pm$ s), and the unpaired *t*-test was used for comparison between groups. The quantitative data with skewness distribution were expressed as median (quartile) [M (QL, QU)], and the Wilcoxon Mann-Whitney test was used for comparison between groups. Categorical data were expressed as percentages, and the chi-square test was used for comparison. Variables with $P \leq 0.05$ (bilateral) were considered to be statistically significant and variables with $P > 0.05$ were excluded. The receiver operator characteristic curve (ROC curve) was used to analyze the retained continuous indicators to determine the cutoff value and were discretized into discrete indicators by referring to clinic. Taking the occurrence of septic shock as the dependent variable, the independent variables were screened by the method of forwarding stepwise regression (LR), and the independent risk factors of shock in patients with DTP were determined by multivariate Logistic regression analysis. Relative risk was expressed by odds ratio (OR) and 95% confidence interval (95%CI). The corresponding score was set according to the β coefficient of each risk factor, and the sum of each risk factor's scores was the patient's total risk score. The diagnostic efficiency of the scoring system was evaluated by area under ROC Curve (AUC). AUC ranged from 0.5 to 1.0, with <0.7 indicating low diagnostic value, 0.7–0.9 indicating moderate diagnostic value, and >0.9 indicating high diagnostic value.

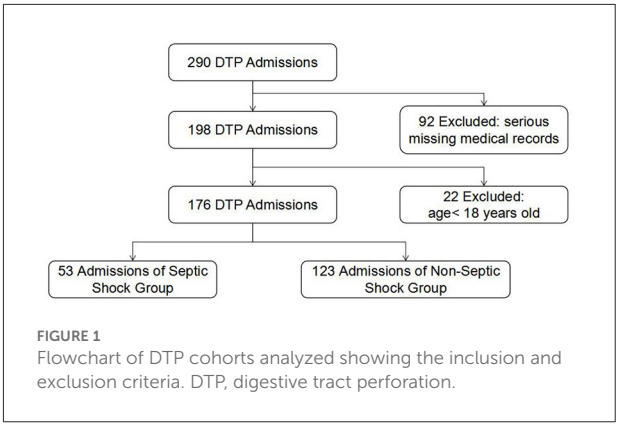

FIGURE 1
Flowchart of DTP cohorts analyzed showing the inclusion and exclusion criteria. DTP, digestive tract perforation.

Results

Characteristics of patients

A total of 290 patients with gastrointestinal perforation were screened. Then, 22 patients who were <18 years old and 92 patients with serious missing electronic medical records were excluded (Figure 1). Finally, 176 patients were included in the analysis, including 53 patients with septic shock and 123 patients without septic shock (Table 1). The average age of the patients was 64.13 ± 14.67 years, and 74.40% were male. The median perforation area was 2.13 (0.64, 3.09) cm^2, and the median time interval from perforation to operation was 4.5(2.37, 53.02) h. The mortality rate within 28 days was 11.40%. APACHE-II score, SOFA score, highest HR, highest K^+, Lac, PCT, CRP, and SCr in the shock group were higher than those in the non-shock group, while GCS score, Alb, pH, PaO2/FiO2 were lower than those in the non-shock group (all $P < 0.05$). However, there were no significant differences in gender, age, perforation area, the time interval from perforation to operation, 24-h urine volume, PLT, TBIL, and other indicators between the two groups.

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

Item	Total ($n = 176$)	Shock group ($n = 53$)	Non-shock group ($n = 123$)	T/x^2/z value	*P*-value
Age (years,x̄±s)	64.13 ± 14.67	64.08 ± 16.61	64.15 ± 13.83	0.33	0.974
Male [cases (%)]	131 (74.40%)	37 (69.80%)	94 (76.40%)	0.85	0.356
Perforation area [cm^2,M(QL, QU)]	2.13 (0.64, 3.09)	2.25 (1.00, 3.09)	1.50 (0.64, 3.09)	0.84	0.399
Time interval from perforation to operation [h,M(QL, QU)]	4.5 (2.37, 53.02)	3.49 (2.45, 53.02)	5.05(2.19,53.02)	0.12	0.906
APACHE-II score (points, x̄±s)	17.30 ± 7.64	21.18 ± 7.69	15.63 ± 7.02	4.67	<0.001
SOFA score (points, =x±s)	8.68 ± 3.65	10.93 ± 3.13	7.71 ± 3.43	5.87	<0.001
GCS score (points,x̄±s)	10.50 ± 4.41	9.37 ± 4.24	10.99 ± 4.40	2.24	0.026
Highest HR (beats/min,x̄±s)	103.46 ± 22.29	111.85 ± 25.93	99.85 ± 19.55	3.02	0.003
Fastest RR (times/min, x̄±s)	22.01 ± 5.59	23.02 ± 7.21	21.58 ± 4.70	1.34	0.185
Minimum MAP (mmHg, x̄±s)	75.17 ± 16.58	72.50 ± 16.664	76.33 ± 16.48	1.41	0.161
24-h urine volume (ml, x̄±s)	1,418.55 ± 979.06	1,308.93 ± 1,103.11	1465.78 ± 921.34	0.98	0.331
Highest Na^+ (mmol/L, x̄±s)	141.09 ± 4.97	141.8 ± 4.60	140.78 ± 5.11	1.25	0.215
Minimum Na+ (mmol/L, x̄±s)	139.36 ± 4.87	139.52 ± 4.28	139.29 ± 5.12	0.28	0.781
Highest K+ (mmol/L, x̄±s)	4.34 ± 0.58	4.51 ± 0.61	4.26 ± 0.56	2.62	0.010
Minimum K+ (mmol/L, x̄±s)	4.06 ± 0.53	4.12 ± 0.61	4.04 ± 0.50	0.97	0.335
PLT (*10^9, x̄±s)	173.79 ± 91.10	163.21 ± 101.19	178.35 ± 86.43	1.01	0.313
Alb (g/L, x̄±s)	20.94 ± 6.54	18.96 ± 6.18	21.79 ± 6.52	2.69	0.008
PaO2/FiO2 (mmHg, x̄±s)	233.72 ± 114.03	204.5 ± 115.19	246.32 ± 111.65	2.26	0.025
pH [M(QL, QU)]	7.31 (7.29, 7.40)	7.30 (7.23, 7.38)	7.33 (7.30, 7.41)	2.77	0.006
Lac [mmol/L,M(QL, QU)]	3.65 (2.10, 4.65)	4.30 (2.45, 4.77)	3.20 (1.90, 4.65)	2.07	0.039
TBIL [umol/L,M(QL, QU)]	17.40 (11.10, 23.77)	17.22 (10.79, 24.46)	17.58 (11.31, 23.80)	0.16	0.877

(Continued)

TABLE 1 (Continued)

Item	Total ($n = 176$)	Shock group ($n = 53$)	Non-shock group ($n = 123$)	T/x^2/z value	*P*-value
SCr [umol/L,M(QL, QU)]	101.00 (74.25, 188.50)	149.47 (84.00, 223.00)	92.00 (71.00, 151.00)	3.11	0.002
PCT [ug/L,M(QL, QU)]	37.27 (7.82, 56.07)	45.41(24.26, 109.30)	27.85 (5.64, 45.41)	3.79	<0.001
CRP (mg/L, $\bar{x}\pm s$)	172.78 ± 77.02	200.11 ± 80.94	161 ± 72.48	3.17	0.002
Mortality [cases (%)]	20(11.40%)	11(20.80%)	9(7.30%)	6.640	0.01

APACHE-II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; GCS, Glasgow Coma Scale; HR, heart rate; RR, respiratory rate; MAP, mean arterial pressure; Na, sodium ion; K, potassium ion; PLT, platelet count; Alb, albumin; PaO2/FiO2, oxygenation index; Lac, blood lactate; TBIL, total bilirubin; SCr, serum creatinine; PCT, procalcitonin; CRP, C-reaction protein; 1 mmHg=0.13 3kPa.

The optimal cut-off value of the continuous index is determined and discretized

ROC curve was used to analyze the continuous indicators, including highest HR, GCS score, Lac, SCr, PCT, CRP, highest K^+, Alb, pH, SOFA score, and APACHE-II score (Table 2). The cut-off value corresponding to the maximum value of the Jorden index was taken as the diagnostic cut-off point to determine the optimal cut-off value (highest HR: 105 beats/min, Lac: 5.75 mmol/L, SCr: 116.5 umol/L, PCT: 41.47 ug/L, CRP: 222.5 mg/L, highest K+: 4.35 mmol/L, Alb: 18.15 g/L, pH: 7.28, PaO2/FiO2: 171.75 mmHg, GCS score: 14.5 points, SOFA score: 8.88 points, APACHE -II score: 22.5 points), and transformed into dichotomous data according to clinic.

Univariate logistic regression analysis was used to screen the risk factors of septic shock in patients with DTP

Univariate Logistic regression analysis was used to screen the risk factors affecting the occurrence of septic shock (Table 3): With the occurrence of septic shock as the factor variable, univariate Logistic regression analysis was performed on the above discrete indicators (highest HR ≥ 105 beats/min, GCS score ≤14 points, Lac ≥5.75 mmol/L, SCr ≥116.5 umol/L, PCT ≥ 41.47 ug/L, CRP ≥ 222.5 mg/L, highest K^+ ≥ 4.35 mmol/L, Alb ≤ 18.15 g/L, pH ≤ 7.28,PaO2/FiO2 ≤ 171.75 mmHg, SOFA score ≥8.88 points, APACHE-II score ≥22.5 points), and the results were all statistically significant indicators (all $P < 0.05$).

Multivariate logistic regression analysis was used to screen the independent risk factors of septic shock in patients with DTP

With the occurrence of septic shock as the dependent variable, the above discrete indicators (highest HR ≥ 105 beats/min, GCS score≤14 points, Lac ≥ 5.75 mmol/L, SCr ≥ 116.5 umol/L, PCT ≥ 41.47 ug/L, CRP ≥ 222.5 mg/L, highest K^+ ≥ 4.35 mmol/L, Alb ≤ 18.15 g/L, pH ≤ 7.28,PaO2/FiO2 ≤ 171.75 mmHg, SOFA score ≥8.88 points, APACHE-II score ≥22.5 points) were included in the multivariate Logistic regression equation for analysis (Table 4). The independent variables were screened by Forward stepwise regression (LR). Independent risk factors of septic shock were: highest HR ≥ 105 beats/min (odds ratio (OR) = 2.977, 95% confidence interval (95% CI) was 1.405∼6.311, $P = 0.004$), GCS score ≤14 points (OR = 2.494, 95% CI was 1.127∼5.522, $P = 0.024$), Lac ≥ 5.75 mmol/L (OR = 4.907, 95%CI was 1.490∼16.165), PCT ≥ 41.47 ug/L (OR = 2.821, 95%CI was 1.321∼6.028, $P = 0.007$), CRP ≥ 222.5 mg/L (OR = 3.298, 95% CI was 1.401–7.760, $P = 0.006$).

Determination of the score of each index

The regression coefficient of the β value obtained by Logistic regression analysis was assigned to calculate the ratio of the β value of the screened variables to the minimum β value and determine the score of the calculated ratio (Table 5). Finally, the clinical diagnostic score system of shock in patients with DTP was successfully constructed: the highest HR ≥ 105 beats /min (one point), GCS score ≤14 points (one point), Lac ≥ 5.75 mmol/L (2 points), PCT ≥ 41.47 ug/L (1 point),

TABLE 2 The optimal cut-off value and assignment of continuous indicators.

Indicator	Optimal cut-off	Assignment
Highest HR	≥105 beats/min	≥105 beats/min = 1,<105 beats/min = 0
Lac	≥5.75 mmol/L	≥5.75 mmol/L = 1,<5.75 mmol/L=0
SCr	≥116.5 umol/L	≥116.5 umol/L = 1,<116.5 umol/L = 0
PCT	≥41.47 ug/L	≥41.47 ug/L= 1,<41.47 ug/L= 0
CRP	≥222.5 mg/L	≥222.5 mg/L = 1,<222.5 mg/L = 0
Highest K+	≥4.35 mmol/L	≥4.35 mmol/L = 1,<4.35 mmol/L = 0
Alb	≤18.15 g/L	≤18.15 g/L = 1,>18.15 g/L = 0
pH	≤7.28	≤7.28 = 1,>7.28 = 0
PaO2/FiO2	≤171.75 mmHg	≤171.75 mmHg=1,>171.75 mmHg =0
GCS score	≤14 points	≤14 points =1,>14 points=0
SOFA score	≥8.88 points	≥8.88 points =1,<8.88 points=0
APACHE-II score	≥22.5 points	≥22.5 points =1,<22.5 points=0

APACHE-II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; GCS, Glasgow Coma Scale; HR, heart rate; K^+, serum potassium ion concentration; Alb, albumin; Lac, blood lactate; SCr, serum creatinine; PCT, procalcitonin; CRP, C-reaction protein; 1 mmHg=0.133 kPa.

TABLE 3 Univariate logistic regression analysis on the occurrence of septic shock.

Variable	β value	S $\bar{x}$	X2 value	OR value	95%CI	*P*-value
Highest HR ≥ 105 beats/min	1.238	0.368	11.332	3.447	1.677∼7.085	0.001
Lac ≥ 5.75 mmol/L	1.631	0.538	9.171	5.107	1.778∼14.673	0.002
SCr ≥ 116.5 umol/L	0.960	0.340	7.968	2.613	1.341∼5.089	0.005
PCT ≥ 41.47 ug/L	1.319	0.352	14.033	3.739	1.875∼7.456	<0.001
CRP ≥ 222.5 mg/L	1.248	0.388	10.368	3.484	1.630∼7.450	0.001
Highest K^+ ≥ 4.35 mmol/L	1.080	0.394	7.531	2.944	1.362∼6.368	0.006
Alb ≤ 18.15 g/L	0.884	0.340	6.774	2.421	1.244∼4.712	0.009
pH ≤ 7.28	1.357	0.374	13.157	3.885	1.866∼8.087	<0.001
PaO2/FiO2 ≤ 171.75 mmHg	1.304	0.357	13.333	3.683	1.829∼7.415	<0.001
GCS score ≤14 points	0.976	0.360	7.345	2.653	1.310∼5.373	0.007
SOFA score ≥8.88 points	2.033	0.410	24.607	7.639	3.421∼17.058	<0.001
APACHE-II score ≥22.5 points	1.711	0.385	19.781	5.534	2.604∼11.763	<0.001

APACHE-II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; GCS, Glasgow Coma Scale; HR, heart rate; K+, serum potassium ion concentration; Alb, albumin; Lac, blood lactate; SCr, serum creatinine; PCT, procalcitonin; CRP, C-reaction protein; 1 mmHg=0.133 kPa; OR, odds ratio; 95% CI was 95% confidence interval.

CRP ≥ 222.5 mg/L (one point), and the total score was 6 points.

Diagnostic efficacy

The scores of all patients were calculated according to the above-established scoring system for the clinical diagnosis of shock in patients with DTP; the clinical diagnostic value of shock was evaluated by the ROC curve (Figure 2). The results showed that the AUC of the scoring system for the septic shock diagnosis was 0.789, the 95% CI was 0.717–0.860 ($P < 0.001$). When the optimal cut-off value was 2.5 points, its sensitivity and specificity were 54.70 and 87.80%, respectively.

Discussion

In this study, an early warning scoring system for septic shock in patients with DTP was successfully established based on general demographic data, perforation-related information, vital signs, common laboratory indicators, GCS score, APACHE-II score, and SOFA score. Early warning score of septic shock included: DTP = highest HR ≥ 105 beats/min (one point) + GCS score ≤14 points (one point) + Lac≥5.75 mmol/L (two points) + PCT ≥ 41.47 ug/L (one point)+CRP ≥ 222.5 mg/L (one point). When the optimal cut-off value was 2.5 points, the sensitivity and specificity were 54.70 and 87.80%, respectively. The early warning scoring system for septic shock in DTP will provide more

TABLE 4 Multivariate logistic regression analysis on the occurrence of septic shock.

Variable	β value	S x̄	X2 value	OR value	95%CI	*P*-value
Highest HR ≥ 105 beats/min	1.091	0.383	8.101	2.977	1.405∼6.311	0.004
Lac≥5.75 mmol/L	1.591	0.608	6.838	4.907	1.49∼16.165	0.009
PCT≥41.47 ug/L	1.037	0.387	7.172	2.821	1.321∼6.028	0.007
CRP≥222.5 mg/L	1.193	0.437	7.467	3.298	1.401∼7.76	0.006
GCS score ≤14 points	0.914	0.405	5.082	2.494	1.127∼5.522	0.024

HR, heart rate; GCS, Glasgow Coma Scale; Lac, blood lactate; PCT, procalcitonin; CRP, C-reactive protein; OR, odds ratio; 95% CI was 95% confidence interval.

TABLE 5 Coefficients and scores of diagnostic indicators of septic shock in patients with DTP.

Indicator	β-value	Ratio	Score
Highest HR ≥ 105 beats/min	1.091	1.194	1
Lac≥5.75 mmol/L	1.591	1.741	2
PCT≥41.47 ug/L	1.037	1.135	1
CRP≥222.5 mg/L	1.193	1.305	1
GCS score ≤14 points	0.914	1.000	1
Total score			6

HR, heart rate; GCS, Glasgow Coma Scale; Lac, blood lactate; PCT, procalcitonin; CRP, C-reactive protein; blank represented none.

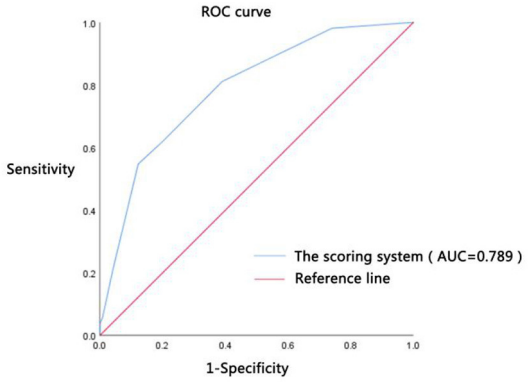

FIGURE 2
Diagnostic efficacy. ROC curve was the receiver operating characteristic curve; AUC was the area under the ROC curve; the scoring system was constructed by the highest HR ≥ 105 beats/min (1 point), Lac ≥ 5.75 mmol/L (two points), PCT ≥ 41.47 ug/L (one point), CRP ≥ 222.5 mg/L (one point), and GCS score ≤14 points (one point).

possibilities for the treatment and diagnosis of patients with DTP.

Tachycardia is a warning sign of internal metabolic stress (23). Persistent tachycardia often suggests a poor prognosis in patients with septic shock (24). Songne *et al.* (25) found that HR > 94 beats/min was a significant predictor of failure of non-surgical treatment in patients with perforated peptic ulcers. Moreover, Møller et al. (26) suggested that tachycardia was one of the poor prognostic factors in patients with perforated peptic ulcers. Our study showed that the highest HR ≥ 105 beats/min was an independent risk factor for septic shock in patients with DTP, which was consistent with previous findings (24–26). Therefore, for patients with DTP, the HR should be closely monitored after admission.

Consciousness change is one of the three major clinical windows for assessing organ perfusion in patients with septic shock (27). Various scores associated with sepsis prognosis, including the SOFA score (28), APAPHE-II score (29), and the National Early Warning Score (NEWS) (30), have been used to assessing patient sanity with GCS score. Multiple studies have confirmed that GCS scores are associated with poor prognosis in patients with sepsis. In 1993, Basto et al. (31) found that lower GCS scores associated with sepsis were associated with higher mortality. A recent study by Wu et al. (32) confirmed that the GCS score was an important risk factor for predicting death in patients with sepsis. However, in the diagnostic criteria for septic shock proposed in Sepsis-3.0 (22), the GCS score is not a necessary condition for the diagnosis of septic shock but one of the detection items of SOFA score and has an auxiliary diagnostic value for septic shock. This study confirmed that a GCS score ≤14 points can be used as an independent risk factor for septic shock in patients with DTP, suggesting that consciousness change has a stronger early predictive value for patients with DTP. In addition, consciousness change was the manifestation of insufficient central perfusion in patients with sepsis, which was easily observed in clinical practice and had good timeliness and promotion. Therefore, compared with the diagnostic criteria of Sepsis-3.0 (22), the early warning

scoring system of septic shock established in this study could assist clinicians in identifying patients with DTP combined with shock, thus guiding clinical diagnosis and treatment strategies.

Elevated arterial lactate is a manifestation of tissue hypoperfusion. In sepsis-3.0 (22), Lac ≥ 2.0 mmol/L is listed as one of the diagnostic criteria for septic shock. As an indicator of tissue hypoperfusion in patients with severe infection associated with patient prognosis, elevated lactate levels could assist clinicians in early predicting outcomes in patients with septic shock (33). In a retrospective study of 1,043 patients with septic shock, Oh et al. found a poorer prognosis in patients with high lactic acid compared to those with low lactic acid, suggesting that arterial lactic acid is a very reliable diagnostic and prognostic predictor of septic shock (34). Moreover, Bakker et al. (35) suggested that Lac >2 mmol/L is an independent risk factor for death in patients with septic shock. However, this study showed that Lac≥5.75 mmol/L was an independent risk factor for septic shock in patients with DTP, and Lac accounted for a high percentage of the early warning scoring system constructed in this study, suggesting that hyperlactatemia had a good early prediction value for septic shock in DTP patients. However, the optimal cut-off value of lactate in this study was significantly higher than the cut-off value of lactate in sepsis-3.0 (22), and the lactate level in the non-shock group was also significantly higher than the normal range which might be related to the combination of stress hyperlactatemia in patients with DTP. When the digestive tract is perforated, stress factors such as inflammation, pain, and surgical trauma could stimulate the secretion of catecholamines, leading to stress hyperlactatemia. Therefore, in a clinical setting, in addition to actively improving the microcirculation perfusion state, stress factors should also be actively controlled to reduce stress injury and avoid secondary injury caused by excessive resuscitation in patients with DTP complicated with hyperlactatemia.

As rapid and reliable markers of inflammation, serum procalcitonin (PCT) and C-reactive protein (CRP) play irreplaceable roles in diagnosing infectious diseases (36–38) and have a good clinical diagnosis and prognostic value for patients with sepsis and septic shock (39). A prospective study (40) of 78 patients with suspected sepsis admitted to the ICU suggested that PCT had good diagnostic and prognostic value in sepsis and septic shock. In a study of 423 patients with DTP, Grupp et al. (41) confirmed that elevated CRP had a predictive value for adverse outcomes in patients with DTP. In this study, we found that PCT ≥ 41.47 ug/L and CRP≥222.5 mg/L are independent risk factors for septic shock in patients with DTP, which further confirms that elevated levels of PCT and CRP could predict septic shock in patients with DTP. In this study, specific cut-off values of PCT and CRP levels were given, which were higher than those of other site infections. Therefore, it suggested that PCT and CRP might respond differently to infection at different sites, and enteric-borne infection might cause higher levels of PCT and CRP. In addition, it should be noted that since CRP was less specific, surgical trauma and other factors could also affect CRP levels, and reducing the interference of other factors on CRP might help obtain more valuable results.

This study has a few limitations. First, this study was a retrospective single-center study with relatively small sample size. Thus, a large-scale multi-center study is needed for further verification. Second, all patients included in this study were admitted to ICU, and those not admitted to ICU were excluded, which might lead to selection bias and affect the clinical characteristics of the non-shock group. Third, patients receiving antibiotics were not excluded in this study, which might affect the experimental results. However, since most patients with DTP in our hospital received emergency surgical treatment immediately after admission, the effect of antibiotic treatment on the experimental results should be relatively small based on the actual situation. Fourth, due to the limited sample size, this study has not been validated, which will limit the diagnostic efficiency and clinical application of the early warning scoring system. We will make further improvements in future larger studies.

In conclusion, the highest HR ≥ 105 beats/min, GCS score ≤14 points, Lac ≥ 5.75 mmol/L, PCT≥ 41.47 ug/L, CRP≥222.5 mg/L were independent risk factors for septic shock in patients with DTP. The early warning scoring system of septic shock in patients with DTP constructed based on these risk factors showed its certain clinical value, providing early warning indicators for clinicians to identify patients with DTP complicated with shock, which might improve the prognosis of patients. These indicators are easy to obtain in clinical practice and have been used in clinical practice for a long time, so they have a good promotion. The establishment of a scoring system based on common indicators may improve the prognosis of patients with septic shock in DTP, which is expected to contribute to the standardization of clinical teaching and practice of intensive care medicine and anesthesiology.

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 Ethics Committee of Fujian Provincial Hospital, Fuzhou, China. The Ethics Committee waived the requirement of written informed consent for participation.

Author contributions

PC and JG collected study data and drafted the present manuscript. XS revised the manuscript. 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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References

1. Chen H, Zhang H, Li W, Wu S, Wang W. Acute gastrointestinal injury in the intensive care unit: a retrospective study. *Ther Clin Risk Manag.* (2015) 11:1523–9. doi: 10.2147/TCRM.S92829

2. Tarasconi A, Coccolini F, Biffl WL, Tomasoni M, Ansaloni L. Picetti E, et al. Perforated and bleeding peptic ulcer: WSES guidelines. *World J Emerg Surg.* (2020) 15:019–0283. doi: 10.1186/s13017-019-0283-9

3. Lau JY, Sung J, Hill C, Henderson C, Howden CW, Metz DC. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality. *Digestion.* (2011) 84:102–13. doi: 10.1159/000323958

4. Søreide K, Thorsen K, Harrison EM, Bingener J, Møller MH, Ohene-Yeboah M, et al. Perforated peptic ulcer. *Lancet.* (2015) 386:1288–98. doi: 10.1016/S0140-6736(15)00276-7

5. Daniel VT, Wiseman JT, Flahive J, Santry HP. Predictors of mortality in the elderly after open repair for perforated peptic ulcer disease. *J Surg Res.* (2017) 215:108–13. doi: 10.1016/j.jss.2017.03.052

6. Søreide K, Thorsen K, Søreide JA. Strategies to improve the outcome of emergency surgery for perforated peptic ulcer. *Br J Surg.* (2014) 101:51–64. doi: 10.1002/bjs.9368

7. Xie F, Yun H, Bernatsky S, Curtis JR. Brief report: risk of gastrointestinal perforation among rheumatoid arthritis patients receiving tofacitinib, tocilizumab, or other biologic treatments. *Arthritis Rheumatol.* (2016) 68:2612–7. doi: 10.1002/art.39761

8. Gisbert JP, Legido J, García-Sanz I, Pajares JM. Helicobacter pylori and perforated peptic ulcer prevalence of the infection and role of non-steroidal anti-inflammatory drugs. *Dig Liver Dis.* (2004) 36:116–20. doi: 10.1016/j.dld.2003.10.011

9. Kujath P, Schwandner O, Bruch HP. Morbidity and mortality of perforated peptic gastroduodenal ulcer following emergency surgery. *Langenbecks Arch Surg.* (2002) 387:298–302. doi: 10.1007/s00423-002-0331-9

10. Hermansson M, Staël von Holstein C, Zilling T. Peptic ulcer perforation before and after the introduction of H2-receptor blockers and proton pump inhibitors. *Scand J Gastroenterol.* (1997) 32:523–9. doi: 10.3109/00365529709025093

11. Chan WH, Wong WK, Khin LW, Soo KC. Adverse operative risk factors for perforated peptic ulcer. *Ann Acad Med Singap.* (2000) 29:164–7.

12. Rajesh V, Chandra SS, Smile SR. Risk factors predicting operative mortality in perforated peptic ulcer disease. *Trop Gastroenterol.* (2003) 24:148–50.

13. Kocer B, Surmeli S, Solak C, Unal B, Bozkurt B, Yildirim O, et al. Factors affecting mortality and morbidity in patients with peptic ulcer perforation. *J Gastroenterol Hepatol.* (2007) 22:565–70. doi: 10.1111/j.1440-1746.2006.04500.x

14. Deus Fombellida J, Gil Romea I, Moreno Mirallas MJ, Urieta Carpi A. Risk factors in the surgical management of perforated duodeno-pyloric ulcer. *Rev Esp Enferm Dig.* 1998.90:503-13.

15. Madiba TE, Nair R, Mulaudzi TV, Thomson SR. Perforated gastric ulcer–reappraisal of surgical options. *S Afr J Surg.* (2005) 43:58–60.

16. Du B, An Y, Kang Y, Yu X, Zhao M, Ma X, et al. Characteristics of critically ill patients in ICUs in mainland China. *Crit Care Med.* (2013) 41:84–92. doi: 10.1097/CCM.0b013e31826a4082

17. Møller MH, Adamsen S, Thomsen RW, Møller AM. Multicentre trial of a perioperative protocol to reduce mortality in patients with peptic ulcer perforation. *Br J Surg.* (2011) 98:802–10. doi: 10.1002/bjs.7429

18. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock:2016. *Intensive Care Med.* (2017) 43:304–77. doi: 10.1007/s00134-017-4683-6

19. Arora R, Campbell JP, Simon G, Sahni N. Does serum procalcitonin aid in the diagnosis of bloodstream infection regardless of whether patients exhibit the systemic inflammatory response syndrome? *Infection.* (2017) 45:291–8. doi: 10.1007/s15010-016-0965-0

20. Kim SH, Shin SS, Jeong YY, Heo SH, Kim JW, Kang HK. Gastrointestinal tract perforation: MDCT findings according to the perforation sites. *Korean J Radiol.* (2009) 10:63–70. doi: 10.3348/kjr.2009.10.1.63

21. Hollerweger A, Maconi G, Ripolles T, Nylund K, Higginson A, Serra C, et al. Gastrointestinal Ultrasound (GIUS) in intestinal emergencies - An EFSUMB position paper. *Ultraschall Med.* (2020) 41:646–57. doi: 10.1055/a-1147-1295

22. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus definitions for sepsis and septic shock. *Jama.* (2016) 315:801–10. doi: 10.1001/jama.2016.0287

23. DellaVolpe JD, Moore JE, Pinsky MR. Arterial blood pressure and heart rate regulation in shock state. *Curr Opin Crit Care.* (2015) 21:376–80. doi: 10.1097/MCC.0000000000000239

24. Datta PK, Rewari V, Ramachandran R, Singh PM, Ray BR, Aravindan A, et al. Effectiveness of enteral ivabradine for heart rate control in septic shock: a randomized controlled trial. *Anaesth Intensive Care.* (2021) 49:366–78. doi: 10.1177/0310057X211009913

25. Songne B, Jean F, Foulatier O, Khalil H, Scotté M. Non operative treatment for perforated peptic ulcer: results of a prospective study. *Ann Chir.* (2004) 129:578–82. doi: 10.1016/j.anchir.2004.06.012

26. Møller MH, Adamsen S, Thomsen RW, Møller AM. Preoperative prognostic factors for mortality in peptic ulcer perforation: a systematic review. *Scand J Gastroenterol.* (2010) 45:785–805. doi: 10.3109/00365521003783320

27. Corradi F, Via G, Tavazzi G. What's new in ultrasound-based assessment of organ perfusion in the critically ill: expanding the bedside clinical monitoring window for hypoperfusion in shock. *Intensive Care Med.* (2020) 46:775–9. doi: 10.1007/s00134-019-05791-y

28. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ

dysfunction/failure. on behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* (1996) 22:707–10. doi: 10.1007/BF01709751

29. Giamarellos-Bourboulis EJ, Norrby-Teglund A, Mylona V, Savva A, Tsangaris I, Dimopoulou I, et al. Risk assessment in sepsis: a new prognostication rule by APACHE II score and serum soluble urokinase plasminogen activator receptor. *Crit Care.* (2012)16:1. doi: 10.1186/cc11463

30. Royal College of Physicians National Early Warning Score (NEWS) 2: Standardizing the Assessment of Acute-Illness Severity in the NHS. *Updated Report of a Working Party* London: RCP (2017).

31. Bastos PG, Sun X, Wagner DP, Wu AW, Knaus WA. Glasgow Coma Scale score in the evaluation of outcome in the intensive care unit: findings from the Acute Physiology and Chronic Health Evaluation III study. *Crit Care Med.* (1993) 21:1459–65. doi: 10.1097/00003246-199310000-00012

32. Wu Y, Huang S, Chang X. Understanding the complexity of sepsis mortality prediction via rule discovery and analysis: a pilot study. *BMC Med Inform Decis Mak.* (2021) 21:334. doi: 10.1186/s12911-021-01690-9

33. Trzeciak S, Dellinger RP, Chansky ME, Arnold RC, Schorr C, Milcarek B, et al. Serum lactate as a predictor of mortality in patients with infection. *Intensive Care Med.* (2007) 33:970–7. doi: 10.1007/s00134-007-0563-9

34. Oh DH, Kim MH, Jeong WY, Kim YC, Kim EJ, Song JE, et al. Risk factors for mortality in patients with low lactate level and septic shock. *J Microbiol Immunol Infect.* (2019) 52:418–25. doi: 10.1016/j.jmii.2017.08.009

35. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg.* (1996) 171:221–6. doi: 10.1016/S0002-9610(97)89552-9

36. Schlattmann P, Brunkhorst FM. Procalcitonin as a diagnostic marker for sepsis. *Lancet Infect Dis.* (2014) 14:189. doi: 10.1016/S1473-3099(13)70325-6

37. Walker C. Procalcitonin-guided antibiotic therapy duration in critically ill adults. *AACN Adv Crit Care.* (2015) 26:99–106. doi: 10.4037/NCI.0000000000000079

38. Du Clos TW, Mold C. C-reactive protein: an activator of innate immunity and a modulator of adaptive immunity. *Immunol Res.* (2004) 30:261–77. doi: 10.1385/IR:30:3:261

39. Cui N, Zhang H, Chen Z, Yu Z. Prognostic significance of PCT and CRP evaluation for adult ICU patients with sepsis and septic shock: retrospective analysis of 59 cases. *J Int Med Res.* (2019) 47:1573–9. doi: 10.1177/0300060518822404

40. Harbarth S, Holeckova K, Froidevaux C, Pittet D, Ricou B, Grau GE, et al. Diagnostic value of procalcitonin, interleukin-6, and interleukin-8 in critically ill patients admitted with suspected sepsis. *Am J Respir Crit Care Med.* (2001) 164:396–402. doi: 10.1164/ajrccm.164.3.2009052

41. Grupp K, Grotelüschen R, Uzunoglu FG, Hofmann B, König A, Perez D, et al. C-reactive protein in the prediction of localization of gastrointestinal perforation. *Eur Surg Res.* (2019) 60:179–85. doi: 10.1159/000501806

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Epidemiological analysis of septic shock in the plateau region of China

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Purpose: Little epidemiological data exist on patients with severe infection in the plateau region of China, and the data that do exist are lacking in quality. Using the medical records of patients with severe infection in the Department of Intensive Medicine (intensive care unit; ICU) of the People's Hospital of Tibet Autonomous Region, this study analyzed the epidemiological and clinical characteristics of patients with septic shock in plateau area (Tibet), with the ultimate aim of reducing the incidence and mortality from this condition.

Methods: Clinical data on 137 patients with septic shock in the studied ICU from November 2017 to October 2019 were retrospectively analyzed using SPSS, Version 21.0.

Results: Among the 137 patients with septic shock, there were 47 survivors and 90 in-hospital or post-discharge deaths. There were 91 male patients and 46 female patients. The incidence of septic shock was 11.3%, and mortality rate was 65.7%. Median age was 55 years old, median APACHE-II score on the day of admission was 17, median SOFA score was 11, and median number of organ injuries was one. APACHE-II score ($P = 0.02$), SOFA score ($P < 0.001$), and the number of organ injuries ($P < 0.001$) were higher among patients who died than among survivors. The infections were mainly pulmonary and abdominal, and the main pathogen was gram-negative bacteria.

Conclusion: The incidence and mortality of septic shock in ICU wards in Tibet are very high. The APACHE-II score, SOFA score, and the number of organ damage on the first day after diagnosis are independent risk factors for septic shock. To some extent, this study reflects the epidemiological characteristics of septic shock in the plateau region of China (≥ 3,650 m above sea level) and provides data that can support the prevention and treatment of sepsis in the future. More and deeper epidemiological studies of septic shock are necessary.

KEYWORDS

high altitude, septic shock, incidence, mortality, risk factors

Introduction

Sepsis is a life-threatening organ dysfunction caused by the host's response to an infection (1). Sepsis is one of the main fatal diseases for patients in intensive care units (ICUs) (1, 2) and is associated with a significant disease burden and negative economic impact (3). The number of sepsis patients worldwide exceeds 19 million each year, six million of whom die. Worldwide, the sepsis mortality rate exceeds 25%, and about three million patients with sepsis who survive have cognitive impairment (4).

At present, the world pays significant attention to septic shock, and research on the epidemiology of septic shock has gradually increased; however, most of these studies have been conducted in developed countries, primarily in Europe and the United States, and only a few studies on the incidence of sepsis in ICUs have been carried out in mainland China. Research on the sepsis mortality in the whole world has concentrated on tertiary teaching hospitals in large cities (5), and data are particularly scarce for plateau areas ($\geq$ 3,650 m above sea level), where the economy is less developed and the distribution of medical resources is unbalanced. Tibet is located in China's southwestern frontier, which has a large area and is sparsely populated. Overall, transportation in the region is inconvenient, and the distribution of medical resources is unbalanced. Most primary hospitals in this area do not have the ability to identify and treat patients with septic shock, who need to be treated in a Grade A hospital. The Department of Critical Care Medicine of the People's Hospital of Tibet Autonomous Region is the first established relatively complete department of its kind in Tibet; thus, most patients with severe infections are treated here. This study first analyzed the medical records of patients with septic shock admitted to this ICU in Tibet which is one of the typical plateau area around world to clarify their epidemiological and clinical features, with the ultimate aim of preventing septic shock and reducing sepsis. The current incidence of shock and the present case fatality rate can serve as reference values for these efforts.

Materials and methods

Sample and data

We used data on 137 patients with septic shock admitted to the Department of Intensive Medicine of the People's Hospital of Tibet Autonomous Region from November 2017 to October 2019.

Patients diagnosed with septic shock in the ICU or during hospitalization were included in the study. As for diagnostic criteria, all included patients met the criteria for the diagnosis of septic shock specified in Sepsis 3.0, which was issued jointly by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine in 2016 (6), patients with infection or suspected infection who develop sepsis-related sequential organ failure, as determined by the Sequential Organ Failure Assessment (SOFA) score increasing $\geq$ 2 points from baseline, can be diagnosed as having sepsis. Septic shock is persistent hypotension caused by sepsis. Patients with septic shock require vasoactive drugs to maintain a mean arterial pressure $\geq$ 65 mmHg (1 mmHg = 0.133 kPa) and blood lactate concentration $>$ 2 mmol/L after full-volume resuscitation. Patients under 15 years of age and those with $<$ 24 h of hospitalization were excluded from the study.

Research methods

Data collection

Data were collected on associated infection indicators [WBC, PLT, procalcitonin (PCT), and CRP], as well as patient age, sex, outcome of hospitalization, major diagnosis, site of infection, underlying disease, pathogens, number of organ injuries, Acute Physiology and Chronic Health Enquiry (APACHE-II) score on the first day of admission, Sequential Organ Failure Assessment (SOFA) score, use of continuous renal replacement therapy (CRRT), and total mechanical ventilation time. At the hospital level, we collected data on the total number of patients admitted and the total number of patients with septic shock.

Zero-time point

The zero-time point was set as the time when the patient was admitted to the ICU for septic shock or the time of diagnosis of septic shock in the ICU. For patients with multiple infections, only the time of the first septic shock was included in the analysis.

Data analysis

The data were analyzed using SPSS, Version 21.0 software. Data on normally distributed variables are expressed as means and standard deviations. For non-normally distributed variables, we present medians and interquartile ranges (IQRs). The independent *t*-test was used for normally distributed variables, and the Mann–Whitney *U* test was used for non-normally distributed variables. For categorical variables, we adopted the chi-square test or Fisher's exact test. We conducted a multiple logistic regression analysis to determine the independent predictors of in-hospital mortality in patients with septic shock, and results are presented as odds ratios and the corresponding 95% confidence intervals. Variables with $P \leq 0.2$ in the univariate analysis, such as demographic characteristics, underlying diseases, disease severity, admission status, and prognosis, were included

TABLE 1 Percentage distribution of age by outcome of septic shock.

Age	Total ($n = 137$)	Survival group ($n = 47$)	Death group ($n = 90$)	*P* value
Oct-40	25 (18.2%)	10 (21.3%)	15 (16.7%)	0.672
41–60	56 (40%)	20 (42.6%)	36 (40%)	
>60	56 (40.9%)	17 (36.2%)	39 (42.2%)	

in the multivariate model. The Hosmer–Lemeshow test was used to evaluate the goodness of fit of the regression model. Unmatched comparisons were performed, and all significance tests were two-tailed, with $P < 0.05$ considered statistically significant.

Related explanations

(1) Patients with septic shock were divided into those who died and those who survived depending on whether they died within 28 days of the zero-time point.

(2) Because of regional and religious customs, the families of critically ill patients in the study area relatively frequently request the patients' discharge. Telephone follow-up indicated that more than 98% of self-discharged patients died within 28 days of discharge; therefore, in this study, self-discharged patients were considered to have the outcome of death within 28 days. These cases were combined with in-hospital deaths for total mortality.

Results

Population characteristics and incidence of septic shock

Table 1 shows that, from November 2017 to October 2019, 1,216 patients were admitted to the studied ICU, and admissions for septic shock accounted for 137 patients. A total of 47 patients with septic shock were in the survivor group. The incidence of septic shock was 11.3%, and the death of 90 patients corresponded to a case fatality rate of 65.7%. Compared with related reports in China and elsewhere, this case fatality rate is notably high (6). Among the 137 patients with septic shock, there were 91 male patients and 46 female patients, and the median age was 55 years old (QR: 45.5–68.5). There were 56 patients aged over 60 years, and 39 of these patients died, accounting for 42.2% of all deaths. The *P* value for the comparison of the survivors and deaths was > 0.05, indicating no statistically significant difference (see Table 1). About half (47.4%) of the patients with septic shock had chronic diseases, mainly cardiovascular and respiratory diseases. On the day of admission, median APACHE-II score was 17 points (IQR: 12–22), median SOFA score was 17 points (IQR: 8–13), median number of organ injuries was one (IQR: 0–3), and median duration of mechanical ventilation was 55 h (IQR: 11.5–154). There were significant differences between those who survived and those who died in median APACHE-II score ($P = 0.02$), median SOFA score ($P < 0.001$), and median number of organ injuries ($P < 0.001$), but not in median duration of mechanical ventilation ($P = 0.889$). See Table 2 for further baseline information.

Infection site and pathogen

The lungs (40.9%) and abdominal cavity (15.3%) were the most common sites of infection in patients with septic shock, as shown in Table 3. Among 34 patients, the infection site comprised two or more mixed infections. There were six cases of influenza infection (4.4%; mortality = 100%). Among the 137 patients with microbial culture, 38 (27.7%) were isolated from gram-negative bacteria, 13 (9.5%) were isolated from gram-positive bacteria, and 10 (7.3%) were isolated from fungi. In 46 cases (33.6%), there was a mixed infection of multiple bacteria (see Tables 3, 4).

Mortality for septic shock

Among the 137 patients with septic shock, 90 died in the hospital or after ceasing treatment because of excessive illness or folk customs. The overall mortality was 65.7%.

Median APACHE-II score in the first 24 h after diagnosis of septic shock was higher among those who died (17; IQR: 13.75–23.25) than among those who survived (13; IQR: 9–20; $P = 0.02$). Likewise, for SOFA score, the median was higher among patients who died (11; IQR: 9–14) than among those who survived (9; IQR: 7–11; $P < 0.001$). The median number of organ injuries was also higher among those who died (2; IQR: 1–3) than among those who survived (0; IQR: 0–2; $P < 0.01$). In terms of the infection index, median PCT was significantly higher among those who died (5.08; IQR: 0.59–32.46) than among those who survived (0.82; IQR: 0.16–16.5; $P < 0.05$; see Table 2).

Risk factors for death from septic shock

The death of patients with septic shock was used as the dependent variable, and indicators that were meaningful in the univariate analysis were used as the independent variables. The multivariate logistic regression analysis showed that APACHE-II score, SOFA score, and the number of organ injuries were statistically significantly associated with the risk of death from

TABLE 2 Population characteristics by septic shock outcom.

Variable	Total ($n = 137$)	Survivors ($n = 47$)	Deaths ($n = 90$)	*P* value
Age, median (IQR)	55 (45.5–68.5)	54 (45–67)	55 (45.5–69.5)	0.812
Gender				
Male	91 (66.4)	30 (21.9%)	61 (44.5%)	0.705
Female	46 (33.6)	17 (12.4%)	29 (21.2%)	0.589
APACHE-II score (IQR)	17 (12–22)	13 (9–20)	17 (13.75–23.25)	0.02
SOFA (IQR)	11 (8–13)	9 (7–11)	11 (9–14)	0
Number of organ injuries (IQR)	1 (0–3)	0 (0–2)	2 (1–3)	0
Mechanical ventilation				
Yes	117 (85.4%)	37 (27%)	80 (58.4%)	0.13
No	20 (14.6%)	10 (7.3%)	10 (7.3%0)	0.427
Time of use of mechanical ventilation	55 (11.5–154)	63 (4–218)	51 (15.25–144)	0.889
CRRT		0.164		
Yes	128 (93.4%)	82 (59.9%)	46 (33.6%)	0.164
No	9 (6.6%)	1 (0.7%)	8 (5.8%)	0.037
WBC	11 (5–17.4)	11 (7–15.9)	11.1 (6.23–18)	0.73
PLT	106 (53–177)	124 (66–210)	97.5 (38.5–226.9)	0.117
PCT	3(0.31–21.54)	0.82 (0.16–16.5)	5.08 (0.59–32.46)	0.042
CRP	136.24 (66.3–220.7)	134.61 (51.97–192.66)	136.24 (68.24–253.13)	0.103
Basic diseases				
Cardiovascular diseases	23 (16.8%)	9 (6.6%)	14 (10.2%)	0.234
Respiratory diseases	16 (11.7%)	3 (2.2%)	13 (9.5%)	0.593
Endocrine diseases	7 (5.1%)	4 (2.9%)	3 (2.2%)	0.142
Cardiovascular + endocrine	8 (5.8%)	2 (1.5%)	6 (4.4%)	0.468
Diseases				
Biliary system	4 (2.9%)	0	4 (2.9%)	0.568
Gastric and duodenal diseases	2 (1.5%)	0	2 (1.5%)	0.191
Disease				
Chronic diseases	1 (0.7%)	0	1 (0.7%)	0.303
Tumor and immune diseases	4 (2.9%)	1 (0.7%)	3 (2.2%)	0.163
Basic diseases	72 (52.6%)	28 (20.4%)	44 (32.1%)	0.399

TABLE 3 Distribution of type septic shock infection by outcome.

	Total ($n = 137$)	Survival group ($n = 40$)	Death group ($n = 97$)	*P* value
Pulmonary infection	56 (40.9%)	19 (40.4%)	37 (41.1%)	0.267
Intraperitoneal infection	21 (15.3%)	9 (19.2%)	12 (13.3%)	0.18
Urinary infections	1 (0.7%)	1 (2.1%)	0	0.083
Blood flow infection	6 (4.4%)	0	6 (6.7%)	1
Intracranial infection	3 (2.2%)	2 (4.3%)	1 (1.1%)	0.999
Mixed infection	34 (24.8%)	7 (14.9%)	27 (30%)	0.115
Other	16 (11.7%)	9 (19.1%)	7 (7.8%)	0.015

TABLE 4 Distribution of pathogens in septic shock by outcome.

	Total ($n = 137$)	Survival group ($n = 40$)	Death group ($n = 97$)	*P* value
Negative	30 (21.9%)	10 (7.3%)	20 (14.6%)	0.296
G−	38 (27.7%)	11 (8%)	27 (19.7%)	0.899
G+	13 (9.5%)	8 (5.8%)	5 (3.6%)	0.413
Fungi	10 (7.3%)	3 (2.2%)	7 (5.1%)	0.30
Mixed infection	46 (33.6%)	15 (10.9%)	31 (22.6%)	0.766

TABLE 5 Risk factors for septic shock death.

Risk factors	*M* (IQR)	*P* value	OR (95% CI)
APACHE-II score	17 (12–22)	0.002	1.099 (1.036–1.167)
SOFA score	11 (8–13)	0	1.198 (1.073–1.338)
Number of organ injuries	1 (0–3)	0	1.929 (1.39–2.678)

septic shock. Table 5 presents the analysis of the independent risk factors for death from septic shock.

Discussion

The incidence of septic shock in the ICU was 11.3% (137 cases of septic shock/1,216 total ICU admissions) in this study. The lungs and abdomen were the most common sites of infection; the most frequently observed pathogen was gram-negative bacteria, and most of the patients had mixed infections. There was no significant difference in mortality between patients with underlying diseases and those without underlying diseases (mortality: 32.1% vs. 33.6%, $P > 0.05$); the case fatality rate for septic shock was high, at 65.7% ($n = 90$). APACHE-II score, SOFA score, and the number of organ injuries were higher among patients who died than among those who survived, and the multivariate analysis showed that these variables were independent risk factors for death from septic shock.

Our results are similar to Bin Du's descriptive analysis of sepsis-related mortality in China (7). Sepsis-related mortality was significantly lower in areas with higher disposable income. Increasing mean years of education was negatively associated with sepsis-related mortality. The incidence and mortality found in this study were higher than the those reported by two multi-center surveys of ICUs in mainland China, which reported the total case fatality rate of patients with severe sepsis to be 48.7% and 33.5%—significantly higher than the mortality for severe sepsis in developed countries (8). In Australia and New Zealand, the hospital case fatality rate for severe sepsis declined from 35% in 2000 to 18.4% in 2012; in the United States, the mortality for sepsis (defined by ICD-9-CM) dropped from 27.8% in 1979 to 18.4% in 2012 and then 17.9% in 2000 (9).

There are several reasons that may explain why the incidence and mortality of sepsis is high in the plateau area of China. First, sepsis is a host reaction disorder caused by infection, leading to life threatening organ dysfunction (10). Acute circulatory dysfunction caused by insufficient oxygen delivery and / or impaired cellular oxygen utilization is a major cause of death due to septic shock (11). Microcirculation plays an important role in tissue perfusion; it can ensure that oxygen is delivered to tissues, exchange nutrients and wastes; and regulate inflammation and coagulation. Plateau area is a special geographical environment, with the increase of altitude and the decrease of air pressure, the oxygen content in the air gradually decreases, resulting in a series of hypoxic reactions. The low oxygen content in the atmosphere can significantly reduce the oxygen content of human arterial blood (12). Whether living at high altitude for a long time or entering the plateau rapidly, chronic hypoxia or acute hypoxia, and septic shock, microcirculation is always characteristically changing. The permeability of endothelial barrier plays an important role in maintaining humoral homeostasis and regulating the physiological functions of tissues and organs. Endothelial cells are the main component of microvascular permeability barrier, and endothelial glycocalyx is a layer of glycosaminoglycan and related proteoglycan lining the vascular lumen. In the case of infection and hypoxia (13), the glycocalyx of endothelium degrades greatly, and the permeability of endothelium increases, which leads to the leakage of fluid into the tissue space, resulting in tissue edema; endothelial cells can also stimulate leukocytes to release a large number of inflammatory mediators (TNF-α, IL etc.), at the same time, endothelial cells are over apoptotic, stimulate the expression of adhesion molecules, and release oxygen free radicals, further amplify the role of leukocytes. The phospholipid membrane of apoptotic endothelial cells is exposed to the blood, forming a coagulation promoting reaction surface and activating the coagulation system (14). Hypoxia in high altitude environment will further stimulate capillary cell damage, aggravate microcirculation and cell dysfunction, and eventually lead to organ dysfunction and increased risk of death (12). Second, the Intensive Care Department of the People's Hospital of Tibet Autonomous Region was established relatively recently—in 2008. This hospital is more advanced than other hospitals in the region and treats most patients with severe infections. Therefore, the number of patients with septic shock is higher at the People's Hospital of Tibet Autonomous Region than that at other hospitals in the region, which may contribute to explaining the high incidence observed in the present study (15). Third, many patients can still be treated, despite being critically ill; however, these people are sometimes self-discharged because of religious beliefs and customs. Additionally, some families of critically ill patients choose to abandon treatment

because of the high cost of hospitalization. When they were followed up, the great majority of patients who were self-discharged for these reasons had died. This is also a reason for the relatively high mortality observed in this study. This finding should stimulate autonomous regions, counties, townships, and towns to increase public awareness of disease, strengthen the training of local doctors, and further improve the population's awareness of disease prevention and control. Fourth, in the present study, those aged over 60 years accounted for about 40.9% of the cases and 42.2% of all deaths. The overall population is aging, and older adults are more heavily affected by sepsis, compared with their younger counterparts (4). In older age, organ function declines, immunity is reduced, and the number of underlying diseases increases. After infection, septic shock also tends to be more severe in older adults than in younger people, and it is more difficult to reverse the effects in those of older ages. This may be an additional reason for the high incidence seen in this study. Fifth, we found that 41–60-year-olds made up about 40% of all people with septic shock, and this age group also accounted for 40% of all deaths. The development of bad habits in daily life, such as staying up late, excessive drinking, smoking, the lack of exercise, and other harmful behaviors, worsen the cardiovascular health of adults in middle age. The incidence rates of cardiovascular diseases, endocrine diseases, respiratory diseases, tumors, and other diseases reveal increasing trends, whereas immunity is declining, which increases the susceptibility to infection (16). Higher risk of infection, in turn, increases morbidity and mortality among middle-aged people.

Our study is consistent with the results of some international multi-center studies. We found that the infection site of septic shock is mainly the lungs and abdominal cavity, followed by bloodstream infection. This finding suggests that, when the cause of septic shock is unclear, lung and abdominal infections should be given priority, but other infection sites should not be neglected. Previous studies have reported that 70–80% of cases of septic shock caused by pulmonary infection are acquired in the community, which requires emergency and primary care to become key targets for awareness raising and early management (17). Unbalanced distributions of medical sources and insufficient ratios of medical staff to patients in hospitals are associated with higher incidence of hospital-acquired pneumonia (18). Common causes of nosocomial infection are low levels of awareness of hospital infection prevention and control and poor hand and environmental hygiene. Additionally, critically ill patients in the ICU often require sedation, analgesia, and open airways, all of which reduce their immune defenses. At the same time, because of improper care, bed rest may cause lung consolidation, atelectasis, and gastric juice reflux. If measures are not in place for the prevention and control of hospital infection and bacteria are spread, a sudden increase in bacterial load may result in fatalities (19, 20). Shock induced by abdominal infection is more common in cases of delayed removal of the infected foci and inadequate surgical drainage, resulting in excessive bacterial load and increased mortality. Therefore, early diagnosis of sepsis, timely intervention, drainage of postoperative infections, and reduction of bacterial load are extremely important and should be the focus of continued efforts in the future. Bloodstream infection has a very high mortality among ICU patients—as high as 100% in this study. Therefore, close attention should be paid to aseptic operations during surgeries. In addition, daily skin disinfection should be standardized to reduce the possibility of retrograde bacterial infection.

The results of this study suggest that the pathogen was mainly gram-negative bacteria, which is similar to the results of other research in China. To reduce bias, this study examined pathogenic specimens within 24 h of the diagnosis of septic shock, which facilitates the accurate identification of the pathogenic microorganisms of septic shock and can further guide the correct use of antibiotics. It is not uncommon for the abuse of antibiotics to cause microbial resistance; therefore, the sensible selection of antibiotics is another area requiring continuous efforts in the future.

This study showed that APACHE-II score, SOFA score, and the number of organ injuries were independent risk factors for death from septic shock. Among infection indicators, PCT showed a strong positive correlation. APACHE-II score, which was developed as early as the 1980s, has been widely used in clinical practice. This score performed well in predicting the risk of hospital death, and previous studies have also reported that a higher APACHE-II score often indicates a higher risk of hospital death (21). Increases in SOFA score and in the number of organ injuries often indicate more serious organ failure (22), which significantly affects the patient's ultimate outcome. Therefore, in clinical practice, patients with higher scores and higher infection indexes should receive strict dynamic observation and monitoring to slow the progress of the condition and formulate a reasonable and refined treatment plan.

Conclusion

The incidence and mortality of septic shock in ICU wards in Tibet are very high. The APACHE-II score, SOFA score, and the number of organ damage on the first day after diagnosis are independent risk factors for septic shock. To a certain extent, this study reflects the epidemiological characteristics of septic shock in plateau areas (3,650 m and above), and provides certain data support for the prevention and treatment of sepsis in this region in the future. In the future, it is necessary to carry out more,

more extensive and more in-depth epidemiological studies of septic shock.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

QL is mainly responsible for writing and statistics of articles. LC, XC, and JF are mainly responsible for data collection. GL, WP, WC, and XW are responsible for guiding the collaboration. 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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References

1. Rhodes A, Laura EW, Waleed A, Mitchell ML, Massimo, Richard F, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med.* (2017) 45:486–552. doi: 10.1097/CCM.0000000000002255

2. Rahmel T, Schmitz S, Nowak H. SchepanekK, Bergmann L, Halberstadt P, et al. Long-term mortality and outcome in hospital survivors of septic shock, sepsis, and severe infections: the importance of aftercare. *PLoS ONE.* (2020) 15:e0228952. doi: 10.1371/journal.pone.0228952

3. Levy MM, Dellinger RP, Townsend SR, Linde–Zwirble WT, Marshell JC, Schorr C, et al. The surviving sepsis campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Inten Care Med.* (2010) 36:222–31. doi: 10.1007/s00134-009-1738-3

4. Prescott HC, Angus DC. Enhancing recovery from sepsis. *JAMA.* (2018) 319:62. doi: 10.1001/jama.2017.17687

5. Cheng B, Xie C, Yao S, Wu X, Guo Q, Gu M, et al. Epidemiology of severe sepsis in critically ill surgical patients in ten university hospitals in China. *Crit Care Med.* (2007) 35:2538–46. doi: 10.1097/01.CCM.0000284492.30800.00

6. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA.* (2016) 315:801–10. doi: 10.1001/jama.2016.0287

7. Weng L, Zeng XY, Yin P, Wang LJ, Wang CY, Jiang W, et al. China critical care clinical trials group (CCCCTG). Sepsis-related mortality in China: a descriptive analysis. *Inten Care Med.* (2018) 44:1071–80. doi: 10.1007/s00134-018-5203-z

8. Lagu T, Rothberg MB, Shieh M-S, Pekow PS, Steingurb JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med.* (2012) 40:754–61. doi: 10.1097/CCM.0b013e318232db65

9. Baykara N, Akalin H, Arslantas MK, Hanci V, Caglayan C, Kahveci F, et al. Epidemiology of sepsis in intensive care units in Turkey: a multicenter, point-prevalence study. *Crit Care.* (2018) 22:93. doi: 10.1186/s13054-018-2013-1

10. Colbert JFM, Schmidt EPM. Endothelial and microcirculatory function and dysfunction in sepsis. *Clin Chest Med.* (2016) 37:263–75. doi: 10.1016/j.ccm.2016.01.009

11. Lipinska-Gediga M. Sepsis and septic shock-is a microcirculation a main player? *Anaesthesiol Intensive Ther.* (2016) 48:261–5. doi: 10.5603/AIT.a2016.0037

12. Ma S, Wu T. Microcirculation changes and prevention strategies of septic shock at high altitude. *J. High Altitud Med.* (2015) 25:59–64.

13. Rovas A, Seidel LM, Vink H, Pohlkotter T, Pavenstadt H, Ertmer C, et al. Association of sublingual microcirculation parameters and endothelial glycocalyx dimensions in resuscitated sepsis. *Crit Care.* (2019) 23:260. doi: 10.1186/s13054-019-2542-2

14. Shih C-C, Liu C-M, Chao A, Lee C-T, Hsu Y-C, Yeh Y-C, et al. Matched comparison of microcirculation between healthy volunteers and patients with sepsis. *Asian J Anesthesiol.* (2018) 56:14–22. doi: 10.6859/aja.201803_56(1).0002

15. Zhou Q, Zhang S. Early diagnosis and clinical treatment of acute severe altitude sickness complicated with multiple organ dysfunction syndrome. *Med J Chin PLA.* (2010) 35:1183–6.

16. Stevenson EK, Rubenstein AR, Radin GT, Wiener RS, Walkey AJ. Two decades of mortality trends among patients with severe sepsis: a comparative meta-analysis. *Crit Care Med.* (2014) 42:625–31. doi: 10.1097/CCM.0000000000000026

17. Thompson K, Venkatesh B, Finfer S. Sepsis and septic shock: current approaches to management. *Intern Med J.* (2019) 49:160–70. doi: 10.1111/imj.14199

18. Caraballo C, Jaimes F. Organ dysfunction in sepsis: an ominous trajectory from infection to death. *Yale J Biol Med.* (2019) 92:629–40.

19. Chai W. Issues needing attention in anti-infection treatment of severe patients. *Chin Clin.* (2014) 42:8–10.

20. Dancer SJ, Kramer A. Four steps to clean hospitals: look, plan, clean and dry. *J Hospital Infect.* (2019) 103:e1–8. doi: 10.1016/j.jhin.2018.12.015

21. Huang J, Xaun D, Li X, Ma Li, Zhou Y, Zou H, et al. The value of APACHE II in predicting mortality after paraquat poisoning in Chinese and Korean population: a systematic review and meta-analysis. *Medicine (Baltimore).* (2017) 96:e6838–8. doi: 10.1097/MD.0000000000006838

22. Lambden S, Laterre PF, Levy MM, Francois B. The SOFA score—development, utility and challenges of accurate assessment in clinical trials. *Crit Care.* (2019) 23:374. doi: 10.1186/s13054-019-2663-7

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Intravenous fentanyl vs. topical lignocaine for ProSeal™ laryngeal mask airway insertion with propofol induction

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Insertion of the laryngeal mask airway (LMA) without muscle relaxant requires adequate obtundation of airway reflexes, which may otherwise lead to incorrect or failed LMA placement. This study compared topical lignocaine spray vs. intravenous (IV) fentanyl, during propofol induction for insertion of the ProSeal™ LMA (PLMA). This was a prospective, randomized, double blind study, in ASA I or II patients, for elective or emergency surgery. Seventy patients ($n = 70$) who fulfilled the inclusion criteria were randomly assigned to receive IV fentanyl 2 mcg/kg or topical lignocaine spray 40 mg, prior to anesthesia induction with IV propofol (2–2.5 mg/kg). ProSeal™ LMA insertion condition was regarded optimal in the absence of adverse responses (gag, cough, laryngospasm and body movements), and successful LMA placement at the first attempt. Hemodynamic parameters were recorded and patients were assessed for sore throat and hoarseness post operatively. Seventy patients were analyzed. The number of patients with optimal PLMA insertion conditions were comparable between the groups (60% vs. 57%, $P = 0.808$). All hemodynamic parameters were comparable between groups with the exception of heart rate. Sympathetic obtundation of heart rate was greater with IV fentanyl than topical lignocaine ($P < 0.05$). The proportion of patients with postoperative sore throat significantly increased with the number of insertion attempts ($P < 0.05$). Topical lignocaine spray to the pharynx is as effective, and may be an alternative to IV fentanyl, during propofol induction for PLMA insertion. Success rate and optimal insertion condition at the first attempt, propofol requirement, blood pressure, adverse events and airway complications were comparable. Heart rate obtundation was less with topical lignocaine spray but remained within clinically acceptable values.

KEYWORDS

lidocaine, laryngeal mask, propofol, anesthesia induction, fentanyl

Introduction

The laryngeal mask airway (LMA) is a supraglottic airway device introduced by Brain in 1983 (1). Its insertion does not require laryngoscopy, and supraglottic placement stimulates less airway reflex and sympathetic response than that associated with endotracheal intubation (2). However, adequate suppression of upper airway reflexes is required, as the LMA is usually inserted without muscle relaxant. Insufficient obtundation of airway reflexes may cause the patient to gag and cough, subsequently leading to incorrect LMA placement or insertion failure (3).

Studies have shown that propofol as an anesthetic induction agent provides superior LMA insertion conditions when compared to thiopentone, as it obtunds better the oropharyngeal and cough reflexes, and decreases sensitivity of the upper airway (4, 5). The recommended propofol dose for LMA insertion ranges from 2.5 to 3.5 mg/kg (6). Larger doses of propofol may cause cardio-respiratory depression, and using it as the sole anesthesia induction agent reduces the success rate of LMA insertion (5, 7).

Laryngeal mask airway insertion conditions are improved when propofol is used in combination with drugs such as midazolam, fentanyl, lignocaine and succinylcholine (5, 7). Opioids such as fentanyl decrease propofol requirement and improve LMA insertion conditions (7, 8). However, significant reductions in systolic and mean arterial blood pressures from baseline values, have been reported after fentanyl 2 μg/kg when compared to fentanyl 1 μg/kg, prior to propofol 2.5 mg/kg induction. Although, blood pressure reduction was not clinically relevant and did not require intervention, caution would have to be exercised in selected patients with poor cardiovascular status, where similar reductions in blood pressure could be clinically significant (9).

Topical and intravenous (IV) lignocaine have been used to obtund airway responses such as coughing and bucking during tracheal intubation (10, 11). Ahmed et al. showed that topical lignocaine spray 40 mg at the posterior pharyngeal wall 3 min before anesthesia induction with propofol 2 mg/kg, provided better LMA insertion conditions than propofol co-induction with IV lignocaine (12). Similarly, prior airway topicalization with lignocaine provided excellent LMA insertion conditions, with lower incidence of gag and cough, compared to IV midazolam (13).

Topical lignocaine provides surface anesthesia to the larynx and pharynx by cell membrane stabilization of the laryngeal and pharyngeal musculature, hence eliminating its sensitivity to airway stimulation during LMA insertion (14). Its anesthetic effect on the pharyngeal wall lasts 20–40 min (15), with lower peak plasma concentration than if it were administered parenterally, hence potentially reduces risk of systemic effects (16, 17).

Blood pressure and heart rate increase after LMA insertion, but were short-lived with values returning to baseline within a minute after airway stimulation (18, 19). Intravenous or topical lignocaine reduced the cardiovascular response to tracheal intubation and LMA insertion (10, 12). Baik et al. showed that hemodynamic stability was comparable between topical lignocaine 40 mg and IV lignocaine 1.5 mg/kg, and the former additionally improved LMA insertion conditions (20).

Airway instrumentation is a risk factor for postoperative sore throat, which is a common complaint post general anesthesia (21). Tanaka et al. showed that both topical and systemic lignocaine reduced the incidence of post-intubation sore throat (22).

There have been no studies comparing topical lignocaine vs. IV fentanyl, for LMA insertion. We compared topical lignocaine and IV fentanyl, prior to propofol induction, during insertion of the ProSeal™ LMA (PLMA). The PLMA is a second-generation LMA with a drainage tube which enables drainage of gastric secretions and content, and a rear cuff that allows higher seal pressure than a Classic LMA of equal intra-cuff pressure (23).

We hypothesized that topical lignocaine was as effective as IV fentanyl, before propofol induction, during PLMA insertion.

Materials and methods

This prospective, randomized, double blinded study was carried out in the general operating theaters of Universiti Kebangsaan Malaysia Medical Centre (UKMMC). It was approved by the Dissertation Committee of the Anaesthesiology and Intensive Care Unit, UKMMC, and the Medical Research and Ethics Committee UKMMC (FF-2020-183; JEP-2019-828). We enrolled 70 patients of American Society of Anesthesiologist (ASA) I and II, aged between 18 and 65 years, who had surgery under general anesthesia with the PLMA. Patients with aspiration risk, allergy to the study drugs, body mass index (BMI) > 30 kg/m^2, and cardiac arrhythmias were excluded.

Anesthesia medical officers were briefed on the study, and informed consent obtained from the patients. The patients were randomly allocated into two groups by computer generated randomization table, and fasted 6 h preoperatively. Group 1 patients received IV fentanyl and propofol, and Group 2 received topical lignocaine and propofol.

In the operation theater, standard monitoring which included the non-invasive blood pressure, electrocardiogram and pulse oximetry were applied, and baseline readings documented. The PLMA was lubricated with KY jelly on its dorsal cuff surface, and prepared for insertion with its curved metal introducer. The appropriate size PLMA was selected, based on the manufacturer's recommendation. ProSeal™ LMA insertion was performed by anesthetic medical officers with at least 2 years of experience in anesthesia.

The study drugs were prepared and administered by the investigator who was not blinded to the patient's group allocation. In the operation room, Group 1 patients received 2 ml normal saline (placebo), and Group 2 patients received 2 ml lignocaine 2% (40 mg), delivered *via* the MADgic™ laryngo-tracheal mucosal atomizer. This was done with the patient sitting, while their posterior pharyngeal wall was topicalized bilaterally before anesthesia induction.

Patients in both groups were then pre-oxygenated for 3 min, while allowing the onset of action of topical lignocaine. Induction of anesthesia proceeded in Group 1 with IV fentanyl 2 μg/kg and propofol 2–2.5 mg/kg, and in Group 2 with IV normal saline and propofol 2–2.5mg/kg. All patients were manually ventilated with 100% oxygen, and anesthesia was maintained with sevoflurane to achieve a minimum alveolar concentration (MAC) of 1–1.2. When pupils were central and constricted, and the jaw well relaxed, the PLMA was inserted by the anesthetic medical officer in charge. If during PLMA insertion the patient gagged or coughed, or if there was gross body movement, additional propofol bolus of 0.5 mg/kg was administered. Laryngospasm was managed with additional propofol 0.5 mg/kg bolus and increased sevoflurane concentration. Laryngospasm was defined as the presence of stridor, or other evidence of upper airway obstruction that subsides with deepening of anesthesia (24).

Successful placement of the PLMA was confirmed visually by adequate chest expansion bilaterally, and the capnograph on the monitor during spontaneous or assisted breathing. If the PLMA was malpositioned, it was removed and additional propofol 0.5 mg/kg bolus was administered before subsequent attempts. A maximum of three PLMA insertion attempts were allowed, after which further airway management was left to the discretion of the anesthesia medical officer in charge. These patients were considered as PLMA insertion failure, but were included in the study as PLMA insertion condition was only assessed during the first insertion attempt. Anesthesia was maintained with sevoflurane at 1–1.2 MAC, in 50% oxygen and air.

The anesthesia medical officer graded the first insertion attempt as optimal if there was absence of cough, gag, laryngospasm, or body movement, and when the PLMA was inserted successfully (24). ProSeal™ LMA insertion was graded as not optimal if one or more of the above adverse responses were present, or insertion was unsuccessful at the first attempt. The number of PLMA insertion attempts, PLMA insertion failure and total propofol required were documented.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) and oxygen saturation SpO_2 were recorded by an assistant at pre-induction (baseline), post induction, immediately following ProSeal™ LMA insertion, and every minute thereafter for 5 min.

Postoperative airway complications of sore throat and voice hoarseness were assessed by the anesthesia medical officer after 30 min at the recovery area, and at 24 h postoperatively by the ward staff nurse, who were both blinded to the patient's group allocation. Sore throat was defined as "throat pain or discomfort" while hoarseness was defined as "a change in quality of voice" (25).

Statistical analysis

Sample size was calculated using the computer program Sealed Envelope Ltd. 2012. Power calculator for binary outcome superiority trial was based on the Pocock formula 1983 (26). Gupta et al. compared IV fentanyl 1.5 μg/kg and propofol 2.5 mg/kg vs. ketamine/propofol and butorphanol/propofol combinations for anesthesia induction, and found excellent LMA insertion conditions in 43% of the patients in the fentanyl/propofol group (26). Ahmed S et al. found improved LMA insertion conditions in 83% of patients given topical lignocaine 40 mg and propofol 2 mg/kg, vs. those given IV lignocaine/propofol for anesthesia induction (11). Statistical analysis showed a significant difference between both results, $P = 0.003$. This study was powered at 95% and sample size calculated was 70 inclusive of a 20% dropout.

Statistical analysis was performed using the SPSS for Windows version 23.0 (IBM Corp, Armonk, NY, USA). The Chi-square test was used for categorical data analysis. Qualitative data was analyzed using the independent *t*-test for normally distributed data, and the Mann-Whitney U test for not normally distributed data. Results are presented as mean ± standard deviation, median (inter quartile range), or frequency (percentage) where appropriate. A $P < 0.05$ was considered statistically significant.

Results

A total of 70 patients were recruited and there were no dropouts. Table 1 shows no difference in patient demographic between the groups.

TABLE 1 Patient demographics.

	Group 1 ($n = 35$)	Group 2 ($n = 35$)	*P*-value
Age (year)	43.22 ± 16.41	45.94 ± 15.25	0.476
Gender (M/F)	13/22	11/24	0.615
Weight (kg)	66.14 ± 12.31	67.63 ± 13.78	0.636
Height (cm)	161.96 ± 9.28	161.00 ± 9.91	0.710
BMI (kg/m^2)	25.08 ± 3.79	25.82 ± 3.72	0.412
ASA (1/2)	22/13	18/17	0.337

Values presented in mean ± standard deviation (SD), and number. P < 0.05 = significant.

TABLE 2 PLMA insertion attempts and insertion condition.

	Group 1 ($n = 35$)	Group 2 ($n = 35$)	*P*-value
Successful insertion at 1st attempt	28 (80.0)	29 (82.8)	0.837
Optimal insertion conditions at 1st successful attempt	21 (60.0)	20 (57.1)	0.808
Suboptimal insertions conditions			
1st attempt successful insertion	7 (20.0)	9 (25.7)	0.789
2nd attempt successful insertion	5 (14.3)	3 (8.6)	0.789
3rd attempt successful insertion	1 (2.8)	2 (5.7)	0.789
Failed insertion	1 (2.8)	1 (2.8)	0.789

Values are presented in number (percentage). P < 0.05 = significant.

TABLE 3 Adverse response during 1st attempt insertion and postoperative airway complications.

	Group 1 ($n = 35$)	Group 2 ($n = 35$)	*P*-value
Adverse responses at 1st attempt insertion:			
Cough/gag	6 (17.1)	4 (11)	0.495
Body movement	12 (34.3)	13 (37)	0.803
Laryngospasm	0 (0.0)	0 (0)	
Postoperative airway complications:			
Sore throat in recovery	8 (22.8)	8 (22.8)	1.000
Sore throat at 24 h	1 (2.8)	0 (0.0)	0.314
Hoarseness in recovery	0 (0.0)	1 (2.8)	0.314
Hoarseness at 24 h	1 (2.8)	0 (0.0)	0.314

Values are presented in number (percentage). P < 0.05 = significant.

The number of patients in which optimal insertion conditions were achieved at the first attempt, and the PLMA was successfully inserted at the first attempt, were comparable in both groups as shown in Table 2. Successful insertions at the first attempt were achieved in both groups despite not achieving optimal conditions for insertion. One patient in each group, with suboptimal PLMA insertion conditions, had failed PLMA insertion after three attempts.

Table 3 shows no difference between the groups with regards to, adverse response during PLMA insertion at the first attempt, and post-operative airway complications. There was no incidence of laryngospasm in both groups.

The proportion of patients with postoperative sore throat significantly increases with the number of ProSeal™ LMA attempts, as shown in Table 4.

Figures 1–3 shows no difference in SBP, DBP and MAP between the groups at all times.

Figure 4 shows that sympathetic obtundation of heart rate was greater in the fentanyl group than the lignocaine group, from post induction until 3 min post PLMA insertion, $P < 0.05$.

Propofol requirement was comparable in both groups, at 2.14 (2.00–2.72) mg/kg and 2.50 (2.00–2.73) mg/kg, in the fentanyl and lignocaine groups, respectively, $P = 0.379$.

Discussion

Laryngeal mask airways are usually inserted after anesthesia induction, without use of muscle relaxants. Various pharmacological agents have alternatively been used to facilitate LMA insertion (5, 7). Intravenous fentanyl is a frequently used opioid for co-induction during LMA insertion (28). However studies have also shown improved insertion conditions with prior topical pharyngeal lignocaine (12, 13, 24).

Optimal PLMA insertion conditions at the first attempt were achieved in about 60% of the patients in both groups. The numbers were comparable, suggesting similar efficacy of topical lignocaine and systemic fentanyl in achieving ideal PLMA placement conditions. Co-induction with fentanyl 2 μg/kg resulted in more of our patients (60%) achieving optimal insertion conditions, than that found in Gupta et al.'s study. The latter used a lower fentanyl dose of 1.5 μg/kg, and ideal insertion conditions were achieved in 43% of patients, despite their higher propofol dose of 2.5 mg/kg (27). When higher doses of fentanyl and propofol ranging 2–2.5 μg/kg and 2–2.5 mg/kg respectively were used, excellent LMA insertions conditions were attained in more than 80% patients (19, 29). However higher doses of fentanyl and propofol may compromise haemodynamic and respiration before the airway is secured. Rao and colleagues achieved optimal insertion conditions in more than 90% of their patients, with 100% success rate at first attempt LMA insertion. Viscous lignocaine gargle was given prior to co-induction with a lower dose of fentanyl 1 μg/kg and propofol 2 mg/kg (30).

We obtained a similar patient proportion (57%) with optimal insertion conditions, using topical lignocaine prior to propofol induction. This approximately mirrors findings by Changchien et al. and Seavell et al. who achieved optimal LMA insertion conditions with topical lignocaine 40 mg, in 66% and 73% of their patients respectively (24, 31). Changchien et al. additionally showed that subsequent anesthesia induction with propofol 2 mg/kg provided optimal LMA insertion conditions comparable to use of propofol 3 mg/kg alone, with the former having the added advantage of reduced incidence of apnea and cardiovascular instability (24). Shazed M. et al. achieved optimal insertion conditions in over 98% of their patients who were administered 200 mg topical lignocaine, which is higher than that utilized in most studies (32).

TABLE 4 Post-operative complications and number of PLMA insertion attempts.

Complications	1st attempt	2nd attempt	3rd attempt	Failed insertion	*P*-value
Sore throat in recovery	8 (14)	4 (50)	2 (67)	2 (100)	0.001*
Sore throat at 24 h	0 (0.0)	0 (0.0)	0 (0.0)	1 (50)	0.029*
Hoarseness in recovery	1 (2)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
Hoarseness at 24 h	0 (0.0)	1 (12)	0 (0.0)	0 (0.0)	0.186

Values are presented in number (percentage). *$P < 0.05$ = significant.

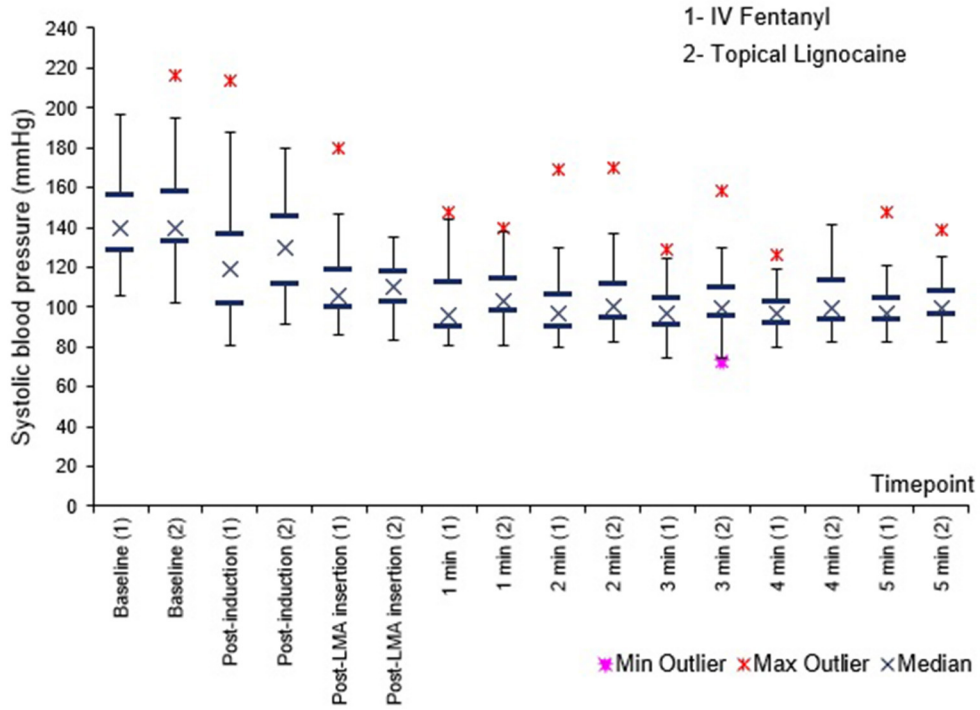

FIGURE 1
Systolic blood pressure (SBP) before, immediately after, and 1–5 min after PLMA insertion. Results presented as median, 25 and 75th percentile, minimum and maximum values.

Successful PLMA insertion at the first attempt was achieved in more than 80% of the patients, and this was comparable between the groups. This was in concordance with a prior study which achieved first attempt success in more than 90% of patients in both fentanyl and topical lignocaine groups (8, 24). Optimal insertion conditions were not achieved in all successful insertions at the first attempt. This was evident in both groups, where the percentage of successful first attempt insertions exceeded the percentage of patients in which optimal conditions were achieved during the first attempt. This may imply that the presence of adverse events, potentially leading to poor PLMA insertion conditions, may not necessarily hamper successful placement. The risk of failed LMA insertion has also been shown to increase with advanced age, high body weight, BMI <20 kg/m^2 and insertions without lignocaine gel (33).

Insufficient obtundation of airway reflexes may trigger gag and cough reflexes which could lead to incorrect LMA placement or insertion failure (3). We found comparable incidence of cough and gag with topical lignocaine (11%) and fentanyl (16%), which were in concordance with that found by Changchien et al. and Dhamotharan et al. with cough and gag reflexes in 10 and 16% of their patients administered topical lignocaine and IV fentanyl respectively (24, 29). In the study by Shazed M, the combination of a higher dose of 200 mg topical lignocaine, followed by the synergistic effects of IV nalbuphine co-induction with propofol 2 mg/kg provided a deeper plane of anesthesia and attenuation of upper airway reflexes, with reduced gag incidence of 3.5% (32). None of our patients developed laryngospasm. Suppression of laryngospasm by prior administration of fentanyl or topical lignocaine was

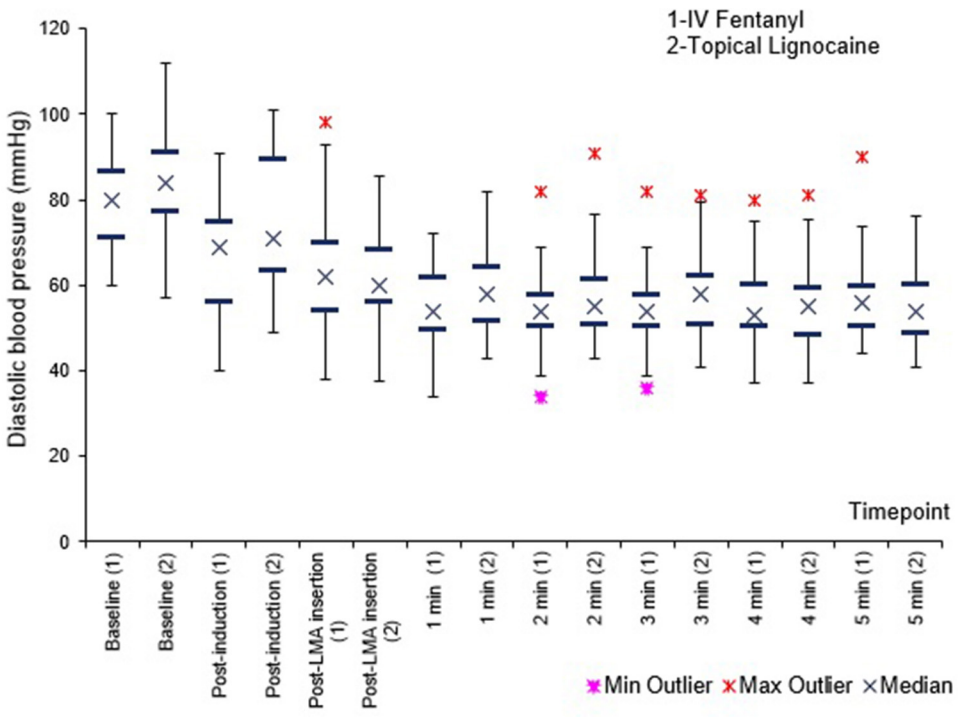

FIGURE 2
Diastolic blood pressure (DBP) before, immediately after, and 1–5 min after PLMA insertion. Results presented as median, 25 and 75th percentile, minimum and maximum values.

appreciated in studies by Cheam et al. and Changchien et al., respectively (8, 24). The incidence of body movements was also comparable between the groups, and similarly so in prior studies (8).

Traumatic insertion of the LMA may cause post-operative sore throat and is preventable with smooth LMA insertion (8). About a fifth of our patients in both groups developed sore throat in recovery, which was short-lived. This was in concordance with a study by Kuppusamy et al., where 25% of their patients had sore throat with PLMA insertion (34). Only one of our patients in the fentanyl group had symptoms persisting at the 24th hour postoperatively. Our study showed that the proportion of patients with postoperative sore throat significantly increased with the number of PLMA attempts ($P < 0.05$), and this was consistent with a prior study by Grady et al. (25). One patient in each group experienced hoarseness, at recovery and at 24 h respectively.

Haemodynamically, SBP, DBP and MAP were comparable between the groups at all times. Heart rate was lower in the fentanyl group than the lignocaine group from post induction up to 3 min post PLMA insertion, $P < 0.05$. Sympathetic obtundation of HR was greater with fentanyl than lignocaine. An earlier study showed similar finding with incidence of bradycardia (29).

Propofol requirement was not significantly different between the groups. Fentanyl 2 μg/kg has been shown to reduce propofol requirement by 60% during LMA insertion (7). Median propofol dose in our patient group given topical lignocaine was 2.50 (2.00–2.73) mg/kg. Topical lignocaine produced excellent LMA insertion conditions during anesthesia induction with propofol 2 mg/kg (12, 24). Higher propofol doses of 2.5–3.5 mg/kg was required if used as a sole anesthesia induction agent (6).

Limitations of this study include possible differences in the individual skills of the medical officer in PLMA insertion, thus confounding results of first attempt success rates and incidence of adverse effects. A single operator performing PLMA insertions may have reduced this bias. Other factors not considered in this study were reduced mouth opening (inter-incisor distance <3 cm), higher Mallampati grade (III, IV), reduced neck mobility, age of >61 years, and BMI of <20 kg/m^2, all of which could have also confound the successful placement of the PLMA (33, 35).

Topical lignocaine spray to the pharynx is as effective, and may be an alternative to IV fentanyl, during propofol anesthesia induction for PLMA insertion. The success rate at first attempt, optimal insertion conditions, propofol requirement, blood

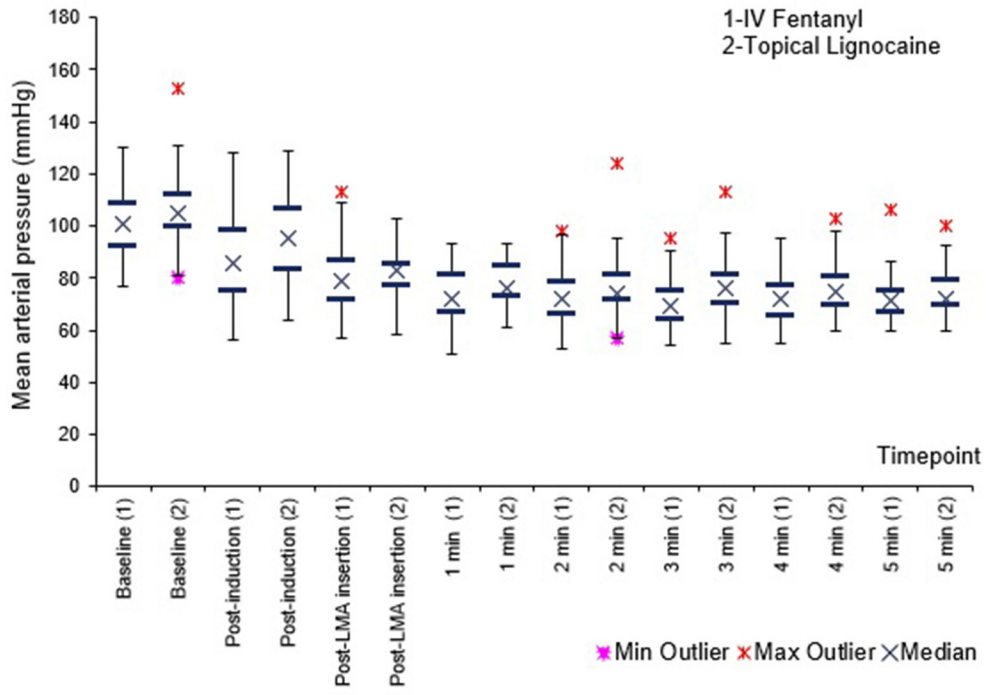

FIGURE 3
Mean arterial pressure (MAP) before, immediately after, and 1–5 min after PLMA insertion. Results presented as median, 25 and 75th percentile, minimum and maximum values.

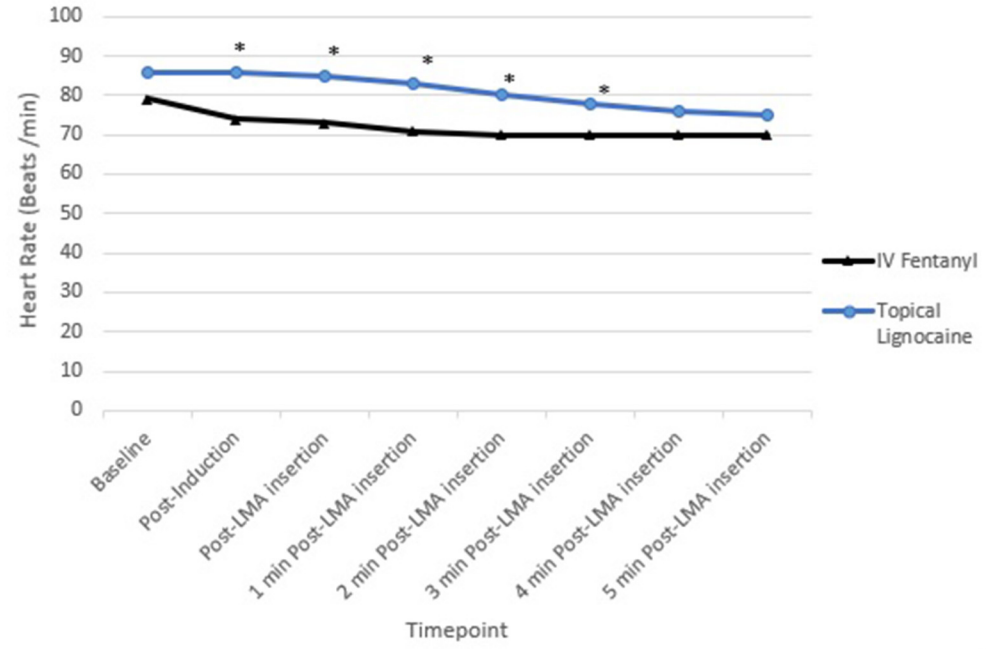

FIGURE 4
Mean heart rate (HR). *$P < 0.05$.

pressure, adverse events and airway complications were comparable. Heart rate obtundation was less with topical lignocaine spray, but remained within clinically acceptable values.

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 Ethics Research Secretariat, Universiti Kebangsaan Malaysia Medical Centre, Malaysia. The patients provided their written informed consent to participate in this study.

Author contributions

NN: article concept, design, intellectual content, literature search, data and statistical analysis, manuscript preparation, and editing and review. NR: article concept, design, intellectual content, literature search, data acquisition, data and statistical analysis, manuscript preparation, and editing and review. JZ, AM, and LY: intellectual content, literature search, data and statistical analysis, manuscript preparation, and editing and review. 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.

Publisher's note

References

1. Brain AIJ. A new concept in airway management. *Br J Anaesth.* (1983) 55:801–5. doi: 10.1093/bja/55.8.801

2. Tahir MS, Khan AN, Masood M, Yousaf M, Waris S. A comparison of pressor responses following laryngeal mask airway vs laryngoscopy and endotracheal tube insertion. *Anaesth Pain Intensive Care.* (2008)12:11–5

3. Stoneham MD, Bree SE, Sneyd JR. Facilitation of laryngeal mask insertion. Effect of lignocaine given intravenously before induction with propofol. *Anaesthesia.* (1995) 50:464–6. doi: 10.1111/j.1365-2044.1995.tb06007.x

4. Scanlon P, Carey M, Power M, Kirby F. Patient response to laryngeal mask insertion after induction of anaesthesia with propofol or thiopentone. *Can J Anaesth.* (1993) 40:816–8. doi: 10.1007/BF03009250

5. Driver IK, Wiltshire S, Mills P, Lillywhite N, Howard-Griffin R. Midazolam co-induction and laryngeal mask insertion. *Anaesthesia.* (1996) 51:782–4. doi: 10.1111/j.1365-2044.1996.tb07897.x

6. Asai T, Morris S. The laryngeal mask airway: its features, effect and role. *Can J Anaesth.* (1994) 41:930–60. doi: 10.1007/BF03010937

7. Goyagi T, Tanaka M, Nishikawa T. Fentanyl decreases propofol requirement for laryngeal mask airway insertion. *Acta Anaesthesiol Scand.* (2003) 47:771–4. doi: 10.1034/j.1399-6576.2003.00123.x

8. Cheam EW, Chui PT. Randomised double-blind comparison of fentanyl, mivacurium or placebo to facilitate laryngeal mask airway insertion. *Anaesthesia.* (2000) 55:323–6. doi: 10.1046/j.1365-2044.2000.01214.x

9. Dutt A, Joad AK, Sharma M. Induction for classic laryngeal mask airway insertion: Does low-dose fentanyl work? *J Anaesthesiol Clin Pharmacol.* (2012) 28:210–3. doi: 10.4103/0970-9185.94877

10. Abou-Madi MN, Keszler H, Yaboub JM. Cardiovascular reactions to laryngoscopy and tracheal intubation following small and large intravenous doses of lignocaine. *Can Anaesth Soc J.* (1977) 24:12–9. doi: 10.1007/BF03006808

11. Poulton TJ, James FM. Cough suppression by lignocaine. *Anaesthesia.* (1979) 50:470–2. doi: 10.1097/00000542-197905000-00018

12. Ahmed S, Jain N, Saksena S. Comparative evaluation of topical and intravenous lignocaine for insertion of laryngeal mask airway with propofol. *Int J Adv Med.* (2018) 5:573–7. doi: 10.18203/2349-3933.ijam20181985

13. Jain N, Ahmed S, Saksena S. Comparative evaluation of intravenous midazolam and topical lignocaine for insertion of laryngeal mask airway with propofol. *Int J Sci Educ.* (2018) 5:524–30.

14. Hussein SA, Alkhashab RH, A. comparison between topical and intravenous administration of lignocaine to aid the insertion of laryngeal mask airway. *Int J Adv Res Biol Sci.* (2018) 5:100–7. doi: 10.37623/SJMR.2019.31103

15. Kirkpatric MB, Sanders RV, Bass JB Jr. Physiologic effects and serum lidocaine concentration after inhalation of lidocaine from a compressed gas-powered jet nebulizer. *Am Rev Respir Dis.* (1987) 136:447–9. doi: 10.1164/ajrccm/136.2.447

16. Sutherland AD, Williams RT. Cardiovascular responses and lidocaine absorption in fiberoptic-asissted awake intubation. *Anaesth Analg.* (1986) 65:389–91. doi: 10.1213/00000539-198604000-00016

17. Loukides S, Katsoulis K, Tsarpalis K, Kalageropoulos N. Serum concentrations of lignocaine before, during and after fiberoptic bronchoscopy. *Respiration.* (2000) 67:13–7. doi: 10.1159/000029456

18. Braude N, Clements EA, Hodges UM, Andrews BP. The pressor response and laryngeal mask insertion. A comparison with tracheal intubation. *Anaesthesia.* (1989) 44:551–4. doi: 10.1111/j.1365-2044.1989.tb11439.x

19. Hickey S, Cameron AE, Asbury AJ. Cardiovascular response to insertion of Brain's laryngeal mask. *Anaesthesia.* (1990) 45:629–33. doi: 10.1111/j.1365-2044.1990.tb14384.x

20. Baik HJ, Kim YJ, Kim HJ. Lignocaine given intravenously improves conditions for laryngeal mask airway insertion during propofol target-controlled infusion. *Euro J Anaesth.* (2009) 26:377–81. doi: 10.1097/EJA.0b013e32831dcd4d

21. El-Boghdadly K, Bailey CR, Wiles MD. Postoperative sore throat: a systemic review. *Anaesthesia.* (2016) 71:706–17. doi: 10.1111/anae.13438

22. Tanaka Y, Nakayama T, Nishimori M, Sato Y, Furuya H. Lidocaine for preventing postoperative sore throat. *Cochrane Database Syst Rev.* (2015) 7:1–58. doi: 10.1002/14651858.CD004081.pub3

23. Brain AI, Verghese C, Strube PJ. The LMA 'Proseal'- a laryngeal mask with an oesophageal vent. *Br J Anaesth.* (2000) 84:650–4. doi: 10.1093/bja/84.5.650

24. Changchien CF, Chen HS, Hsieh SW, Tan PH, Lin CH, Liu CC, et al. & Hung KC. Topical lidocaine improves conditions for laryngeal mask airway insertion. *Can J Anaesth.* (2010) 57:446–52. doi: 10.1007/s12630-010-9281-9

25. Grady DM, McHardy F, Wong J, Jin F, Tong D, Chung F. Pharyngolaryngeal morbidity with the laryngeal mask airway in spontaneously breathing patients: does size matter? *Anesthesiology.* (2001) 94:760–6. doi: 10.1097/00000542-200105000-00012

26. Pocock SJ. *Clinical Trials: A Practical Approach*. New York, NY: John Wiley and Sons. (1983).

27. Gupta A, Kaur S, Saini N. Comparative evaluation of ketamine-propofol, fentanyl- propofol and butorphanol-propofol on haemodynamics and laryngeal mask airway insertion conditions. *J Anaesthesiol Clin Pharmacol.* (2011) 27:74–8. doi: 10.4103/0970-9185.76655

28. Park HJ, Kang HS. Comparison of propofol ED50 and insertion conditions of LMA between fentanyl and alfentanil adjuvant group. *Korean J Anesthesiol.* (2007) 52: 21–4. doi: 10.4097/kjae.2007.52.6.S21

29. Dhamotharan S, Ratan Singh N, Sarat Singh S. Comparative evaluation of fentanyl and midazolam with propofol induction on laryngeal mask airway insertion conditions: A study. *J Med Soc.* (2014) 28:185–9. doi: 10.4103/0972-4958.148519

30. Rao M, Chaitanya J, Subhadra P. Comparative evaluation of 2% lignocaine viscous gargling and intravenous lignocaine for insertion of laryngeal mask airway. *J Clin Sci Res.* (2020) 9:31–6 doi: 10.4103/JCSR.JCSR_121_19

31. Seavell MB, Cook TM, Cox CM. Topical lignocaine and thiopentone for the insertion of a laryngeal mask airway. *Anaesthesia.* (1996) 51:699–701. doi: 10.1111/j.1365-2044.1996.tb07860.x

32. Shazad M, Nadeem SM. Topical and intravenous lignocaine comparison on laryngeal mask airway insertion conditions quality. *Med Forum.* (2020) 31:40–4

33. Wang J, Shi X, Xu T, Wang G. Predictive risk factors of failed laryngeal mask airway insertion at 1st attempt. *J Int Med Res.* (2018) 46:1973–81. doi: 10.1177/0300060518762666

34. Kuppusamy A, Azhar N. Comparison of bougie-guided insertion of ProSeal™ LMA with digital technique in adults. *Indian J Anaesth.* (2010) 54:35–9. doi: 10.4103/0019-5049.60494

35. Di Filippo A, Adembri C, Paparella L, Esposito C, Tofani L, Perez Y, Di Giacinto I, Micaglio M. Risk factors for difficult Laryngeal Mask Airway LMA-Supreme™(LMAS) placement in adults: a multicentric prospective observational study in an Italian population. *Minerva Anestesiol.* (2021) 87:533–40. doi: 10.23736/S0375-9393.20.15001-6

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Comparison between 10 and 12 mg doses of intrathecal hyperbaric (0.5%) bupivacaine on sensory block level after first spinal failure in cesarean section: A double-blind, randomized clinical trial

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Background: Reducing adverse effects during cesarean delivery and improving the quality of sensory blocks with appropriate doses of intrathecal hyperbaric bupivacaine can play an important role in the safe management of cesarean delivery. The aim of this study was to compare the doses of 10 and 12 mg of intrathecal hyperbaric bupivacaine 0.5% on sensory block level after first spinal failure in cesarean section (CS).

Methods: In this double-blind, randomized clinical trial, 40 candidates of CS after first spinal failure with class I-II based on American Society of Anesthesiologists (ASA) were randomly assigned into two equal groups (n = 20). Group A and B received the spinal anesthesia with 10 mg and 12 mg of hyperbaric bupivacaine (0.5%), respectively. Maximum levels of sensory block, motor block quality, and vital signs were measured in two groups by 60 min after SPA. Incidence of SPA complications during surgery were also recorded. Data were analyzed by SPSS ver.21 software using repeated measures analysis of variance at 95% confidence interval (CI) level.

Results: Excellent quality of sensory blocks and complete quality of motor blocks were achieved in all participants (100%). However, the mean time to onset of anesthesia (4.47 ± 0.69 vs. 3.38 ± 0.47, $P < 0.001$) and time to reach T10 level (60.73 ± 11.92 vs. 79.00 ± 19.21, $P < 0.001$) in the Group A, were significantly shorter than in the patients of Group B. The incidence of hypotension ($P = 0.001$), nausea/vomiting ($P = 0.007$) and bradycardia ($P = 0.012$) as well as administration of ephedrine and atropine were significantly higher in Group B compared to Group A.

Conclusion: Spinal anesthesia can be safely repeated with a 10 mg of hyperbaric bupivacaine 0.5% in a caesarean section after the initial spinal failure.

Clinical trial registration: [https://en.irct.ir/trial/40714], identifier [IRCT20120915010841N20].

KEYWORDS

motor block, cesarean section, bupivacaine, failed spinal, spinal anesthesia, sensory block

Introduction

Spinal anesthesia (SPA) is the most common, safest, and most rational choice for cesarean section (1). SPA is secure and effective, but not a 100% successful technique and complications have been part of the method (2), including failed or insufficient sensory block (3), postdural puncture headache (PDPH) (4), hypotension (5), bradycardia (6), nerve damage (7), nausea and vomiting (8). A specific level of sensory block is required in any surgery performed under SPA. In cesarean section (CS), the level of T4-T6 anesthesia is appropriate (9). Elevated level of sensory block ($\geq$ T4) will cause hypotension, nausea and vomiting, decreased level of consciousness and maternal discomfort. Conversely, lower level of sensory block ($\leq$ T6) will not provide adequate anesthesia for CS, and causes discomfort and dissatisfaction in the patient (10). Intrathecal anesthetic spread has an unpredictable extent and duration that can be related to various factors such as dosage, patient variables, cerebrospinal fluid (CFS) volume, injection rate, and injection site (11).

One of the issues of SPA is the failure of spinal anesthesia, which means that SPA has been performed but not enough sensory block has been provided for surgery (12). Failed SPA can be identified as partial or incomplete spinal block within 10 minutes after hyperbaric bupivacaine injection and 25 minutes after isobaric bupivacaine anesthesia (13). Failure rates in SPA have been reported from 1 to 17% in various 1-17% (14). However, major studies have reported a prevalence range of 2 to 4% (12, 15). Obesity, dry cerebrospinal fluid (CSF), bloody CSF, improper dose, incorrect anesthesia distribution, multiple lumbar puncture attempts, use of the L4/L5 interspace, history of previous anesthesia and technical errors are significantly associated with failed SPA (3, 16). Complete failure of the SPA can be managed by switching to general anesthesia or by repeating the SPA procedure (12). However, since most pregnant patients are at risk for aspiration and intubation problems, general anesthesia carries a relatively higher risk for this population and re-performing SPA is a better and safer choice (17).

Administration of an appropriate dose hyperbaric bupivacaine can minimize potential side effects while improving block quality (18). However, the optimal intrathecal dose of hyperbaric bupivacaine for SPA is still being debated. Previous studies have investigated and demonstrated the effects of different doses on sensory and motor blocks in different ways (19, 20). In addition, very few studies have been found on the appropriate dose of hyperbaric bupivacaine for cesarean section during repeated spinal anesthesia (21). Therefore, we conducted this study to compare the doses of 10 and 12 mg of intrathecal hyperbaric (0.5%) bupivacaine on sensory block level and PDPH after first spinal failure in cesarean section.

Materials and methods

Study design

This prospective, double blind, parallel-group, randomized clinical trial study was conducted in Fatemiyeh Hospital in Hamadan, Iran, from July 2018 to July 2019. The protocol study was reviewed and approved by the Ethics Committees of Hamadan University of Medical Sciences (IR.UMSHA.REC.1398.232). This study Registered at Iranian Registry of Clinical Trials (IRCT20120915010841N20). Written informed consent were obtained from each patient. The study was conducted in accordance with the Declaration of Helsinki of the World Medical Association (22). This study was performed and reported in accordance with the recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement (23).

Population of study and sample size

The study population consisted of parturient with class I-II of American Society of Anesthesiologists (ASA), aged 18 to 46 years, the height range 170-155 cm, a second SPA candidate

after the first failed SPA (Bromage score 0 and no sensory block even at L4 dermatome after 10 min of first hyperbaric bupivacaine injection). Patients with a history of hypertensive pregnancy disorders, heart disease, Bromage scale >0, lack of pinprick sensation below umbilicus after spinal anesthesia, and of allergies to the study drug were excluded from the trial.

Randomization and blinding

Forty parturient were selected by a convenience sampling method based on inclusion criteria. Patients were then randomized into two SPA groups containing 10 mg of hyperbaric bupivacaine 0.5% (Group A) and 12 mg of hyperbaric bupivacaine 0.5% (Group B). Equal number of patients were assigned to each group using the block randomization method (n = 20). Patients were assigned to Group A or Group B on a computer-generated random number selected by the patient using Random Allocation Software © (RAS; Informer Technologies, Inc., Madrid, Spain). The level of spinal block and the duration of hemodynamic sensory variables were compared between the two groups. Both the patients and the evaluator were blind to the assignments.

Pre-SPA procedure

The Pre-SPA procedure was started for each patient as follows: Lactated Ringer serum (10 ml/kg) was injected using an 18-gauge needle depending on the patient's weight. Standard monitoring includes electrocardiography, pulse oximetry and non-invasive blood pressure (NIBP), vital signs such as systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR) and oxygen saturation (SpO2) was measured and recorded using an X162 monitor (Saadat Company, Iran).

First SPA procedure

SPA contains 10 mg of hyperbaric bupivacaine 0.5% (AstraZeneca Company, France) plus 2.5 μg of sufentanil (Abu Rayhan Company, Iran) using Quinke needle size 25 through lower lumbar (L3-4 or L4-5) intervertebral spaces in a sitting position was administered. The patient immediately lay on his back with a wedge under his right hip and was monitored for vital sign (SBP, DBP, MBP, HR, and SpO2). The effects of sensory and motor blocks were observed within 5 min, those that did not show efficacy within 5 min were observed for an additional 5 min and tested for motor and sensory blocks again. Those ASA I-II patients with insufficient motor and sensory block (Bromage score 0 and no sensory block even at L4 dermatome after 10 min of first hyperbaric bupivacaine injection) were considered for inclusion in the present study and they randomly (as described above) allocated to either Group A (10 mg of hyperbaric bupivacaine 0.5%) or Group B A (12 mg of hyperbaric bupivacaine 0.5%).

Repeat procedure of SPA

Patients in Group A received 10 mg and patients in Group B received 12 mg of 0.5% high hyperbaric bupivacaine (AstraZeneca Company, France), respectively and 2.5 μg of sufentanil (Abu Rayhan Company, Iran). Taking the same precautions, a 25-gauge Quincke needle was placed above or below the gap in the first attempt and the submucosal block was performed again (one space above in patients where previous spinal was attempted at L4-5 interspace or one space below in those patients who had previous spinal at L3-4 interspace) by a senior anesthesiologist who have worked in anesthesiology for over 10 years. The patient immediately lay on his back, a wedge under his right buttock displaced the left uterus, and monitoring (sensory block, motor block, and vital signs) was initiated. Surgery could be started after the initiation of spinal anesthesia was confirmed by a proper movement block of the lower extremities without a pinching sensation. If the patient complained of a pin-stab sensation 10 minutes after repeated spinal cord administration, general anesthesia was given and the patient was excluded from the study.

Measurements

The maximum level of sensory block was assessed by the pin-prick method using a 25-gauge needle, the time to reach the maximum level of anesthesia and the time to reach the T10 level as primary outcomes, were recorded for each patient. The sensory block quality and pain were assessed using the visual analog scale (VAS). VAS scores were recorded by creating a handwritten mark on a 10 cm line indicating the chain between "excellent" and "poor" (24), which described excellent postoperative quality as none (0), mild (< 3), moderate (3-6), or severe (7-10). The quality of the motion block was assessed using the Bromage Scale (25). A modified Bromage Scale was used: 0 = no motor block; 1 = able to flex knee free movement of feet, unable to raise extended leg (partial motor block); 2 = free movement of feet only (almost complete motor block); 3 = unable to move hips, knees, feet (complete motor block). Sedation was evaluated by Ramsay scale, it divides a patient's level of sedation into six categories ranging from severe agitation to deep coma; 1 = anxious and agitated or restless or both; 2 = co-operative, oriented and tranquil; 3 = responding to commands only; 4 = brisk response to light glabellar tap or loud auditory stimulus; 5 = sluggish response to light glabellar tap or loud auditory stimulus; 6 = no response to stimulus (26).

Vitals parameters including SBP, DBP, MBP, HR, and SpO2 were measured at baseline (pre-SPA procedure), immediately after SPA procedure, and 2,4,6,8, 10, 15, 20, 30, 40, 50, and 60 min of post postoperatively. SBP less than 90 mmHg and bradycardia (heart rate less than 60 beats per minute) were treated with incremental intravenous doses of 10 mg ephedrine and 0.5 mg intravenous atropine, respectively. Finally, the amount of ephedrine and atropine used, the occurrence of nausea and vomiting during surgery, the time of onset of anesthesia and the maximum level of anesthesia (using a needle or pinprick), the quality of sensory (VAS scores) and motor block (Bromage Scale), the time of anesthesia to T10, sedation score (Ramsay scale) and Apgar score (in minutes 1 and 5) for infants was examined and recorded for each participants. Nausea and Vomiting, headache, hypotension (BP < 90/60mmHg), bradycardia (HR < 60/min), chills and high spinal were recorded during procedure for each patient. In addition, one week after surgery, patients were evaluated and questioned by researcher over the phone about the presence or absence of postdural puncture headache (PDPH).

Statistical analysis

Power calculations was done based on primary outcome, time to reach T10 level in two group of study (60.73 ± 11.92 in 10 mg of hyperbaric 0.5% vs. 79.00 ± 19.21 in 12 mg of hyperbaric 0.5%, $P < 0.001$). Analyses according to the sample size of 20 patients in each group with considering the type I error (α) set as two-sided 5% (Z1-α/2 = 1.96) and type II error (β) set as 20% (Z1-β = 0.84), estimated the power of the test equal to 100%. It should be noted that with a power level of 80 and 95% confidence interval (CI), a sample size equal to 13 patients in each group was sufficient to detect clinically significant differences between the two groups. Analyzing the power of the test using Stata 11 software. Variables were expressed as mean ± standard deviation (SD) or percentage (%) for continuous and discrete variables, respectively. Results were analyzed by independent *t*-test (between groups), and paired *t*-test (within group) for parametric data and Mann–Whitney *U*-test for non-parametric data. Fisher's exact test and Chi-square test were used for categorical data as appropriate. The Shapiro-Wilk test was conducted to test whether the data were normally distributed. Using a general linear model, hemodynamic changes and complications between the two groups were compared using a repeated measurement ANOVA test, with the baseline values (age) used as covariates in the model. The assumption of sphericity was addressed by Mauchly's test of sphericity, and when the assumption was not satisfied, the Greenhouse-Geiser correction of *P*-value were utilized. To assess the effect of intervention, the analysis of covariance (ANCOVA) was used after controlling for baseline measures and confounders in a two-step hierarchical model. Logistic regression analysis was used to predict incidence of complications according to influencing 12 mg dose of hyperbaric bupivacaine 0.5% compare to 10 mg, and the significant variables were reported as odds ratio (OR) with 95% confidence interval (CI). GraphPad Prism 9© (GraphPad Software Inc., La Jolla, CA) was used to show the changes of hemodynamic parameters in two groups of study (12 mg vs. 10 mg of hyperbaric 0.5%) over times. Statistical analysis was carried out using SPSS software (ver.21) (SPSS Inc., IL, Chicago, United States). In all analyses, *P*-values less than 0.05 were considered as significant.

Results

Participants of study

A total of forty parturient were included in the study and Figure 1 shows the patient registration flow chart. Fifty parturient with class I-II of ASA, who candidate of SPA for non-emergent cesarean section after the first failed SPA with Bromage score 0 and no sensory block after 10 min of first hyperbaric bupivacaine injection were screened for eligibility criteria. Out of 50 cases, 40 patients met the inclusion criteria and randomly assigned into two equal groups ($n = 20$); Group A (received 10 mg of hyperbaric bupivacaine 0.5%) and Group B (received 12 mg of hyperbaric bupivacaine 0.5%). During the intervention and follow-up stages, only one patient in the group A underwent general anesthesia due to failed of SPA and was excluded from the study. Totally 39 patients were analyzed, 19 and 20 patients in the Group A and B, respectively.

Demographic and baseline hemodynamic parameters

Comparison of baseline demographics and hemodynamic parameters between the two groups of study is presented in Table 1. There were no statistically significant differences in demographic and baseline hemodynamic parameters of parturient such as; age ($P = 0.722$), SBP ($P = 0.985$), DBP ($P = 0.398$), MBP ($P = 0.531$), HR ($P = 0.372$) and SpO2 ($P = 0.682$) in the Group A and Group B.

Spinal anesthesia characteristics and outcomes

Comparison of spinal anesthesia characteristics and outcomes between the two groups of study are presented in Table 2. Excellent and complete quality of sensory and motor blocks was observed in all participants in the both groups. However, the mean time to onset of anesthesia (4.47 ± 0.69

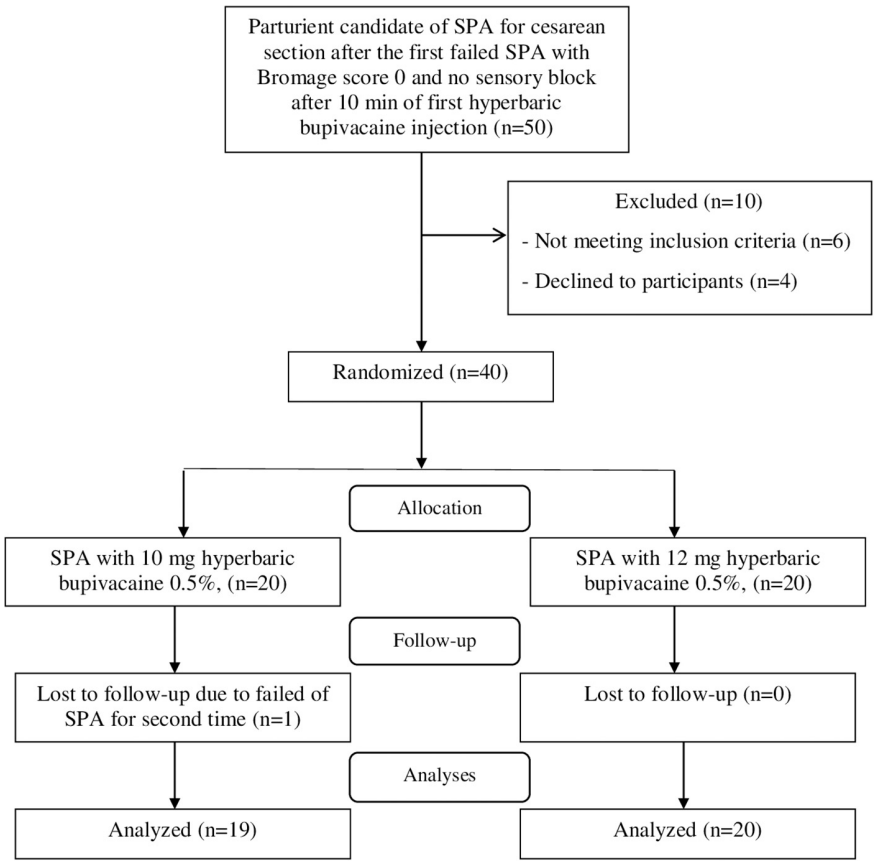

FIGURE 1
CONSORT flow diagram.

vs. 3.38 ± 0.47, $P < 0.001$) and the mean time to reach T10 level (60.73 ± 11.92 vs. 79.00 ± 19.21, $P < 0.001$) in the Group A were significantly shorter than in the Group B. According to the results, in most patients in Group A the sensory level reached to T6 (n = 17, 89.5%), while the sensory level of more than half of the patients in Group B reached to T4 (n = 13, 65%). In terms of sensory level at recovery, nearly half of the patients (47.4%) in Group A had sensory level T12, while 50% of participants in the Group B had sensory level T8. There was statistically significant difference between two groups of the study in terms on maximum sensory level ($P < 0.001$) and also in sensory level in recovery ($P < 0.001$). The use of Ephedrine (85% vs. 31.6%, $P < 0.001$) and Atropine (30% vs. 0) in the group B who received SPA with 12 mg of hyperbaric bupivacaine 0.5% was significantly higher than the Group A. And finally, the satisfaction of patients in the Group B was significantly lower than the Group A. However, there was no significant difference in the Apgar scores of the neonates in the first minute (8.78 ± 0.71 vs. 8.95 ± 0.39, $P = 0.387$), and fifth minutes (9.94 ± 0.22 vs. 9.90 ± 0.31, $P = 0.591$) between two groups.

Changes in hemodynamic parameters and sedation rate over time

The time trend of hemodynamic parameters (SBP, DBP, MBP, HR, and SpO2) in the two study groups is presented in Table 3. This parameters were recorded at pre-SPA and immediately after SPA and then every 2 min up to 10-min, and then every 5 min up to 30-min, and then every 10 min up to 60-min after injection of anesthetic drug. Figure 2A shows the mean values of SBP changes in each group over time. The results showed that there was no significant difference in SBP between the two groups except for 4 and 8 min when SBP in Group A was significantly higher than Group B ($P = 0.002$ and $P = 0.038$, respectively), also in 30 min that the SBP in Group B was higher than Group A ($P = 0.033$). In within group, the effect of time on SBP in each group was statistically significant (a within-subject difference based on time effect) ($P = 0.05$). However, based on repeated measures analysis of variance (RMANOVA), the trend of changes in SBP levels between the two groups was not statistically significant (group * time interaction or an interaction effect) ($P = 0.362$).

TABLE 1 Comparison of demographic and baseline hemodynamic parameters between the two study groups.

Variables		Group A (n = 19)	Group B (n = 20)	P-value	95% Confidence interval (CI)
Age	Mean ± SD	30.94 ± 4.81	31.70 ± 7.96	0.722	−3.54 to 5.05
	(Range)	(24-42)	(18-44)		
Systolic BP	Mean ± SD	121.53 ± 11.48	121.60 ± 13.19	0.985	−7.97 to 8.11
	(Range)	(97-136)	(100-150)		
Diastolic BP	Mean ± SD	71.84 ± 11.31	75.20 ± 13.08	0.398	−4.59 to 11.31
	(Range)	(47-97)	(52-99)		
MBP	Mean ± SD	86.63 ± 12.29	89.35 ± 14.37	0.531	−5.98 to 11.41
	(Range)	(61-111)	(59-119)		
HR	Mean ± SD	87.94 ± 17.27	92.55 ± 14.48	0.372	−5.71 to 14.92
	(Range)	(56-120)	(62-118)		
SpO2	Mean ± SD	96.84 ± 1.06	97.00 ± 1.29	0.682	−0.615 to 0.931
	(Range)	(95-99)	(93-99)		

Group A (who received 10 mg of hyperbaric bupivacaine 0.5%), Group B (who received 12 mg of hyperbaric bupivacaine 0.5%), HR: Heart Rate, BP: Blood Pressure, MBP: Mean Blood Pressure, SpO2: oxygen saturation.

TABLE 2 Comparison of spinal anesthesia characteristics and outcomes between the two study groups.

Variables		Group A (n = 19)	Group B (n = 20)	P-value
Time to reach T10 level	Mean ± SD (min)	60.73 ± 11.92	79.00 ± 19.21	< 0.001*
Maximum sensory level	T2	0	3 (15)	
	T4	2 (10.5)	13 (65)	< 0.001*
	T6	17 (89.5)	4 (20)	
Time to onset of anesthesia	Mean ± SD (min)	4.47 ± 0.69	3.38 ± 0.47	< 0.001*
Sensory block quality	Excellent (%)	19 (100)	20 (100)	–
	Moderate (%)	0	0	
	Poor (%)	0	0	
Motor block quality	Complete (%)	19 (100)	20 (100)	–
	Semi-complete (%)	0	0	
	Non-motion block (%)	0	0	
Sensory level in recovery	T8	2 (10.5)	10 (50)	< 0.001*
	T10	8 (42.1)	9 (45)	
	T12	9 (47.4)	1 (5)	
Ephedrine doses consumed	Median (IQR)	0 (0-10)	20 (20-30)	< 0.001*
Ephedrine consumed	Yes (%)	6 (31.6)	17 (85)	< 0.001*
Atropine consumed	Yes (%)	0	6 (30)	0.009*
Apgar score	Mean ± SD (1min)	8.78 ± 0.71	8.95 ± 0.39	0.387
	Mean ± SD (5 min)	9.94 ± 0.22	9.90 ± 0.31	0.591
Satisfaction rate	Low (%)	3 (15.8)	13 (65)	0.003*
	Moderate (%)	2 (10.5)	1 (5)	
	High (%)	10 (52.6)	5 (25)	
	Very high (%)	4 (21.1)	1 (5)	

Group A (who received 10 mg of hyperbaric bupivacaine 0.5%), Group B (who received 12 mg of hyperbaric bupivacaine 0.5%), * statistical significant.

TABLE 3 Comparison of hemodynamic parameters and sedation rate based on Ramsay scale in two groups of study.

Variables/Groups		Pre-SPA	After SPA	2 Min	4 Min	6 Min	8 Min	10 Min	15 Min	20 Min	25 Min	30 Min	40 Min	50 Min	60 Min	P-value ##	P-value ###	P-value ####
SBP	**A**	121.52 (11.48)	118.73 (11.51)	107.2 (13.9)	102.7 (11.8)	100.3 (16.4)	104.5 (15.4)	105.42 (9.61)	107.31 (10.05)	108.7 (11.8)	106.94 (11.57)	107.3 (10.1)	110.2 (9.17)	110.1 (8.60)	110.84 (9.05)	**0.002**	< **0.001**	0.362
	B	121.60 (13.19)	115.95 (12.35)	98.5 (15.4)	87.5 (16.1)	90.5 (19.4)	92.2 (19.9)	104.15 (15.48)	104.65 (23.87)	112.8 (9.16)	113.1 (8.40)	113.9 (8.58)	113.8 (5.10)	112.4 (5.26)	112.5 (4.41)	**0.011**		
P-value#		0.985	0.471	0.072	**0.002**	0.097	**0.038**	0.761	0.655	0.243	0.069	**0.033**	0.131	0.298	0.469			
DBP	**A**	71.84 (11.3)	68.89 (13.9)	62.63 (10.6)	58.63 (13.2)	55 (11.3)	58.05 (10.8)	56.31 (7.68)	57.94 (8.42)	58.36 (8.96)	58.21 (8.83)	57.15 (8.43)	60.94 (7.43)	60.84 (7.04)	61.36 (6.72)	**0.002**	< **0.001**	0.643
	B	75.20 (13.1)	74.05 (12.8)	59.2 (12.5)	50.55 (9.92)	53.10 (14.2)	54.4 (13.1)	57.3 (10.3)	59.9 (8.57)	62.85 (7.84)	62.6 (7.80)	62.3 (7.80)	62.55 (7.13)	63.75 (7.09)	62.6 (5.33)	< **0.001**		
P-value#		0.398	0.236	0.365	**0.037**	0.649	0.325	0.739	0.478	0.105	0.108	0.053	0.496	0.207	0.513			
MBP	**A**	86.63 (14.3)	84.52 (13.3)	75.57 (11.1)	72.63 (12.9)	69.78 (12.1)	72.84 (12.2)	71.31 (8.01)	73.73 (8.89)	73.42 (9.44)	72.84 (8.68)	75.42 (9.91)	75.47 (8.77)	77.21 (6.53)	77.26 (6.81)	**0.004**	< **0.001**	0.973
	B	89.35 (14.3)	86.85 (12.2)	70.75 (12.9)	61.75 (12.7)	65.10 (15.3)	66.30 (14.7)	75.12 (12.1)	75.45 (8.28)	78.55 (8.04)	78.45 (8.00)	78.60 (5.88)	78.95 (5.88)	78.80 (4.49)	78.65 (3.36)	**0.005**		
P-value#		0.531	0.573	0.220	**0.012**	0.299	0.142	0.801	0.537	0.075	**0.043**	0.267	0.153	0.380	0.422			
HR	**A**	87.94 (17.2)	93.47 (15.7)	97.5 (18.3)	102.9 (16.1)	97.94 (13.6)	97.26 (11.4)	95.89 (12.5)	94.84 (12.4)	94.94 (10.6)	94.36 (10.3)	93.89 (9.97)	94.05 (7.26)	93.94 (8.48)	92.73 (7.15)	0.296	0.126	0.067
	B	92.55 (14.4)	99.40 (28.3)	101.1 (22.3)	93.7 (29.2)	98.10 (20.8)	104.6 (15.3)	106.7 (11.9)	105.2 (10.6)	105.5 (9.19)	104.1 (6.64)	99.90 (7.90)	99.15 (6.50)	95.60 (5.26)	94.80 (4.68)	0.454		
P-value#		0.372	0.428	0.595	0.232	0.979	0.101	**0.009**	**0.008**	**0.002**	**0.001**	**0.044**	**0.026**	0.467	0.291			
SpO_2	**A**	96.84 (1.06)	97.42 (1.12)	97.73 (0.99)	97.73 (0.99)	97.47 (1.71)	97.78 (1.27)	97.84 (1.16)	97.63 (1.57)	97.78 (1.18)	97.94 (1.12)	97.94 (1.12)	97.42 (2.06)	97.94 (1.12)	97.47 (2.06)	0.259	0.107	**0.036**
	B	97 (1.29)	97.35 (0.87)	96.90 (1.41)	96.65 (1.42)	96.55 (1.39)	96.75 (1.11)	96.80 (1.01)	97 (1.02)	97.10 (0.91)	97.15 (0.98)	97.25 (0.85)	97.25 (0.85)	97.20 (0.89)	97.25 (0.85)	0.287		
P-value#		0.632	0.826	**0.040**	**0.009**	0.072	**0.010**	**0.005**	0.144	**0.048**	**0.024**	**0.038**	0.735	**0.027**	0.658			
Sedation rate	**A**	–	2	2	1.93 (0.25)	1.87 (0.34)	1.93 (0.25)	2.18 (0.40)	2.25 (0.44)	2.25 (0.44)	2.17 (0.39)	2.25 (0.44)	2.18 (0.40)	2	2	–	0.057	0.102
	B	–	2	1.95 (0.39)	1.75 (0.55)	1.70 (0.57)	1.95 (0.39)	2.05 (0.22)	2.05 (0.22)	2.10 (0.30)	2	2.05 (0.22)	2.05 (0.22)	2.05 (0.22)	2	–		
P-value#		–	–	0.616	0.216	0.288	0.913	0.203	0.089	0.242	0.052	0.089	0.203	0.379	–			

Group A: 10 mg of hyperbaric bupivacaine 0.5%, Group B: 12 mg of hyperbaric bupivacaine 0.5%, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: Mean Arterial Pressure, HR: Heart Rate, SpO2: oxygen saturation, $P < 0.05$ was considered as significant, # *P*-value based on independent *t*-test and analysis of covariance (ANCOVA) adjusted for age between two groups, ##*P*-value based on paired t-test within group, ### Time main effect based on two way analysis of variance with repeated measures (RMANOVA), #### Assessing the interaction effect of group and time based on RMANOVA after Greenhouse-Geiser correction (adjusted and non-adjusted models). Bold values are $P < 0.05$ which was considered as significant.

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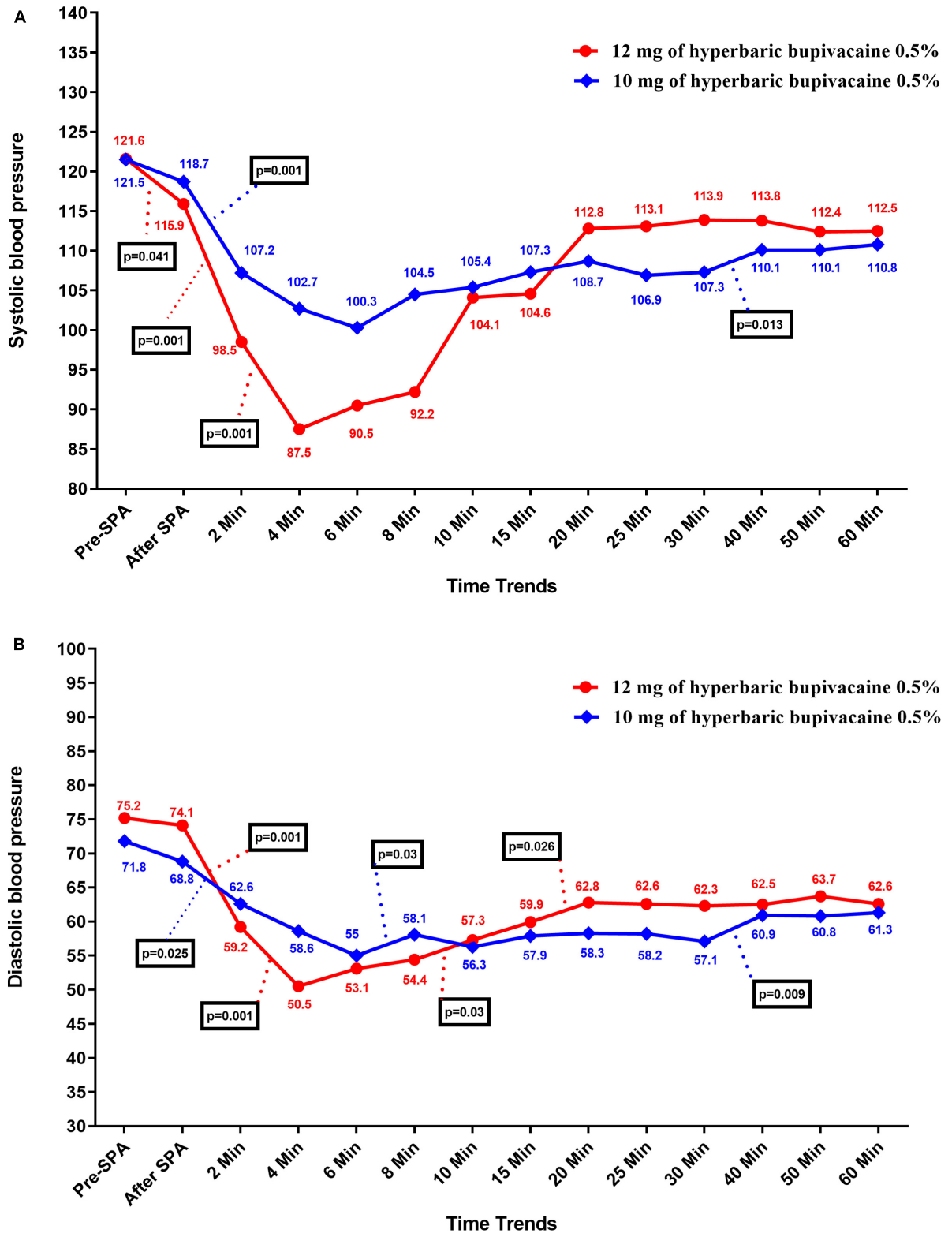

FIGURE 2
Changes **(A)** systolic and **(B)** diastolic blood pressure in two groups of study over times, *P-values shows statistically significant between two times within groups.

As shown in Figure 2B, there was no significant difference in DBP between the two groups except at 4 min, when DBP in Group A was significantly higher than Group B (58.63 ± 13.25 vs. 50.55 ± 9.92, $P = 0.037$). Within the group, the effect of time on DBP was statistically significant in each group (difference within the subject based on the effect of time) ($P < 0.05$). However, the trend of changes in DBP levels between the two groups (group * time interaction or an interaction effect) ($P = 0.643$).

Figure 3A shows the mean values for changes of MBP in each group over times. According to the results, there was no significant difference in MBP between the two groups except at 4 min (72.63 ± 12.95 vs. 61.75 ± 12.73, $P = 0.012$) and 25 min (72.84 ± 8.68 vs. 78.45 ± 8, $P = 0.043$) when MBP in Group A was significantly higher and lower than Group B, respectively. In within group, the effect of time on MBP was statistically significant in Group A ($P = 0.004$) and Group B ($P = 0.005$) (a within-subject difference based on time effect). However, the trend in changes in MBP levels was not statistically significant between two groups (group * time interaction or an interaction effect) ($P = 0.935$).

Figure 3B shows the mean values for changes of HR in each group over times. The results showed that there was a significant difference in HR between the two groups at 10 min to 40 min, when HR in Group B was significantly higher than Group A ($P < 0.05$). In within group, time effect on HR was not statistically significant in Group A ($P = 0.296$) and Group B ($P = 0.454$) (a within-subject difference based on time effect). Moreover, the trend in changes in HR levels was not statistically significant between two groups (group × * time interaction or an interaction effect) ($P = 0.067$).

Figures 4A,B shows the mean values for changes of SpO2 and sedation rate in each group over times, respectively. According to our findings, the mean SpO2 was significantly higher in the Group A than in the Group B ($P < 0.05$), except at pre-SPA ($P = 0.682$), immediately after SPA ($P = 0.826$), at 6 min ($P = 0.072$), 15 min ($P = 0.144$) and 60 min ($P = 0.658$). In within group, time effect on SpO2 was not statistically significant in each group (a within-subject difference based on time effect) ($P > 0.05$). While, the trend in changes in SpO2 levels was statistically significant between two groups (group × time interaction or an interaction effect) ($P = 0.036$). In terms of sedation rate, no significant difference was observed between the two groups and also within each group ($P > 0.05$). In addition, the trend in changes in sedation rate was not statistically significant between two groups (group * time interaction or an interaction effect) ($P = 0.102$).

Complications

Table 4 shows comparison of complications related to the SPA procedure during operation, at recovery and after operation in two groups of study. According to our findings, hypotension was a common SPA side effect in both groups, which was occurring in 59% of the all participants. The results indicated that the incidence of hypotension (85 vs. 31.6%, $P = 0.001$), nausea/vomiting (70 vs. 26.3%, $P = 0.007$) and bradycardia (30% vs. 0, $P = 0.012$) were significantly higher in Group B compared to Group A. However, there was no significant difference in chills, headache, pain, high spinal and PDPH in the two groups ($P > 0.05$). Based on logistic regression analysis, 12 mg of hyperbaric bupivacaine (0.5%) can be increases the risk of hypotension (OR: 12.278, 95% CI: 2.573-58.589, $P = 0.002$), nausea/vomiting during operation (OR: 6.533, 95% CI: 1.613-26.469, $P = 0.009$) and ephedrine consumed (OR: 12.278, 95% CI: 2.573-58.589, $P = 0.002$) (Table 5).

Discussion

The failure of a SPA to produce adequate block is not an uncommon occurrence in cesarean section. However, little information is available to provide guidance on duplicate dosing. The main purpose of this clinical trial was to compare the doses of 10 mg and 12 mg of intrathecal hyperbaric bupivacaine (0.5%) on sensory block level after first spinal failure in cesarean section. The excellent quality of sensory block and the complete quality of motor block were obtained in all participants. Although, both doses (10 mg and 12 mg) of intrathecal hyperbaric bupivacaine (0.5%) showed similar satisfactory block profiles. But our results revealed that the SPA with 12 mg hyperbaric bupivacaine (0.5%) can increase the mean anesthesia time and time to reach the T10 level.

Technical errors are common causes of failed spinal such as drug deposition at lower spinal level than surgical site, improper rate of injection, failure to detect dural puncture, needle from inside/outside the dural sac, patient co-operation, needle in ventral epidural space, and cerebrospinal fluid (CSF) tap. Therefore, due to the risk of aspiration and intubation problems in pregnant patients, repeating the procedure of SPA is the safer option (3, 27). Managing failure SPA or repeating the procedure is an event that is of concern to both the patient and the anesthesiologist, and several factors must be considered. Adequate dose of local anesthetic and the skills of anesthetist to prevent technical errors are of this factors. The superior quality of sensory blocks and the complete quality of motor blocks in both research groups may be attributed to the ability of anesthesia providers to prove their effectiveness with experienced hands (28). SPA is safer in skilled hands, but several factors are believed to affect SPA, including anatomical abnormalities such as kyphoscoliosis, sclerosis, and spinal stenosis following previous intrathecal surgery or chemotherapy and reduced anesthetic potency due to prolonged exposure to light (12, 29, 30).

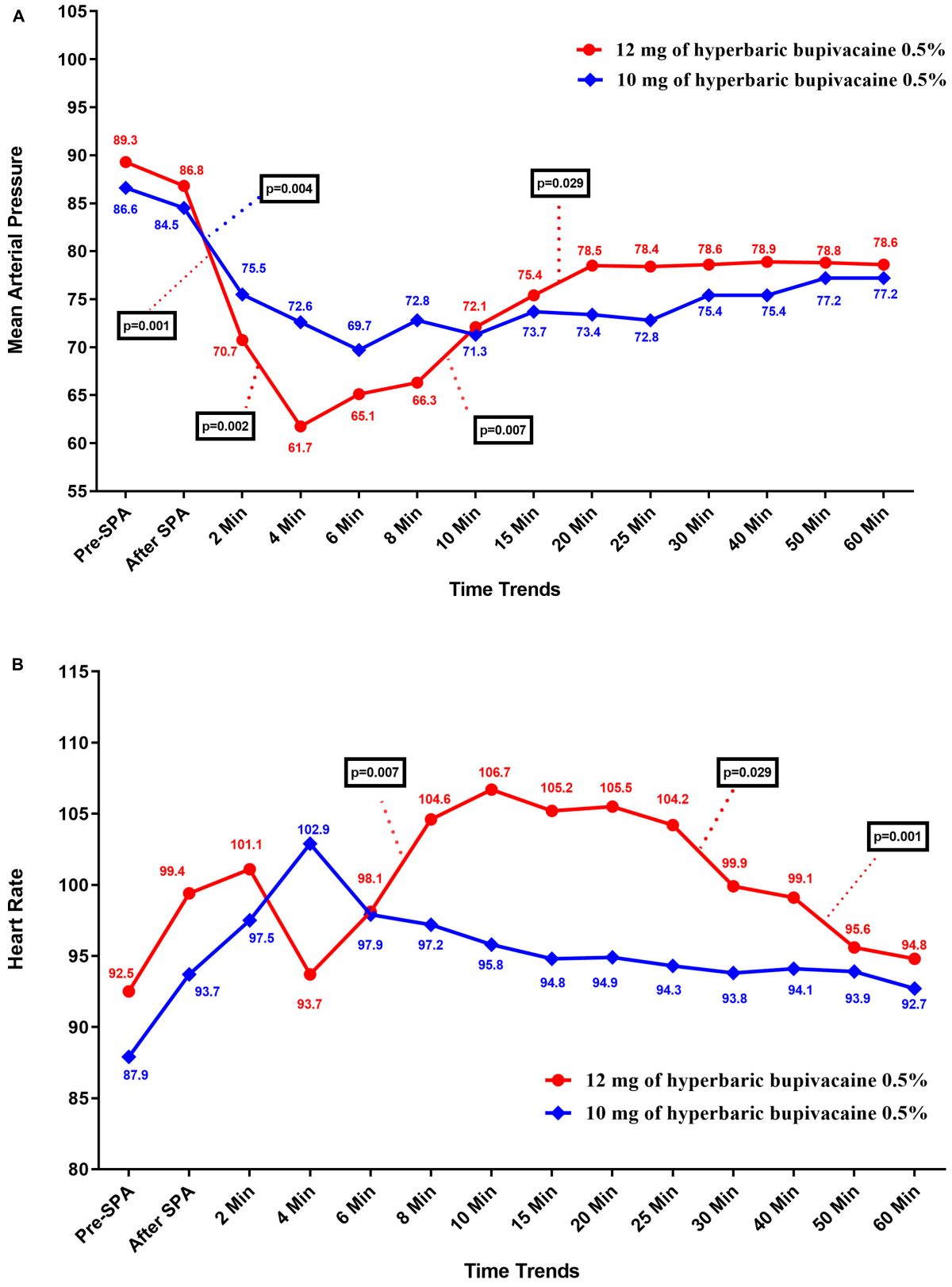

FIGURE 3
Changes **(A)** main blood pressure and **(B)** heart rate in two groups of study over times, * *P*-values shows statistically significant between two times within groups.

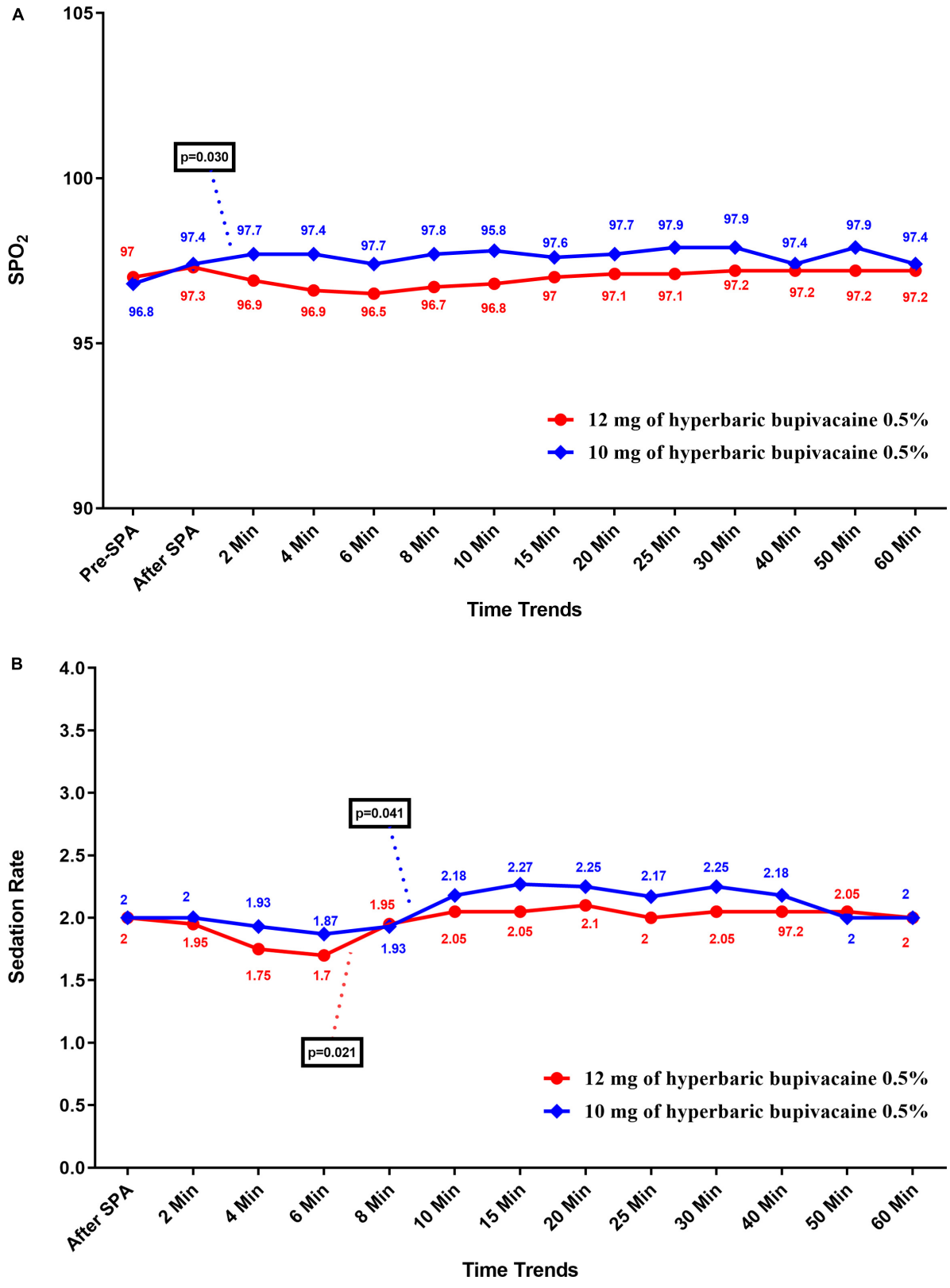

FIGURE 4
Changes **(A)** SpO2, and **(B)** sedation rate in two groups of study over times, * *P*-values shows statistically significant between two times within groups.

TABLE 4 Comparison of SPA-related complications in two groups of study.

Side effects	Group A ($n = 19$)	Group B ($n = 20$)	*P*-value
During operation			
Nausea and Vomiting	5 (26.3%)	14 (70%)	0.007*
Headache	0	1 (5%)	0.513
Hypotension	6 (31.6%)	17 (85%)	0.001*
Bradycardia	0	6 (30%)	0.012*
Chills	6 (31.6%)	6 (30%)	0.915
High spinal	0	3 (15%)	0.125
At recovery			
Nausea and Vomiting	0	1 (5%)	0.513
Pain	0	1 (5%)	0.513
After operation			
PDPH	1 (5.3%)	1 (5%)	0.744

Group A: 10 mg of hyperbaric bupivacaine 0.5%, Group B: 12 mg of hyperbaric bupivacaine 0.5%, *, $P < 0.05$ was considered as significant, PDPH: Postdural puncture headache.

TABLE 5 Logistic regression analysis of influencing 12 mg dose of hyperbaric bupivacaine 0.5%, to predict incidence of complications.

Variables	Logistic regression analysis	
	OR (95% CI)	*P*-value
Nausea and Vomiting during operation (yes vs. no)	6.533 (1.613-26.469)	0.009*
Headache during operation (yes vs. no)	0.972 (0.879-1.074)	0.571
Headache after operation (yes vs. no)	0.947 (0.055-16.309)	0.970
Hypotension (yes vs. no)	12.278 (2.573-58.589)	0.002*
Chills (yes vs. no)	0.929 (0.238-3.619)	0.915
Ephedrine consumed (yes vs. no)	12.278 (2.573-58.589)	0.002*

*$P < 0.05$ was considered as significant.

In terms of dose of local anesthetic, previous studies have suggested that a dose of 12 mg (2.4 ml) of bupivacaine provides reliable anesthesia for cesarean section (27, 31). However, in the repetition of the SPA procedure there is a fear of over-expansion of the sensory block (12, 32). As in this study, high spinal block was occurred in 3 patients who received 12 mg hyperbaric bupivacaine (0.5%). So, our findings showed that the lower dose (10 mg) of anesthetic drug is safer and did not observed any high spinal block in Group A. On the other hand, by reviewing the literature, we found an association between hypotension and bradycardia in cesarean section with a higher dose of anesthetic, which was completely consistent with the results of this study (21, 33, 34). Our findings indicated that the higher dose of bupivacaine (12 mg) was related to higher nausea/vomiting, hypotension, and bradycardia as well as administration of more ephedrine and atropine, which ultimately reduces patient satisfaction. The high and very high satisfaction rate of parturients in this study was significantly higher in Group A compare to Group B (73.7 vs.30%, $P < 0.05$). Evidence suggests that overall satisfaction level of parturients decreases with number of attempt, pain during block, inadequate intraoperative analgesia, postoperative nausea/vomiting, hypotension, bradycardia and headache during operation and high level of PDPH (35). However, by ensuring the quality of spinal anesthesia, improving the clinical skills of anesthesiologists, preventing side effects, and educating mothers about cesarean section under local anesthesia and familiarity with the process, patients You can increase your satisfaction (36). Therefore, choosing the adequate dose of anesthetic drug can be increases the quality of local anesthesia and prevents side effects, and subsequently increase patient satisfaction. The results of this study are consistent with previous studies showing that reducing the dose of local anesthesia during repeated spinal anesthesia is safe and satisfactory (21, 32).

The limitations of our study were, we compared the only two doses of bupivacaine, based on the known optimal doses and low sample size. However, a large sample size study s need to be conducted to determine the optimal dose of hyperbaric bupivacaine that can be safely and successfully used to repeat SPA in parturient women. However, the important teaching concepts of this study are as follows; considering that failure in spinal anesthesia often happens to assistants and less experienced anesthesiologists, and the text books do not mention reducing the dose of bupivacaine in spinal re-injection, if these specialists regardless of reducing the dose of spinal drug, use bupivacaine with the same initial dose as mentioned in the text books, it can lead to an increase in the spinal level and cause problems for patients and anesthesiologists. Since we also work in the obstetric anesthesia training department and deal with spinal failure, we decided to investigate the reduction of bupivacaine dose following spinal failure so that less experienced

specialists can use this experience and have fewer problems such as increasing the level of block and hypotension, etc.

Conclusion

Spinal anesthesia can be safely repeated with a 10 mg of hyperbaric bupivacaine 0.5% in a caesarean section after the initial spinal failure. SPA with 10 mg of hyperbaric bupivacaine 0.5% can be improves the quality of local anesthesia, prevents side effects and, as a result, increases patient satisfaction.

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 Ethics Committees of Hamadan University of Medical Sciences (IR.UMSHA.REC.1398.232). The patients/participants provided their written informed consent to participate in this study.

Author contributions

FR-B, NM, and AP: study concept and design. FR-B, NM, and FS: analysis and interpretation of data, study concept and design, and Critical revision of the manuscript for important intellectual content. AP: acquisition of data and drafting of the manuscript. FS: statistical analysis. 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.

Publisher's note

References

1. Ghaffari S, Dehghanpisheh L, Tavakkoli F, Mahmoudi H. The effect of spinal versus general anesthesia on quality of life in women undergoing cesarean delivery on maternal request. *Cureus.* (2018) 10:e3715. doi: 10.7759/cureus.3715

2. Ring L, Landau R, Delgado C. The current role of general anesthesia for cesarean delivery. *Curr Anesthesiol Rep.* (2021) 11:18–27. doi: 10.1007/s40140-021-00437-6

3. Parikh KS, Seetharamaiah S. Approach to failed spinal anaesthesia for caesarean section. *Indian J Anaesth.* (2018) 62:691–7. doi: 10.4103/ija.IJA_457_18

4. Kwak KH. Postdural puncture headache. *Korean J Anesthesiol.* (2017) 70:136–43. doi: 10.4097/kjae.2017.70.2.136

5. Hofhuizen C, Lemson J, Snoeck M, Scheffer GJ. Spinal anesthesia-induced hypotension is caused by a decrease in stroke volume in elderly patients. *Local Reg Anesth.* (2019) 12:19–26. doi: 10.2147/lra.s193925

6. Lesser JB, Sanborn KV, Valskys R, Kuroda M. Severe bradycardia during spinal and epidural anesthesia recorded by an anesthesia information management system. *Anesthesiology.* (2003) 99:859–66. doi: 10.1097/00000542-200310000-00018

7. Kent CD, Bollag L. Neurological adverse events following regional anesthesia administration. *Local Reg Anesth.* (2010) 3:115–23. doi: 10.2147/lra.s8177

8. Jelting Y, Klein C, Harlander T, Eberhart L, Roewer N, Kranke P. Preventing nausea and vomiting in women undergoing regional anesthesia for cesarean section: challenges and solutions. *Local Reg Anesth.* (2017) 10:83–90. doi: 10.2147/lra.s111459

9. Kocarev M, Watkins E, McLure H, Columb M, Lyons G. Sensory testing of spinal anaesthesia for caesarean section: differential block and variability. *Int J Obstet Anesth.* (2010) 19:261–5. doi: 10.1016/j.ijoa.2010.02.002

10. Fakherpour A, Ghaem H, Fattahi Z, Zaree S. Maternal and anaesthesia-related risk factors and incidence of spinal anaesthesia-induced hypotension in elective caesarean section: a multinomial logistic regression. *Indian J Anaesth.* (2018) 62:36–46. doi: 10.4103/ija.IJA_416_17

11. Sushma KS, Ramaswamy AH, Shaikh SI. Correlation between Weight of the baby and the level of sensory blockade in spinal anaesthesia for caesarean section: an observational study. *Anesth Essays Res.* (2018) 12:318–21. doi: 10.4103/aer.AER_164_17

12. Fettes PDW, Jansson J-R, Wildsmith JAW. Failed spinal anaesthesia: mechanisms, management, and prevention. *Br J Anaesth.* (2009) 102:739–48. doi: 10.1093/bja/aep096

13. Ashagrie HE, Ahmed SA, Melesse DY. The incidence and factors associated with failed spinal anesthesia among parturients underwent cesarean section, 2019: a prospective observational study. *Int J Surg Open.* (2020) 24:47–51. doi: 10.1016/j.ijso.2020.03.009

14. Alabi AA, Adeniyi OV, Adeleke OA, Pillay P, Haffajee MR. Factors associated with failed spinal anaesthesia for caesarean sections in Mthatha general hospital,

Eastern Cape, South Africa. *S Afr Fam Pract.* (2017) 59:128–32. doi: 10.1080/20786190.2017.1292696

15. At A, So O. Failed spinal anaesthesia for caesarean section. *J West Afr Coll Surg.* (2011) 1:1–17.

16. Colish J, Milne AD, Brousseau P, Uppal V. Factors associated with failure of spinal anesthetic: an 8-year retrospective analysis of patients undergoing elective hip and knee joint arthroplasty. *Anesth Analg.* (2020) 130:e19–22. doi: 10.1213/ane.0000000000004304

17. Auroy Y, Benhamou D, Péquignot F, Jougla E, Lienhart A. [Survey of anaesthesia-related mortality in France: the role of aspiration of gastric contents]. *Ann Fr Anesth Reanim.* (2009) 28:200–5. doi: 10.1016/j.annfar.2008.12.018

18. Alimian M, Mohseni M, Faiz SHR, Rajabi A. The effect of different doses of intrathecal hyperbaric bupivacaine plus sufentanil in spinal anesthesia for cesarean sections. *Anesthesiol Pain Med.* (2017) 7:e14426. doi: 10.5812/aapm.14426

19. Chambers WA, Littlewood DG, Edstrom HH, Scott DB. Spinal anaesthesia with hyperbaric bupivacaine: effects of concentration and volume administered. *Br J Anaesth.* (1982) 54:75–80. doi: 10.1093/bja/54.1.75

20. Burlacu CL, Buggy DJ. Update on local anesthetics: focus on levobupivacaine. *Ther Clin Risk Manag.* (2008) 4:381–92. doi: 10.2147/tcrm.s1433

21. Bhar D, RoyBasunia S, Das A, Chhaule S, Mondal SK, Bisai S, et al. Repeat spinal anesthesia in cesarean section: a comparison between 10 mg and 12 mg doses of intrathecal hyperbaric (0.05%) bupivacaine repeated after failed spinal anesthesia: a prospective, parallel group study. *Anesth Essays Res.* (2016) 10:362–9. doi: 10.4103/0259-1162.172725

22. World Medical Association. Declaration of helsinki: ethical principles for medical research involving human subjects. *JAMA.* (2013) 310:2191–4. doi: 10.1001/jama.2013.281053

23. Jayaraman J. Guidelines for reporting randomized controlled trials in paediatric dentistry based on the CONSORT statement. *Int J Paediatr Dent.* (2020) 31(Suppl. 1):38–55. doi: 10.1111/ipd.12733

24. Delgado DA, Lambert BS, Boutris N, McCulloch PC, Robbins AB, Moreno MR, et al. Validation of digital visual analog scale pain scoring with a traditional paper-based visual analog scale in adults. *J Am Acad Orthop Surg Glob Res Rev.* (2018) 2:e088. doi: 10.5435/JAAOSGlobal-D-17-00088

25. Graham AC, McClure JH. Quantitative assessment of motor block in labouring women receiving epidural analgesia. *Anaesthesia.* (2001) 56:470–6. doi: 10.1046/j.1365-2044.2001.01524-6.x

26. Rasheed A, Amirah M, Abdallah M, Parameaswari PJ, Issa M, Alharthy A. RAMSAY sedation scale and richmond agitation sedation scale (RASS): a cross sectional study. *Health Sci J.* (2018) 12:604. doi: 10.21767/1791-809X.1000604

27. Pokharel A. Study of failed spinal anesthesia undergoing caesarean section and its management. *Postgrad Med J NAMS.* (2011) 11:11-5.

28. Klimek M, Rossaint R, van de Velde M, Heesen M. Combined spinal-epidural vs. spinal anaesthesia for caesarean section: meta-analysis and trial-sequential analysis. *Anaesthesia.* (2018) 73:875–88. doi: 10.1111/anae.14210

29. Westphal M, Götz T, Booke M. Failed spinal anaesthesia after intrathecal chemotherapy. *Eur J Anaesthesiol.* (2005) 22:235–6. doi: 10.1017/s0265021505220409

30. Kumar R, Singh K, Prasad G, Patel N. Repeat spinal anesthesia after a failed spinal block in a pregnant patient with kyphoscoliosis for elective cesarean section. *J Obstet Anaesth Crit Care.* (2014) 4:84–6. doi: 10.4103/2249-4472.143879

31. Ginosar Y, Mirikatani E, Drover DR, Cohen SE, Riley ET. ED50 and ED95 of intrathecal hyperbaric bupivacaine coadministered with opioids for cesarean delivery. *Anesthesiology.* (2004) 100:676–82. doi: 10.1097/00000542-200403000-00031

32. Deshpande S, Idriz R. Repeat dose after an inadequate spinal block. *Anaesthesia.* (1996) 51:892. doi: 10.1111/j.1365-2044.1996.tb12639.x

33. Fitzgerald JP, Fedoruk KA, Jadin SM, Carvalho B, Halpern SH. Prevention of hypotension after spinal anaesthesia for caesarean section: a systematic review and network meta-analysis of randomised controlled trials. *Anaesthesia.* (2020) 75:109–21. doi: 10.1111/anae.14841

34. Somboonviboon W, Kyokong O, Charuluxananan S, Narasethakamol A. Incidence and risk factors of hypotension and bradycardia after spinal anesthesia for cesarean section. *J Med Assoc Thai.* (2008) 91:181–7.

35. Demilew BC, Getu D, Tesfaw D, Taye MG. Assessment of satisfaction and associated factors of parturients underwent cesarean section with spinal anesthesia at the General Hospital, Ethiopia; 2019. *Ann Med Surg.* (2021) 65:102282. doi: 10.1016/j.amsu.2021.102282

36. Dharmalingam TK, Ahmad Zainuddin NA. Survey on maternal satisfaction in receiving spinal anaesthesia for caesarean section. *Malays J Med Sci.* (2013) 20:51–4.

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The calibration of esophageal pressure by proper esophageal balloon filling volume: A clinical study

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Background: Esophageal pressure (Pes) can be used as a reliable surrogate for pleural pressure, especially in critically ill patients requiring personalized mechanical ventilation strategies. How to choose the proper esophageal balloon filling volume and then find the optimal value of esophageal pressure remains a challenge. The study aimed to assess the feasibility of catheters for Pes monitoring in mechanically ventilated patients.

Materials and methods: Twelve patients under pressure-controlled mechanical ventilation were included in this study. Raw esophageal pressure was recorded at different balloon filling volumes. Then, the P-V curves were determined. V_{WORK} was the intermediate linear section on the end-expiratory P-V curve, and V_{BEST} was the filling volume providing the maximum difference between Pes at end-inspiration and end-expiration. The raw value of Pes was recorded, and the calibrated values of Pes were calculated by calculating the esophageal wall pressure (Pew) and esophageal elastance (Ees).

Results: Twenty-four series of Pes measurements were performed. The mean V_{MIN} and V_{MAX} were 2.17 ± 0.49 ml (range, 1.0–3.0 ml) and 6.79 ± 0.83 ml (range, 5.0–9.0 ml), respectively, whereas V_{BEST} was 4.69 ± 0.16 ml (range, 2.0–8.0 ml). Ees was 1.35 ± 0.51 cm H_2O/ml (range, 0.26–2.38 cm H_2O/ml). The estimated Pew at V_{BEST} was 3.16 ± 2.19 cm H_2O (range, 0–7.97 cm H_2O). Patients with a body mass index (BMI) $\geq$ 25 kg/m^2 had a significantly lower V_{MAX} (5.88 [5.25–6] vs. 7.25 [7–8] ml, p = 0.006) and a significantly lower V_{BEST} (3.69 [2.5–4.38] vs. 5.19 [4–6] ml, p = 0.036) than patients with a BMI < 25 kg/m^2. Patients with positive end-expiratory pressure (PEEP) $\geq$ 10 cm H_2O had a lower V_{MIN} and V_{BEST} than patients with PEEP < 10 cm H_2O, $P > 0.05$. Patients in the supine position had a higher esophageal pressure than those in the prone position with the same balloon filling volume.

Conclusions: Calibration of esophageal pressure to identify the best filling volume of esophageal balloon catheters is feasible. The esophageal pressure can be influenced by BMI, PEEP, and position. It is necessary to titrate the optimal inflation volume again when the PEEP values or the positions change.

KEYWORDS

esophageal pressure, esophageal balloon catheter, balloon filling volume, mechanical ventilation, calibration

Introduction

An increasing number of clinicians have been focusing on esophageal pressure (Pes) manometry because of its vital role in understanding pulmonary pathophysiology since the end of the 19th century. Due to the impossibility of directly measuring pleural pressure in clinical practice, esophageal pressure has been proposed as a reliable surrogate for pleural pressure (Ppl) (1–3). We can estimate Ppl and hence transpulmonary pressure (P_L), which is the distending pressure of the lungs. In the past 20 years, this technique has been used in critically ill patients, especially patients with acute respiratory failure (ARF).

It is extremely useful to understand each patient's individual respiratory physiology, particularly for patients with morbid obesity and acute respiratory distress syndrome (ARDS) (4, 5). First, it is useful to characterize the respiratory system mechanics during passive mechanical ventilation, such as titration of positive end-expiratory pressure (PEEP) and monitoring transpulmonary driving pressure (ΔP_L). Second, it can be used to monitor patients' respiratory muscle activity during assisted ventilation. Last, it contributes to assessing patient-ventilator interaction (i.e., synchrony and asynchrony) at bedside. Therefore, esophageal pressure can be monitored during the entire process of mechanical ventilation, especially personalized mechanical ventilation strategies (6). The esophageal pressure was described by Luciani L more than 100 years ago (1), however, esophageal manometry is still not widespread. The LUNG SAFE study showed that esophageal pressure is monitored in <1% of ARDS patients receiving invasive therapy (7, 8). It is difficult to monitor in clinical practice because the quality, accuracy, and reliability of the measurement can be affected by the characteristics of the balloon catheter, the balloon-filling pressure, the position of the catheter in the patient, and the position of the esophagus' (7). In recent years, several researchers have focused on balloon-filling volume selection in esophageal pressure *in vitro* and *in vivo* studies. Accurate measurement of esophageal pressure was found to be clearly correlated with the balloon-filling volume. Pes can be underestimated because of underfilled balloon volume or overestimated due to overfilled balloon volume (9–13). However, the range of appropriate filling volumes varies among catheters. Any catheter needs to be verified for reliable esophageal pressure measurement by finding the optimal filling volume of the balloon. This study used Mindray second-generation balloon catheters to investigate the quality and accuracy of the catheter for Pes monitoring in mechanically ventilated patients and to analyze related factors. A fast and practical cannulation procedure is provided.

Materials and methods

The study was approved by the Institutional Research and Ethics Committee of the Peking Union Medical College Hospital (NO. ZS-2458). Informed consent was obtained as required before data were included in the study.

We enrolled heavily sedated ICU patients (Richmond Agitation-Sedation Scale score ≤ -3) with ARF under controlled mechanical ventilation. ARF was by a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen less than 300 mmHg. Exclusion criteria were as follows: (1) age under 18 years; (2) any contraindication for esophageal balloon catheter insertion (diagnosed or suspected esophageal varices, history of esophageal or gastric surgery, evidence of severe coagulopathy, etc.); (3) evidence of active air leakage from the lung, including bronchopleural fistula, and pneumomediastinum; and (4) lack of informed consent.

While undergoing treatment, the included patients remained in the supine position without elevating the head of the bed. The esophageal balloon had a length of 10 cm and a nominal volume of 10 ml. The tube with esophageal and gastric balloon (SDY-2, AMK Medical, Guangzhou, China) was inserted in the mid-lower third of the thoracic esophagus for clinical purposes. Appropriate catheter position was confirmed by cardiac oscillations on Pes tracing and radiopaque markers on chest X-ray. A positive pressure occlusion test was performed at end-expiratory occlusion, and the ratio of changes in Pes to changes in Paw ($\Delta Pes/\Delta Paw$) during the compression of the chest wall was calculated and maintained at 0.8∼1.2. To obtain esophageal balloon pressure-volume curves, we filled the Mindray esophageal balloon with air in 1 ml increments from 0 to 10 ml unless the esophageal pressure clearly rose. At each volume step, the balloon was completely deflated by applying a negative pressure, fully

inflated with 10 ml of air, and finally deflated. Then dynamic pressures were obtained at end-inspiration or end-expiration (the esophageal pressure monitoring procedure is shown in **Supplementary Video 1**).

We recorded the Pes at end-inspiration (PesEI) and end-expiration (PesEE) for each filling volume in each patient. From those data, we obtained two curves to express the patient pressure-volume (P-V) relationship between balloon filling volume and esophageal balloon pressure of end-inspiration and end-expiration. On the end-expiratory P-V curve, the intermediate linear section was identified as V_{WORK}, and the lower and upper limits were expressed as minimum and maximum filling volumes (V_{MIN} and V_{MAX}). The filling volume providing the maximum difference between PesEI and PesEE was identified as V_{BEST}. The slope of the intermediate linear section on the end-expiratory P-V curve obtained by least square fitting was defined as the elastance of the esophagus (Ees) (14). As Milic-Emili et al. (3) and Francesco Mojoli et al. (9) said, the esophageal wall pressure (Pew), for any filling volume (V_X) above V_{MIN}, was calculated as: Pew = (V_X–V_{MIN}) × Ees. The calibrated values of Pes (Pes_{CAL}) were obtained by measuring the end-expiration Pes of the best filling volume and Pes_{CAL} = Pes-Pew (3, 14).

To obtain gastric balloon pressure (Pga), the Mindray gastric balloon was completely deflated by applying a negative pressure, fully inflated with 10 ml of air, and finally withdrawn by 5 ml. Then, the Pga of end-inspiration and end-expiration was recorded.

Statistics

Patient demographics and relevant clinical data are expressed as the mean and standard deviation (SD) or median (25th–75th percentile) for continuous, variables, and numbers (percentages) for categorical variables. Differences between body mass index (BMI), position, and PEEP groups were compared by using the *t*-test or the Wilcoxon signed-rank test where appropriate. Bland-Altman analysis was used to verify the consistency of Pes_{VBEST} and Pes_{CAL} at V_{BEST}. Upper and lower limits of agreement were defined as bias ± 1.96 SD of the mean. Statistical analyses were computed using GraphPad Prism 8.0.2 software (GraphPad Software, San Diego, CA, USA).

Results

Population characteristics and ventilator and respiratory parameters

Twenty-four series of measurements were collected from 12 patients (age, 48.9 ± 19.9 years, 66.7% male) under pressure-controlled mechanical ventilation. The baseline characteristics are reported in **Table 1**. Four patients were measured twice, one patient was measured three times, and one patient was measured five times at different ventilator parameters or underlying different disease states. Twenty-one series of measurements were taken with the patient in the supine position with the bed at 0 degrees while three series of measurements were taken with the patient in the prone position. Three series were taken with the patient receiving mechanical ventilation and VV ECMO treatment. Four series were taken where the patient had undergone thoracotomy. Eighteen series were measured for Pes and gastric internal pressure (Pga). The baseline scores of APACHE II and SOFA were 20.8 ± 7.1 and 12.4 ± 2.9, respectively. We recorded a PaO_2/FiO_2 of 228.6 ± 86.6 mmHg, a tidal volume/predicted body weight of 5.9 ± 1.1 ml/kg, Pplat of 21.0 ± 3.9 cm H_2O, Pdriv of 11.5 ± 2.8 cm H_2O, and Crs of 34.1 ± 12.2 ml/cm H_2O.

TABLE 1 Baseline characteristics of the patients (n = 12).

Characteristic	Value
Age, years	48.9 ± 19.9
Male, *n* (%)	8 (66.7%)
Body mass index, kg/m^2	25.8 ± 4.7
APACHE II score	20.8 ± 7.1
SOFA score	12.4 ± 2.9
PaO_2/FiO_2, mmHg	228.6 ± 86.6
Tidal volume/PBW, ml/kg	5.9 ± 1.1
PEEP, cm H_2O	9.6 ± 2.8
Pplat, cm H_2O	21.0 ± 3.9
Pdriv, cm H_2O	11.5 ± 2.8
Crs, ml/cm H_2O	34.1 ± 12.2

APACHE, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; PaO_2/FiO_2: ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PBW: predicted body weight; PEEP: positive end-expiratory pressure; Pplat: airway plateau pressure; Pdriv: airway driving pressure; Crs: respiratory system compliance; Continuous data are shown as the mean value ± standard deviation.

Parameters of end-expiratory and end-inspiratory P-V curves

End-expiratory and end-inspiratory raw esophageal balloon P-V curves were obtained in all patients (**Figure 1**). An intermediate linear section was identified on the end-expiratory esophageal balloon P-V curve in each of the clinical measurements. The mean V_{MIN} and V_{MAX} were 2.17 ± 0.49 (range, 1.0–3.0 ml) and 6.79 ± 0.83 ml (range, 5.0–9.0 ml), respectively, while the best filling volume was 4.69 ± 0.16 ml (range, 2.0–8.0 ml). The slope of the linear section of the curve, i.e., Ees, was 1.35 ± 0.51 cm H_2O/ml (range 0.26–2.38 cm H_2O/ml). The estimated Pew at V_{BEST} was 3.16 ± 2.19 cm H_2O (range, 0–7.97 cm H_2O). Four different patients' end-inspiratory and end-expiratory P-V curves are shown in **Figure 2**.

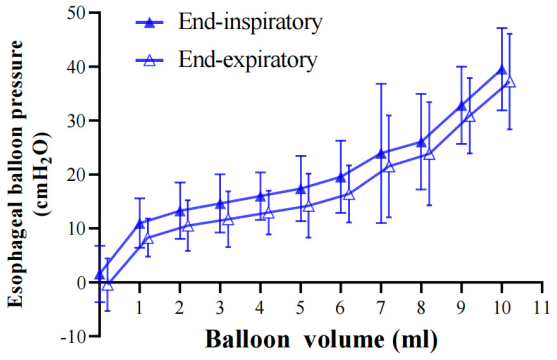

FIGURE 1
Esophageal balloon pressure-volume curves. Relationship between balloon filling volume and Pes values, both at end-inspiration (PesEI, solid blue triangle) and at end-expiration (PesEE, hollow blue triangle). On the end-expiratory pressure-volume (P-V) curve, the intermediate linear section was graphically detected and analyzed for its lower and upper limits (V_{MIN} and V_{MAX}, respectively). The range between V_{MIN} and V_{MAX} was considered to correspond to appropriate balloon filling, with volumes below V_{MIN} denoting underfilling and volumes above V_{MAX} denoting overdistention. Within the appropriate filling range, we identified V_{BEST}, i.e., the filling volume associated with the maximum difference between PesEI and PesEE. Pes: esophageal pressure. Data are shown as mean value ± standard deviation.

Calibration procedure

The calibration procedure is shown in Figure 3.

Influence factors of the best esophageal balloon filling volume

Patients with a BMI ≥25 kg/m^2 had a lower V_{MIN} (1.88 [1.25–2.0] vs. 2.3 [2–3] ml, $p = 0.11$), a significantly lower V_{MAX} (5.88 [5.25–6] vs. 7.25 [7–8] ml, $p = 0.006$), and a significantly lower V_{BEST} (3.69 [2.5–4.38] vs. 5.19 [4–6] ml, $p = 0.036$) than patients with BMI < 25 kg/m^2 (Figure 4).

Patients with PEEP ≥ 10 cm H_2O had a lower V_{MIN} (2.09 [2.0–3.0] vs. 2.23 [2.0–3.0] ml, $p = 0.6$), V_{MAX} (6.55 [6.0–7.0] vs. 7 [6.5–8] ml, $p = 0.29$), and V_{BEST} (4.59 [4–6] vs. 4.77 [3.5–6] ml, $p = 0.8$) than patients with PEEP < 10 cm H_2O (Figure 5).

Patients in the supine position had a higher esophageal pressure than those in the prone position with the same balloon filling volume according to three patients' data (Figure 6).

Moreover, the gastric pressure was relatively stable when the esophageal balloon filling volume increased (Figure 7).

Discussion

We performed esophageal pressure monitoring in patients with ARF under invasive passive mechanical ventilation. We had three main findings: (1) The best filling volume (V_{BEST}) can be quickly confirmed by the maximum esophageal pressure swing (ΔPes) of the intermediate linear section on the balloon P-V curve; (2) V_{BEST} varies widely in different patients or in different PEEPs, BMIs, and positions; and (3) Mindray catheters are suitable for esophageal manometry in critically ill patients. The gastric pressure was stable when the esophageal balloon filling volume increased.

There have been few clinical studies on esophageal balloon inflation pressure. Mojoli et al. monitored 36 patients under controlled ventilation with 50 series of esophageal pressure measurements. The esophageal pressure data were recorded from 0 to the maximum inflation volume recommended. The study showed that calibrated values of Pes are different from the absolute value of the esophageal pressure and the esophageal wall pressure value. The research steps are cumbersome, but it is of great significance for clinicians to accurately understand the esophageal pressure (9). Their research suggested that the intermediate linear section on the end-expiratory P-V curve was closely parallel to each other (*in vitro* and *in vivo*), when pressure generated by the esophageal wall was subtracted from Pes. Although the *in vitro* study showed that Pes is stable within the V_{WORK} on the P-V curve, the Pes *in vivo* linearly increased because of esophageal elastance (Ees) (9, 10, 12). Sun et al enrolled 40 patients under passive ventilation and verified the reliability of the method on a Cooper balloon catheter (geometric volume of 2.8 ml) (11). The method of calibrating Pes values was verified again during pressure support ventilation (15). Compared with the *in vitro* study, V_{BEST} was significantly increased in the *in vivo* test, suggesting that the pressure of the esophageal wall may have an effect on it. Mojoli et al. (9) showed that V_{MIN} is positively related to the surrounding pressure; that is, the greater the inflation volume is, the higher the esophageal pressure. Their research showed that the V_{BEST} was 3.5 ± 1.9 ml (range, 0.5–6.0 ml), which was larger than the traditional recommended small inflation volume. The study also found that the inflation volume that can pass the validation occlusion test is greater than 0.5 ml, so 0.5 ml may not be able to accurately assess the accurate value of the patient's esophageal pressure. Sun et al showed that the V_{BEST} for smaller balloons (geometric volume of 2.8 ml) is 1.0 ml (range, 0.6–1.4 ml) and was highly variable among different patients and conditions (11). In this study, an esophageal pressure balloon with an inflation volume of 10 ml was used. V_{BEST} was 4.69 ± 1.36 ml (range, 2.0–8.0 ml), which was larger than that reported by Mojoli et al's. Our study enrolled patients with lower PEEP and lower BMI compared with Mojoli's research (9). Our study shows that this method should be used with different balloon catheters to determine the inflation volume for more accurate esophageal pressure measurement (Table 2).

The intrathoracic pressure in critically ill patients can be affected by many factors, such as the accurate measurement of esophageal pressure. Therefore, the following factors may

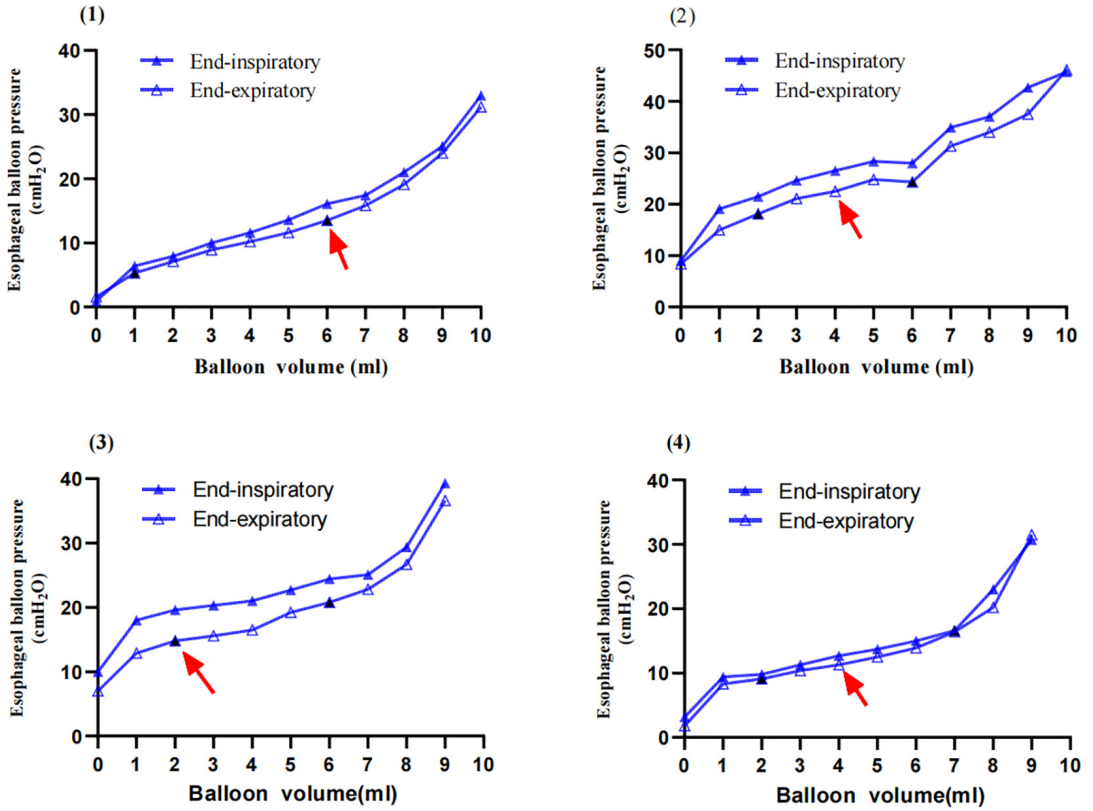

FIGURE 2
Examples of inspiratory and expiratory esophageal balloon pressure-volume curves. The solid blue triangle refers to end-inspiratory esophageal pressure (PesEI); the hollow blue triangle refers to end-expiratory esophageal pressure (PesEE). The solid black triangle refers to V_{MIN} and V_{MAX}, and the red arrow represents the V_{BEST}. (1) A 42-years-old female patient, BMI 21.5 kg/m^2, with severe pneumonia (methicillin-sensitive Staphylococcus aureus, MSSA), pulmonary ARDS with focal lesion, VV-ECMO. PC 8 cm H_2O, PEEP 10 cm H_2O, TV 200.9 ml, Pplat 18 cm H_2O, esophageal elastance 1.59 cm H_2O/ml, and Pew at V_{BEST} 7.97 cm H_2O; V_{MIN} 1 ml; V_{MAX} 6 ml; and V_{BEST} 6 ml. (2) An 18-years-old female patient, BMI 23.4 kg/m^2, with infective endocarditis (IE), severe pneumonia (methicillin-resistant staphylococcus aureus, MRSA) and post-operative mitral valve replacement and ARDS with Diffuse lesion; PC 13 cm H_2O, PEEP 8 cm H_2O, TV 216.5 ml, Pplat 26 cm H_2O; V_{MIN} 2 ml, V_{MAX} 6 ml, and V_{BEST} 4 ml, esophageal elastance 1.61 cm H_2O/ml, and Pew at V_{BEST} 3.22 cm H_2O. (3) A 29-years-old male patient, BMI 38 kg/m^2, with severe acute pancreatitis (SAP), abdominal compartment syndrome (ACS), extrapulmonary ARDS with diffuse lesion, VV-ECMO; PC 10 cm H_2O, PEEP 15 cm H_2O, TV 475 ml, Pplat 25 cm H_2O; V_{MIN} 2 ml, V_{MAX} 6 ml, and V_{BEST} 2 ml, esophageal elastance 1.56 cm H_2O/ml, and Pew at V_{BEST} 0 cm H_2O. (4) A 74-years-old male patient in the prone position, BMI 24.8 kg/m^2, with severe pneumonia, septic shock, ARF with diffuse lesion; PC 9 cm H_2O, PEEP 9 cm H_2O, TV 358 ml, Pplat 18 cm H_2O; V_{MIN} 2 ml, V_{MAX} 7 ml, and V_{BEST} 4 ml, esophageal elastance 1.41 cm H_2O/ml, and Pew at V_{BEST} 2.81 cm H_2O.

cause different measurement results. The first is body position. Previous studies have suggested that esophageal pressure when patients are in the supine position is higher than that in other positions due to the influence of mediastinal organs and tissues (16, 17). Washko et al. (18) showed that higher Pes in the supine position can be affected by a direct compression artifact and the change in lung relaxation volume in different positions. Yoshida's study in an animal model and human cadavers showed that esophageal pressure measurement in the supine position as a substitute for Ppl at the mid-chest is suitable (19). Previous research was performed with patients in different body positions (supine with the bed at 20–30 degrees head up, lateral and prone at 45 degrees), while our study was performed with patients in the supine position or prone position without elevating the head of the bed. Our research showed the same results as other studies that esophageal pressure was higher in the supine position than in the prone position (**Figure 6**).

Our findings also showed that the higher the BMI and PEEP value were, the higher the esophageal pressure was (**Figures 4**, **5**). Although previous studies (9) have suggested that, at increasing Pes, filling volumes should increase, our results on patients with higher PEEP and higher BMI (both having higher Pes) do not confirm such a finding; indeed, filling volumes were, overall, not significantly different from patients with lower PEEP and lower BMI, respectively. This suggests that more work is required in this regard. Next, patients in this study had more severe conditions with higher APACHE II scores and SOFA scores. The same patients at different disease stages

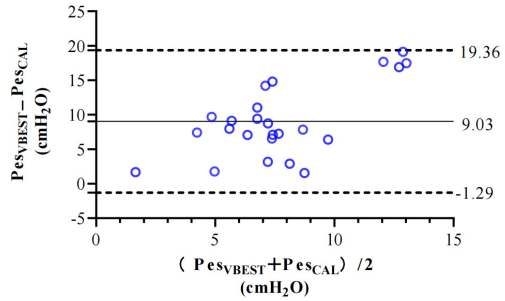

FIGURE 3
Bland-Altman limits of agreements analysis for Pes_{VBEST} and Pes_{CAL} at V_{BEST}. Compared to Pes_{VBEST}, bias (mean difference, continuous line) and precision (± 1.96 SD of the difference, dotted lines) of Pes_{VCAL} were 9.03 ± 10.33 cm H_2O.

had different V_{BEST} values ranging from 3 to 6 ml. Finally, the V_{BEST} was catheter-specific, such as in NutriVent and Marquat catheters, even at the same catheter volume, in an *in vitro* study (12). Similar conclusions may be drawn in *in vivo* tests. The results confirmed the accuracy of the current method used to determine V_{BEST}. Therefore, the filling volume of the esophageal balloon catheter should be rechecked for more accurate results when the factors that may affect esophageal pressure change.

Hence, from the perspective of overall evaluation, the vital contribution to this study was that Mindray's esophageal pressure catheters can be used to guide personalized lung protection strategies. The esophageal pressure will increase as the esophageal balloon volume increases *in vivo* and we should calibrate the esophageal pressure accordingly. In addition, we also found that different positions and different BMI and PEEP values affected the optimal inflation value. We recommend that when we perform esophageal pressure monitoring, the optimal filling volume of Pes should be routinely reselected to clarify the exact esophageal pressure, and calibration of esophageal pressure is also needed.

It shows that there is an overall bias of 10 cm H_2O between raw and calibrated Pes at V_{BEST}, with large limits of

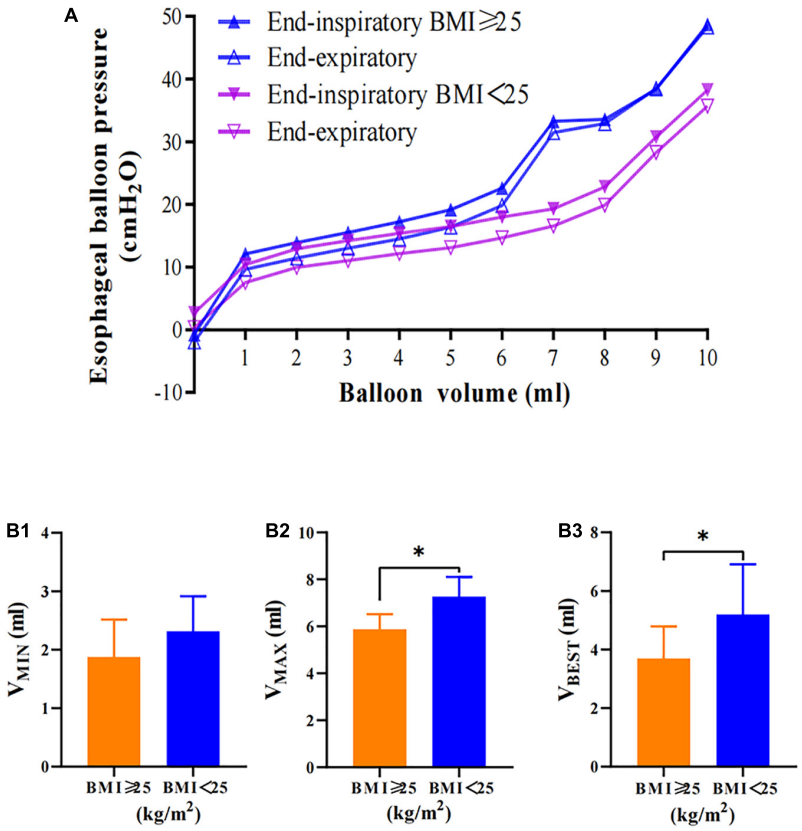

FIGURE 4
Esophageal balloon pressure-volume curves of different BMI groups. **(A)** Relationship between balloon filling volume and values of Pes in the BMI ≥ 25 kg/m^2 (Pes_{EI}, solid blue triangle; Pes_{EE}, hollow blue triangle) and BMI < 25 kg/m^2 (Pes_{EI}, solid purple triangle; Pes_{EE}, hollow purple triangle) groups. Patients in the BMI < 25 kg/m^2 group had lower Pes than those in the BMI ≥ 25 kg/m^2 group. **(B)** Patients in the BMI < 25 kg/m^2 group had higher balloon volume than those in the BMI ≥ 25 kg/m^2 group. *P < 0.05 compared with the BMI ≥ 25 kg/m^2 group. Pes: esophageal pressure.

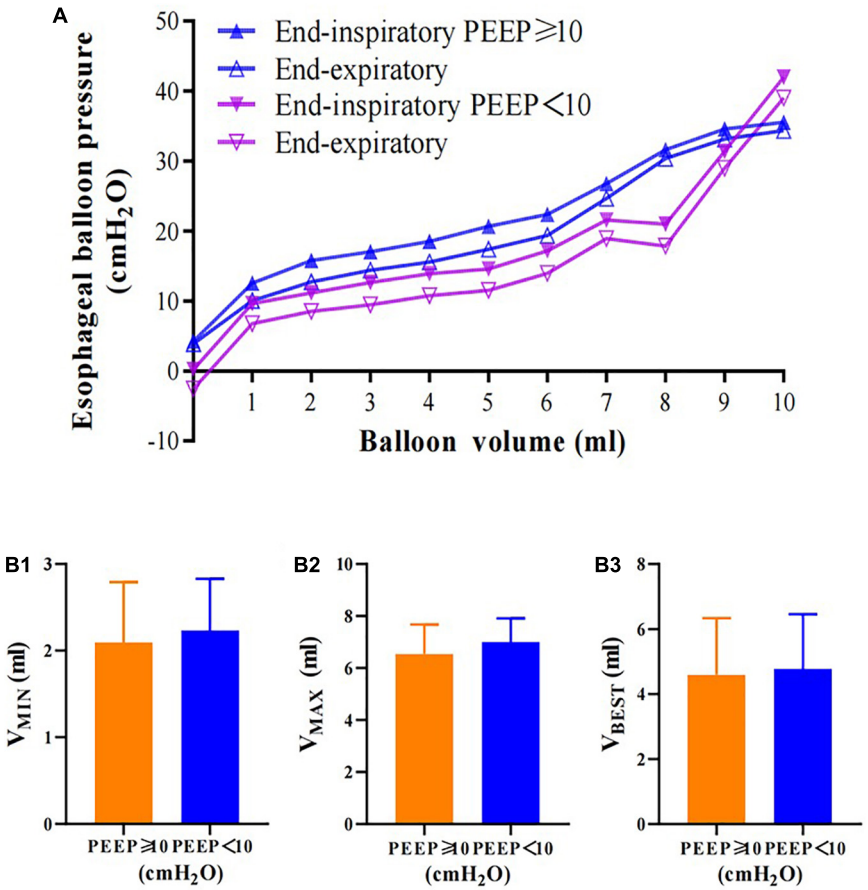

FIGURE 5
Esophageal balloon pressure-volume curves of different PEEP groups. **(A)** Relationship between balloon filling volume and values of Pes in the PEEP $\geq$ 10 cm H_2O (Pes_{EI}, solid blue triangle; Pes_{EE}, hollow blue triangle) and PEEP $<$ 10 cm H_2O (Pes_{EI}, solid purple triangle; Pes_{EE}, hollow purple triangle). Patients in the PEEP $<$ 10 cm H_2O group had lower Pes than those the PEEP $\geq$ 10 cm H_2O group. **(B)** Patients in the PEEP $<$ 10 cm H_2O group had higher V_{MIN}, V_{MAX}, and V_{BEST} than those in the PEEP $\geq$ 10 cm H_2O group. Pes: esophageal pressure. No significant difference was observed.

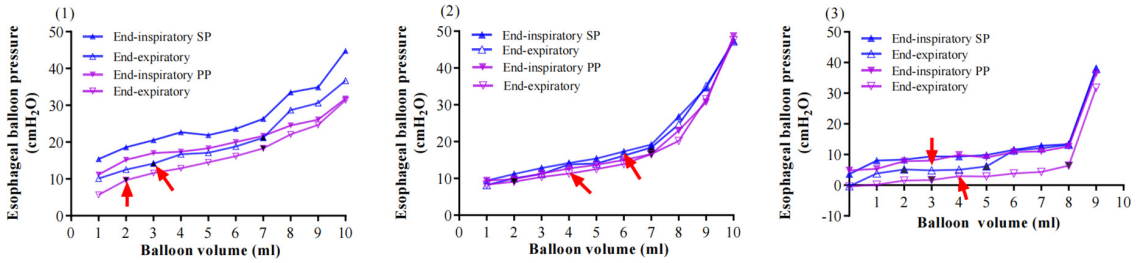

FIGURE 6
Examples of inspiratory and expiratory esophageal balloon pressure-volume curves in different positions. Three patients' relationships between balloon filling volume and values of Pes in the supine position (Pes_{EI}, solid blue triangle; Pes_{EE}, hollow blue triangle) and the prone position (Pes_{EI}, solid purple triangle; Pes_{EE}, hollow purple triangle). The red arrow represents the V_{BEST}, while the solid black triangle represents V_{MIN} and V_{MAX}. Patients in the prone position had lower Pes than those in the supine position. (1) An 18-years-old female patient, BMI 23.4 kg/m^2, with infective endocarditis (IE), severe pneumonia (methicillin-resistant staphylococcus aureus, MRSA), post-operative mitral valve replacement, and pulmonary ARDS with diffuse lesion. PC 13 cm H_2O, PEEP 8 cm H_2O; V_{MIN} 3 vs. 2 ml, V_{MAX} 6 vs. 6 ml and V_{BEST} 3 vs. 2 ml. (2) A 74-years-old male patient, BMI 24.8 kg/m^2, with severe pneumonia, septic shock and pulmonary ARDS with diffuse lesions. PC 9 cm H_2O, PEEP 9 cm H_2O; V_{MIN} 2 vs. 2 ml, V_{MAX} 7 vs. 7 ml and V_{BEST} 6 vs. 4 ml. (3) A 74-years-old male patient, BMI 22.9 kg/m^2, with severe pneumonia, and pulmonary ARDS with diffuse lesions. PC 12 cm H_2O, PEEP 6 cm H_2O; V_{MIN} 2 vs. 3 ml, V_{MAX} 8 vs. 8 ml and V_{BEST} 3 vs. 4 ml.

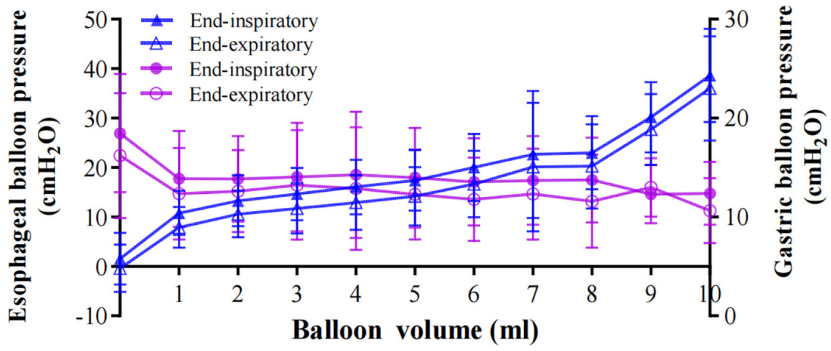

FIGURE 7
The relationship between gastric pressure and esophageal pressure. Solid blue triangles represent Pes_{EI} and hollow blue triangles represent *PesEE*. Gastric balloon pressure of end-inspiration (Pga_{EI}) and end-expiration (Pga_{EE}) are represented by solid purple circles and hollow purple circles, respectively. As the esophageal balloon volume increased, the gastric pressure remained relatively stable. Data are shown as the mean value ± standard deviation.

TABLE 2 Balloon filling volumes in different esophageal catheters.

	Balloon volume (ml)	Vrec (ml)	V_{BEST} (ml)
NutriVent, Sidam, Mirandola, Italy	10	4.0	3.5 ± 1.9 (range, 0.5–6.0)
Cooper, LOT 177405, cooper surgical, United States	2.8	1.0	1.0 (range, 0.6–1.4)
Mindray, SDY-2, AMK Medical, Guangzhou, China	10	5.0	4.69 ± 1.36 (range, 2.0–8.0)

Vrec: factory-recommended inflating volume; V_{BEST}: balloon volume with the largest difference between end-expiratory and end-inspiratory esophageal balloon pressure.

agreement (Figure 3). This is higher than Mojoli and Sun's study, showing that the esophageal wall pressure leads to an overestimation of Pes around 10.33 cm H_2O (9, 11). The esophageal pressure catheter used in our study is different from other studies (7). Some of the included patients are either post-thoracotomy or have focal lung involvement disease. The effects of PEEP, BMI, and position on patients require further study. This may be the reason why our study is different from other studies.

To best of our knowledge, this is the first study to use esophageal and gastric balloon catheters to titrate the proper esophageal balloon filling volume and clarify the relationship between esophageal pressure and intragastric pressure. Diaphragmatic pressure (Pdi) can be used to assess breathing, respiratory muscle function, and the presence of diaphragm paralysis (20). It is well known that Pdi can be calculated by Pga minus Pes. Our research showed that the gastric pressure (Pga) is relatively stable, while Pes increased with increased balloon filling volume. So, the value of Pes can have an effect on Pdi.

Limitations of the study

In this study, the supine and prone positions were used to measure esophageal pressure, and the effect of different body positions on esophageal pressure is still inconclusive. This study, based on the method of Mojoli et al. (9), used the calibrated values of Pes to minimize possible factors affecting the accuracy of esophageal pressure and requires further evaluation. The research was performed with only one Mindray esophageal balloon catheter. Although our research and previous studies have confirmed the reliability of the method (9, 11, 15), whether the results can be directly generalized to other esophageal catheters and other patient populations is still in question. The sample size of this study was small, and one patient underwent up to five tests, which may be a factor that led to the overall higher esophageal pressure values in this study than in other studies (9, 11). The esophageal pressure mainly indicates the intrathoracic pressure in the middle of the lung, and whether it can be used to assess post-thoracotomy or focal lung disease needs more research to be confirmed.

Conclusion

In summary, the method to identify the best filling volume of esophageal balloon catheters is feasible. This approach is well validated in Mindary's intercropping. It might aid in developing personalized mechanical ventilation at bedside, such as different body positions and different intervention methods. Further study is required to validate the clinical applicability of this method.

Data availability statement

The datasets used or analyzed in this study are available from the corresponding authors on reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Research and Ethics Committee of the Peking Union Medical College Hospital (NO. ZS-2458). The patients/participants provided their written informed consent to participate in this study.

Author contributions

YL and HH took responsibility for the integrity of the study as a whole. JJ was responsible for the collection of data, data management, statistical analysis, and drafted the manuscript. LS was responsible for the study design, conception, data management, and statistical analysis. WC and CW participated in the collection of data and data management. XR, BT, and HZ took responsibility for the study design and conception. All authors revised the manuscript for content and 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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Supplementary material

The Supplementary Material for this article can be found online at: https://figshare.com/articles/media/The_calibration_of_esophageal_pressure_by_proper_esophageal_balloon_filling_volume_A_clinical_study_esophageal_pressure_monitoring_procedure_Supplementary_Video_1_mp4/21667745

References

1. Luciani L. *Esame Comparativo Dei Metodi Per Registrare la Pressione Toracica e Addominale. Delle Oscillazioni Della Pressione Intratora Cica e Intraddominale*. Torino: Vicenzo Bona (1877). p. 2–18.

2. Cherniack RM, Farhi LE, Armstrong BW, Proctor DF. A comparison of esophageal and intrapleural pressure in man. *J Appl Physiol.* (1955) 8:203–11. doi: 10.1152/jappl.1955.8.2.203

3. Milic-Emili J, Mead J, Turner JM, Glauser EM. Improved technique for estimating pleural pressure from esophageal balloons. *J Appl Physiol.* (1964) 19:207–11. doi: 10.1152/jappl.1964.19.2.207

4. De Santis Santiago R, Teggia Droghi M, Fumagalli J, Marrazzo F, Florio G, Grassi LG, et al. High pleural pressure prevents alveolar overdistension and hemodynamic collapse in acute respiratory distress syndrome with class III obesity. A clinical trial. *Am J Respir Crit Care Med.* (2021) 203:575–84.

5. Fumagalli J, Santiago RRS, Teggia Droghi M, Zhang C, Fintelmann FJ, Troschel FM, et al. Lung recruitment in obese patients with acute respiratory distress syndrome. *Anesthesiology.* (2019) 130:791–803. doi: 10.1097/ALN.0000000000002638

6. Pelosi P, Ball L, Barbas CSV, Bellomo R, Burns KEA, Einav S, et al. Personalized mechanical ventilation in acute respiratory distress syndrome. *Crit Care.* (2021) 25:250. doi: 10.1186/s13054-021-03686-3

7. Pham T, Telias I, Beitler JR. Esophageal manometry. *Respir Care.* (2020) 65:772–92. doi: 10.4187/respcare.07425

8. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA.* (2016) 315:788–800. doi: 10.1001/jama.2016.0291

9. Mojoli F, Iotti GA, Torriglia F, Pozzi M, Volta CA, Bianzina S, et al. In vivo calibration of esophageal pressure in the mechanically ventilated patient makes measurements reliable. *Crit Care.* (2016) 20:98. doi: 10.1186/s13054-016-1278-5

10. Walterspacher S, Isaak L, Guttmann J, Kabitz HJ, Schumann S. Assessing respiratory function depends on mechanical characteristics of balloon catheters. *Respir Care.* (2014) 59:1345–52. doi: 10.4187/respcare.02974

11. Sun XM, Chen GQ, Huang HW, He X, Yang YL, Shi ZH, et al. Use of esophageal balloon pressure-volume curve analysis to determine esophageal wall elastance and calibrate raw esophageal pressure: a bench experiment and clinical study. *BMC Anesthesiol.* (2018) 18:21. doi: 10.1186/s12871-018-0488-6

12. Mojoli F, Chiumello D, Pozzi M, Algieri I, Bianzina S, Luoni S, et al. Esophageal pressure measurements under different conditions of intrathoracic pressure. An in vitro study of second generation balloon catheters. *Minerva Anestesiol.* (2015) 81:855–64.

13. Yang YL, He X, Sun XM, Chen H, Shi ZH, Xu M, et al. Optimal esophageal balloon volume for accurate estimation of pleural pressure at end-expiration and end-inspiration: an in vitro bench experiment. *Intensive Care Med Exp*. (2017) 5:35. doi: 10.1186/s40635-017-0148-z

14. Hedenstierna G, Jarnberg PO, Torsell L, Gottlieb I. Esophageal elastance in anesthetized humans. *J Appl Physiol Respir Environ Exerc Physiol.* (1983) 54:1374–8. doi: 10.1152/jappl.1983.54.5.1374

15. Cammarota G, Verdina F, Santangelo E, Lauro G, Boniolo E, Tarquini R, et al. Oesophageal balloon calibration during pressure support ventilation: a proof of concept study. *J Clin Monit Comput.* (2020) 34:1223–31. doi: 10.1007/s10877-019-00436-3

16. Attinger EO, Herschfus JA, Segal MS. The mechanics of breathing in different body positions. II. In cardiopulmonary disease. *J Clin Invest.* (1956) 35:912–20. doi: 10.1172/JCI103344

17. Attinger EO, Monroe RG, Segal MS. The mechanics of breathing in different body positions. I. In normal subjects. *J Clin Invest.* (1956) 35:904–11. doi: 10.1172/JCI103343

18. Washko GR, O'Donnell CR, Loring SH. Volume-related and volume-independent effects of posture on esophageal and transpulmonary pressures in healthy subjects. *J Appl Physiol (1985).* (2006) 100:753–8. doi: 10.1152/japplphysiol.00697.2005

19. Yoshida T, Amato MBP, Grieco DL, Chen L, Lima CAS, Roldan R, et al. Esophageal manometry and regional transpulmonary pressure in lung injury. *Am J Respir Crit Care Med.* (2018) 197:1018–26. doi: 10.1164/rccm.201709-1806OC

20. Benditt JO. Esophageal and gastric pressure measurements. *Respir Care.* (2005) 50:68–75; discussion75–7.

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Comparison of paravertebral block vs. general anesthesia for percutaneous nephrolithotomy: A retrospective study

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Background: General anesthesia is used in the majority of patients undergoing percutaneous nephrolithotomy. To reduce the general anesthesia-related risks and complications, this study evaluated the efficacy and safety of the paravertebral block as a novel and alternative anesthetic method for percutaneous nephrolithotomy.

Methods: This was a retrospective study. A total of 198 patients under percutaneous nephrolithotomy were included. Among them, 76 patients received paravertebral block and 122 received general anesthesia. Patients' characteristics, surgical outcomes, anesthetic outcomes, and perioperative complications and the visual analog scale (VAS) were recorded to evaluate the efficacy and safety of paravertebral block compared with general anesthesia. Intergroup differences of the parameters were analyzed using an independent *t*-test and χ^2-tests appropriate.

Results: Seventy-six patients who underwent paravertebral block completed the surgery successfully, three patients were supplemented with propofol for discomfort during ureteroscopy, and two patients were supplemented with remifentanil for incomplete nerve blockade. Patients who underwent paravertebral block had a higher American Society of Anesthesiologists grade and heart function grade, including patients with contraindications to general anesthesia. Intraoperative and postoperative adverse events and the anesthesia costs were less in patients who underwent paravertebral block. VAS pain scores during the postoperative period in patients who underwent paravertebral block were lower than those in patients who underwent general anesthesia without the use of patient-controlled intravenous analgesia.

Conclusion: In this retrospective study, paravertebral block was found to be effective and safe in providing intraoperative anesthesia for percutaneous nephrolithotomy, and had less adverse events and anesthesia costs. Paravertebral block is an attractive alternative anesthesia for patients at increased risk of comorbidities following general or neuraxial anesthesia.

KEYWORDS

paravertebral block (PVB), general anesthesia (GA), percutaneous nephrolithotomy (PCNL), postoperative analgesia, the visual analog scale (VAS) pain score

Introduction

Urolithiasis is one of the most common disorders among urinary diseases (1). A review of recent epidemiological studies indicated that the prevalence of urolithiasis is more than 10% (2), and that the recurrence rate approaches 50% after 10 years (3, 4). Approximately 70% of the population affected by this disorder is between 20 and 50 years old. One of the major symptoms is renal colic, a sudden intense flank pain (5). Nephrolithiasis, a subtype of urolithiasis, affects millions of people each year in China (6), and this high prevalence is associated with frequent surgical interventions (7, 8). Percutaneous nephrolithotomy is a widely used surgical procedure for the elimination of large and complex upper renal calculi (9, 10), and is the gold standard for treating nephrolithiasis with fewer complications than open surgery (11, 12). However, even though percutaneous nephrolithotomy is a minimally invasive procedure, the intra- and postoperative pain perceived by patients is intense (13, 14). General and neuraxial anesthesia are commonly used for percutaneous nephrolithotomy (15, 16). However, they are often associated with an increased risk of complications or are contraindicated (17), especially in the elderly or patients with multiple comorbidities.

The paravertebral block is a technique involving the injection of a local anesthetic adjacent to the intervertebral foramina where the spinal nerves exit the thoracic vertebral canal, resulting in ipsilateral segmental sympathetic nerve blockade (18–20). Paravertebral block is a simple and effective technique for unilateral procedures, with minimal incidence of hypotension and urinary retention (7, 21). There are several reports on the use of paravertebral block for percutaneous nephrolithotomy, though it is mainly used for intra- and postoperative analgesia (13, 21–23). Mei et al. presented reports to share their experience with paravertebral block as the main anesthesia used for percutaneous nephrolithotomy (24, 25). Other studies compared paravertebral block combined with moderate sedation with intraspinal anesthesia for percutaneous nephrolithotomy (26). These demonstrate the effectiveness of paravertebral block. However, reports about the application of paravertebral block for anesthesia in percutaneous nephrolithotomy are still few, and available data are limited. Thus, more studies are needed to explore the efficacy and safety of the paravertebral block for percutaneous nephrolithotomy. In the present retrospective study, we aimed to evaluate the effects of ultrasound-guided six-segment paravertebral block to provide anesthesia for percutaneous nephrolithotomy.

Materials and methods

This study was approved by the Institutional Research Ethics Committee of the Shanghai Fourth People's Hospital (approval number: 202011115-001). As a retrospective study, that is, a re-exploration and utilization of past data, the Ethics Committee approved our waiver of informed consent.

Patients

This retrospective study was conducted on patients who attended the Shanghai Fourth People's Hospital from January 2019 to October 2020. All data were obtained from the anesthesia system, the anesthesia record, and the postoperative visit record. A total of 198 patients who had large or complex renal calculi and underwent percutaneous nephrolithotomy were included in the study. The patients were assigned to the paravertebral block group (PVB group) or the general anesthesia group (GA group) according to the anesthesia type they received. Seventy-six of the patients underwent paravertebral block and 122 received general anesthesia. Moreover, the patients in the GA group were further divided into two subgroups based on whether a patient-controlled intravenous analgesia (PCIA) was not used (GA-1) or used (GA-2 group). Age, sex, body mass index, and comorbidities were recorded, including hypertension, diabetes, chronic obstructive pulmonary disease, chronic renal failure, and coronary heart disease.

Paravertebral block

The patients were positioned in the prone position, and standard monitoring was performed with non-invasive blood pressure measurement, electrocardiography, and pulse oximetry. The ultrasound-guided paravertebral block was performed using a linear array 5–10 MHz probe (Sonosite, Bothell, WA, USA). The probe was positioned on the lumbar spine, parallel to the ribs. The probe was moved cephalad until the 12th rib was visualized. Then, the probe was rotated anticlockwise for a standard sagittal slice of the rib. The probe was moved medially to identify the T_{11} and T_{12} transverse processes. The T_8-L_1 transverse processes were also identified by moving the probe cephalad and caudad. The T_8-L_1 paravertebral spaces were chosen for the procedure, and 5 mL of 0.33% ropivacaine was intermittently injected at each segment, the total dose of ropivacaine was 100 mg (**Figure 1**). The blocking effect was evaluated 15 min later, and based on the patient's condition, additional sedatives or analgesics were administered or not. After a successful block, lidocaine gel was injected into the urethra for 2 min before ureteroscopy. Surgery was performed after the patient's pain was resolved.

General anesthesia

The patients induced by sufentanil (0.3 μg/kg), propofol (2 mg/kg), and cisatracurium (0.2 mg/kg), and dexmedetomidine (1 μg/kg) was administered *via* intravenous pump; tracheal intubation was performed 2 min later. General anesthesia was maintained with propofol (5 mg/kg/h) and remifentanil (10 μg/kg/h). Anesthesia of patient was monitored using the standard anesthetic observation for changes in vital signs, such as heart rate, blood pressure, respiratory effort, $EtCO_2$, and body temperature in response to surgical stimulation. PCIA was provided with sufentanil (2 μg/kg) and butorphanol (1 mg/kg) to 150 mL at the end of surgery.

Surgical procedure

Swabs were used to test the effect of blocking ipsilateral T_8 to L_1 region anesthesia 15 min later, surgery was performed after the patient's pain was resolved. Percutaneous nephrolithotomy was

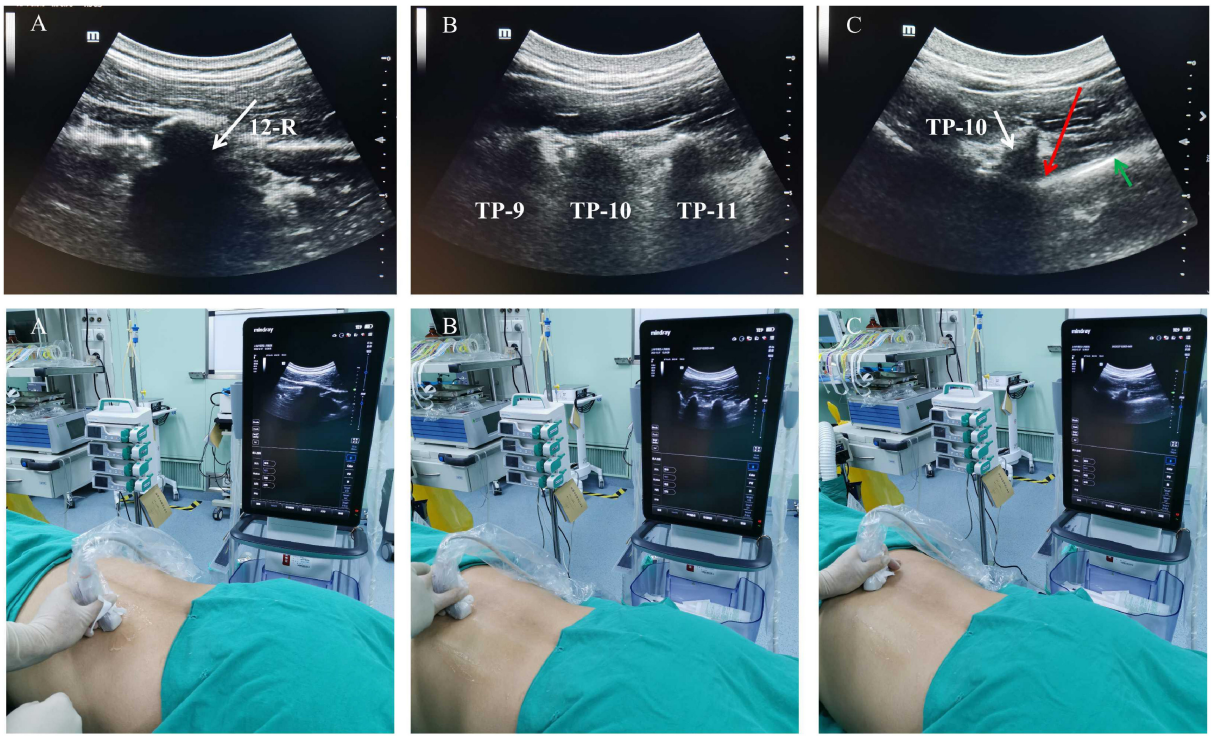

FIGURE 1
Illustration of the step-wise technique for paravertebral block. **(A)** The probe is moved cephalad to determine the position of the 12th (white arrow). **(B)** The probe is rotated to the sagittal plane and the transverse process of T_9, T_{10}, and T_{11} is in the same visual field. **(C)** The probe is moved to determine the paravertebral spaces (red arrow), transverse process of T_{10} and the pleura (green arrow) is identified. R, rib; TP, transverse process.

performed in two stages: first, the patient was placed in the lithotomy position, ureteroscopy was performed, and the ureteral and urinary catheters were indwelled. Then, the patient was moved into the prone position, and after ultrasonic positioning, nephroscopy and lithotripsy were performed for percutaneous nephrolithotomy.

Evaluation of the effects and safety of paravertebral block and general anesthesia

The American Society of Anesthesiologists (ASA) grade and heart function grade according to the New York Heart Association (NYHA) were recorded to evaluate the tolerance to paravertebral block and general anesthesia in different patients, especially the elderly and patients in poor general condition. Our primary outcome was operative pain as measured by the visual analog scale (VAS, 0–10; 0: no pain, 10: maximum pain) in patients who received the paravertebral block. The secondary outcomes include intra- or postoperative adverse events, such as hypoxia (SPO_2 < 90), hypertension (MAP more than 20 percent above baseline), hypotension (MAP less than 20 percent above baseline), postoperative itching, nausea, and vomiting, were recorded to assess the safety of the two types of anesthesia. Moreover, the satisfaction with anesthesia among surgeons and patients, the number of patients who required additional sedation and analgesia, including propofol, and remifentanil, was recorded. Hospitalization days and procedural costs were also analyzed to compare the economic factors between the two types of anesthesia. Other data, including anesthesia duration, the volume of fluid infused, and surgical data, were also recorded and compared.

Statistical analysis

All data are presented as medians, means, or incidence, as appropriate. The categorical and continuous variables were analyzed using χ^2-tests and independent *t*-tests, respectively. Microsoft Excel 2013 (Microsoft Corp., Redmond, WA, USA) was used to record the data, and the analyses were performed using SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, NY, USA). $P < 0.05$ indicated statistical significance.

Results

A total of 198 patients were included in this study. Among them, 76 patients were anesthetized with paravertebral block and 122 received general anesthesia. The patients' characteristics are summarized in Table 1. There were no significant differences in sex, age, weight, height, and body mass index between groups. The PVB group had significantly higher ASA ($P = 0.005$) and NYHA heart function grades ($P = 0.001$). There were no significant between-group differences in comorbidities, except for hypertension, which was more frequent in the GA group ($P = 0.03$).

The clinical parameters of surgery are summarized in Table 2. There were no significant differences regarding the duration of surgery between groups. Surgical complications and surgeon

TABLE 1 Characteristics of included patients.

	PVB group (n = 76)	GA group (n = 122)	P-value
Gender (males/females)	68/8	108/14	0.84
Age (years)	62.86 ± 11.41	60.48 ± 11.23	0.98
Weight (kg)	75.14 ± 10.22	74.97 ± 9.94	0.99
Height (cm)	1.69 ± 0.55	1.70 ± 0.52	0.88
BMI	26.25 ± 3.04	26.04 ± 3.18	0.78
ASA grade (I/II/III/IV)	3/58/11/4	19/91/12/0	0.01
Heart function grade of NYHA (I/II/III/IV)	4/56/16/0	27/84/11/0	<0.01
Comorbidity			
Hypertension	53 (69.7%)	66 (54.1%)	0.03
Diabetes	45 (59.2%)	58 (47.5%)	0.11
COPD	10 (13.2%)	13 (10.7%)	0.59
CRF	3 (3.9%)	3 (2.5%)	0.55
CHD	17 (22.4%)	20 (16.4%)	0.29
The history of stroke	7 (9.2%)	6 (4.9%)	0.24

Values are given as n (%) or means ± SD. PVB group, paravertebral block group; GA group, general anesthesia group; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CHD, coronary heart disease.

TABLE 2 Clinical parameters of surgery.

	PVB group (n = 76)	GA group (n = 122)	P-value
Duration of Surgery (min)	75.79 ± 8.94	77.38 ± 10.39	0.27
Duration of ureteroscopy (min)	14.42 ± 2.62	14.18 ± 2.39	0.51
Duration of PCNL (min)	61.37 ± 9.38	63.20 ± 10.42	0.24
Surgical complications			
Pneumothorax	0 (0)	0 (0)	1.00
Bleed	0 (0)	1 (0.8%)	0.43
Infection	1 (1.3%)	1 (0.8%)	0.73
Organ injury	0 (0)	0 (0)	1.00
Self-positioning without assistance	68 (89.5%)	0 (0)	<0.01
Surgeon satisfaction with anesthesia (0–10 score)	9.37 ± 1.08	9.35 ± 0.97	0.91

Values are given as n (%) or means ± SD. PVB group, paravertebral block group; GA group, general anesthesia group.

satisfaction with anesthesia did not differ between groups ($P > 0.05$). Among the 76 patients who underwent paravertebral block, three received sedation during ureteroscopy and five in feeble conditions required assistance with repositioning during the procedure.

The anesthesia parameters of the patients are shown in Table 3. The anesthesia duration was longer in patients who underwent paravertebral block than that of patients receiving general anesthesia (99.41 ± 7.79 vs. 88.93 ± 11.80 min, $P < 0.001$). The fluid infusion volume was less in the PVB group (785.52 ± 99.60 vs. 1,045.08 ± 151.22 mL, $P = 0.007$). The VAS pain score during the procedure in the PVB group was 1.49 ± 0.90; however, this value could not be compared between groups since patients under general anesthesia could not provide this score. Three patients were supplemented with propofol (1 mg/kg, intravenous injection) because of discomfort during ureteroscopy and 2 patients were supplemented with remifentanil (2 μg/kg/h, intravenous pump) for incomplete nerve blockade. All patients in the GA group also received these medicines. Intraoperative adverse events such as hypotension were less frequent in patients with paravertebral block ($P = 0.01$), and there were no between-group differences in hypertension and hypoxia.

TABLE 3 Anesthesia parameters of the patients.

	PVB group (n = 76)	GA group (n = 122)	P-value
Duration of anesthesia, min	99.41 ± 7.79	88.93 ± 11.80	<0.01
VAS during PCNL	1.49 ± 0.90	–	–
Usage of sedative and analgesic drugs			
Propofol	3 (3.9%)	122 (100%)	<0.01
Remifentanil	2 (2.6%)	122 (100%)	<0.01
Volume of fluid infused, ml	785.52 ± 99.60	1,045.08 ± 151.22	<0.01
Intraoperative adverse events			
Hypoxia	1 (1.3%)	0 (0%)	0.81
Hypertension	10 (13.2%)	13 (10.7%)	0.59
Hypotension	1 (1.3%)	13 (10.7%)	0.01

Values are given as n (%) or means ± SD. PVB group, paravertebral block group; GA group, general anesthesia group. Hypoxia is defined as SPO_2 < 90, Hypertension is defined as MAP more than 20 percent above baseline, Hypotension is defined as MAP lower than 20 percent above baseline.

The GA group was subdivided according to the use of PCIA; there were 68 patients in the GA-1 group (general anesthesia without PCIA) and 54 patients in the GA-2 (general anesthesia with PCIA) group. Table 4 shows the postoperative data of the three groups. The patients in the PVB group had a lower incidence of postoperative itching, nausea and vomiting ($P = 0.01$); PCIA had no significant effect on these symptoms in patients with general anesthesia. No significant differences emerged in hospitalization and patient satisfaction. The anesthesia cost was lower for paravertebral block than that of general anesthesia, without or with PCIA (93.58 ± 27.25 vs. 278.89 ± 29.08 and 387.39 ± 20.44 $, respectively; $P < 0.001$).

The PVB group did not receive postoperative analgesia, we compared the VAS scores among the three groups in the postoperative period in Figure 2. The mean VAS scores in the PVB and GA-2 group at the end of the surgery were not significantly different; however, they were both lower than those in the GA-1 group ($P < 0.001$ and $P = 0.01$, respectively). Six hours after the procedure, the mean VAS score in the PVB group was higher than that in the GA-2 group and lower than that in the GA-1 group ($P < 0.001$ and $P < 0.001$, respectively). At the 24-h time point, the difference between the PVB and the GA-1 group was not significant; patients who received PCIA had a significantly lower VAS score than those in the other two groups ($P = 0.047$ and $P = 0.001$, respectively). The mean VAS pain score differences among the three groups were not statistically significant at the 48-h time point.

TABLE 4 Postoperative complications and other related indicators.

	PVB group (n = 76)	GA group (n = 122)		P-value
		GA 1 group (n = 68)	GA 2 group (n = 54)	
PONV	1 (1.3%)	7 (10.3%)	9 (16.7%)	0.01
Itching	0 (0)	1 (1.5%)	2 (3.7%)	0.23
Postoperative analgesia	0 (0)	0 (0)	54 (100%)	<0.01
Hospitalization, days	7.09 ± 0.61	7.06 ± 0.79	7.18 ± 0.68	0.59
Anesthesia cost, $	93.58 ± 27.25	278.89 ± 29.08	387.39 ± 20.44	<0.01
Patient's satisfaction with anesthesia (0–10)	8.78 ± 1.11	8.81 ± 0.97	8.53 ± 1.00	0.30

Values are given as n (%) or means ± SD. PVB group, paravertebral block group; GA 1 group, general anesthesia without PICA Group; GA 2 group, general anesthesia with PICA Group; PONV, postoperative nausea and vomiting.

Discussion

In this retrospective study, paravertebral block was found to be feasible for providing intraoperative anesthesia for percutaneous nephrolithotomy. Three patients experienced severe discomfort and bladder irritation during ureteroscopy; however, the combination of a low dose of propofol and to pical lidocaine gel met the surgical requirements. Since the failure rate of paravertebral block for percutaneous nephrolithotomy in some reports was 6.1–20% (27, 28), VAS scores were assessed after paravertebral block treatment. Analgesia was given to patients with VAS > 3 to ensure their comfort. In our study, the average VAS pain score was <2 in PVB group, suggesting that paravertebral block can meet the operation needs of most patients, except for two patients who were administered remifentanil because the blocking effect was incomplete. Since six-segment injections were applied rather than a single one (29), the failure rate in our study was lower than those of previous reports. All patients, except those who were administered propofol, were awake and satisfied with the level of anesthesia, indicating that this technique is effective and meets the surgery requirements. Achieving adequate analgesia for percutaneous nephrolithotomy requires the blockage of skin and muscle innervation and visceral nerves for the kidney and ureter (30). The tract to block for lithotripsy typically includes the 10th and 11th intercostal spaces (31). Sensory nerves in this area are readily anesthetized by a thoracic paravertebral block, while kidney and ureter nerves originate from T_{10} to L_1 (13, 25). In contrast to previous reports (26), we observed that blocking the homolateral spinal nerves from T_8 to L_1 led to satisfying sensation reduction and provided effective anesthesia for percutaneous nephrolithotomy.

In our study, there were no significant differences in terms of age, sex, weight, height, and comorbidities between the patients who underwent paravertebral block and general anesthesia. Owing to the aging population in Shanghai (32), the patients treated at our hospital were mainly elderly, although the typical onset age of calculi is in young adulthood (3); the mean age of the patients in our study was >60 years. In elderly patients, the physical conditions often decay (33). The PVB group had higher ASA and heart function scores, including several patients with ASA IV, who were at high risk of receiving general anesthesia; however, nephrolithiasis pain is severe and must be treated promptly and effectively (34). Paravertebral block affects circulation and respiration less than general anesthesia and can be administered to high-risk patients in poor general conditions or with several underlying diseases, in contrast to general or neuraxial anesthesia. Several patients still required sedatives or analgesics, which might have increased the anesthesia risks. However, the small doses of sedatives or analgesics had minimal effect on circulation and respiration (35, 36). Moreover, the percentage of patients requiring propofol or remifentanil was low; all ASA III–IV patients in our study received only the paravertebral block, without additional sedatives or analgesics. The incidence of intraoperative hypotension, a risk factor for malignant cardiovascular and cerebrovascular events (37),

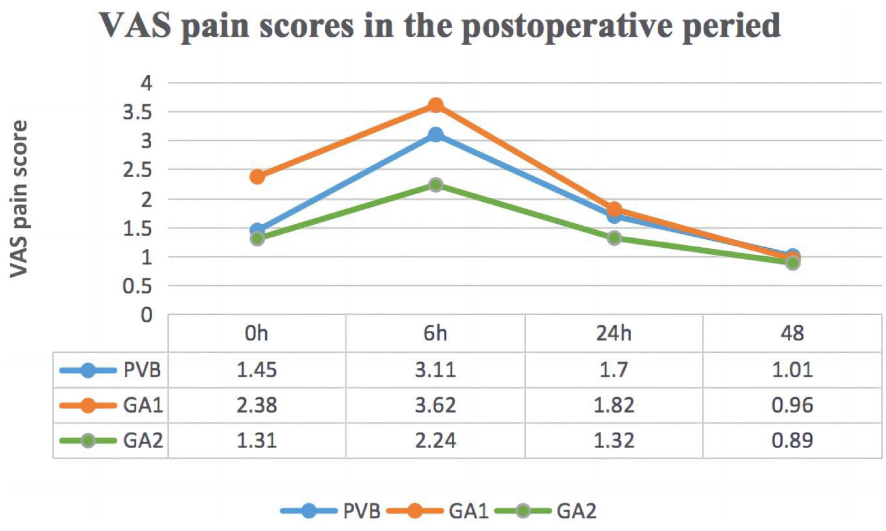

FIGURE 2
The visual analog scale (VAS) pain scores in the postoperative period. PVB group, paravertebral block group; GA 1 group, general anesthesia without PICA Group; GA 2 group, general anesthesia with PICA Group.

was significantly lower in the PVB group compared with the GA group. There was only one patient that had oxygenation decline during surgery in the PVB group due to the additional sedatives or analgesics (38). However, the hypoxemia was promptly corrected with effective treatment. In addition, potential complications of paravertebral block, including bleeding and nerve damage, were not identified. Overall, the incidence of adverse events was low in the PVB group, and this technique was deemed safe for percutaneous nephrolithotomy.

Furthermore, there were no significant differences between groups regarding the surgical data. The anesthesia duration was longer in the PVB group since ultrasound-guided nerve block requires more time to be fully effective. Other differences included the volume of infused fluids, as the patients often needed extra fluids under general anesthesia due to peripheral vasodilation. No significant differences were found in hospitalization and anesthesia satisfaction in both surgeons and patients. The overall cost for the paravertebral block was significantly lower than for general anesthesia, alleviating the economic burden for the patients. Overall, the paravertebral block was similar to general anesthesia in ensuring surgical safety and patient comfort at a lower cost.

As some of the patients in the GA group received PCIA, we compared the postoperative data of the three groups. We found that the incidence of nausea and vomiting was significantly higher in patients who underwent general anesthesia than in the paravertebral block group. Postoperative analgesia had no significant effect on nausea and vomiting in the two general anesthesia groups. Although we did not analysis postoperative throat pain and hoarseness caused by intubation, or adverse reactions such as slow peristalsis and hypothermia caused by general anesthesia, the use of paravertebral block obviously prevented them from occurrence.

Regarding postoperative pain, the scores of the paravertebral block and GA-2 group (with PCIA) were lower than that in the GA-1 group (without PCIA) immediately after surgery. However, after 6 h, the VAS score in paravertebral block patients increased due to the gradual decay of the blocking effect, approaching the pain score of the general anesthesia patients without PCIA (21). The patients with PCIA had a lower VAS score than those in the other two groups at the 24-h time point. Nonetheless, the mean VAS scores of the three groups at this time were <2, suggesting that the postoperative pain was generally limited to the first day after surgery; this finding is consistent with previous reports (13, 23). There was no significant difference in pain scores among the three groups 48 h after surgery. Overall, paravertebral block was more effective than general anesthesia alone in relieving postoperative pain, although it does not play a continuous analgesic role.

There are some limitations both to this study and the application of paravertebral block. First, retrospective studies are prone to data bias, and the intra- and postoperative data were incomplete. Second, VAS scores may be unreliable due to the subjective nature of experiencing and reporting pain (13). Additionally, since paravertebral block is unilateral, patients may feel uncomfortable after bladder flush and expansion during ureteroscopy. Bladder irritation signs are evident after ureter catheter placement; thus, additional sedative and analgesic drugs are sometimes needed. In future clinical practice and research, optimizing this anesthesia method to ensure safe and comfortable operating conditions is necessary. Furthermore, we retrospectively compared the effects of paravertebral block and general anesthesia; however, a prospective randomized controlled trial should be conducted.

In this retrospective study, paravertebral block was effective and safe in providing intraoperative anesthesia for percutaneous nephrolithotomy, and had less adverse events and anesthesia costs. Paravertebral block is an attractive alternative for patients at increased risk of comorbidities following general or neuraxial anesthesia.

Data availability statement

The original contributions presented in this 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 Institutional Research Ethics Committee of the Shanghai Fourth People's Hospital (approval number: 202011115-001). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

LX, CL, MF, and WQ: substantial contribution to conception and design. GA, DL, and MF: analysis and interpretation of data. MF and CL: writing manuscript. All authors: acquisition of data and revising manuscript.

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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.

Publisher's note

References

1. Pradere B, Doizi S, Proietti S, Brachlow J, Traxer O. Evaluation of guidelines for surgical management of urolithiasis. *J Urol.* (2018) 199:1267–71.

2. Monico CG, Milliner DS. Genetic determinants of urolithiasis. *Nat Rev Nephrol.* (2011) 8:151–62.

3. Gottlieb M, Long B, Koyfman A. The evaluation and management of urolithiasis in the ED: a review of the literature. *Am J Emerg Med.* (2018) 36:699–706. doi: 10.1016/j.ajem.2018.01.003

4. Seth JH, Promponas J, Hadjipavlou M, Anjum F, Sriprasad S. Urolithiasis following urinary diversion. *Urolithiasis.* (2016) 44:383–8.

5. Borofsky MS, Lane GI, Neises SM, Portis AJ. Patient-reported outcomes measurement system (PROMIS((R))) for patients with urolithiasis: initial report. *J Urol.* (2017) 198:1091–7. doi: 10.1016/j.juro.2017.05.080

6. Zhao A, Dai M, Chen YJ, Chang HE, Liu AP, Wang PY. Risk factors associated with nephrolithiasis: a case-control study in China. *Asia Pac J Public Health.* (2015) 27:N414–24.

7. Saigal CS, Joyce G, Timilsina AR, Urologic Diseases in America Project. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management? *Kidney Int.* (2005) 68:1808–14. doi: 10.1111/j.1523-1755.2005.00599.x

8. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, et al. Surgical management of stones: American urological association/endourological society guideline, PART I. *J Urol.* (2016) 196:1153–60.

9. Opondo D, Tefekli A, Esen T, Labate G, Sangam K, De Lisa A, et al. Impact of case volumes on the outcomes of percutaneous nephrolithotomy. *Eur Urol.* (2012) 62:1181–7.

10. Patel SR, Nakada SY. The modern history and evolution of percutaneous nephrolithotomy. *J Endourol.* (2015) 29:153–7.

11. Ghani KR, Andonian S, Bultitude M, Desai M, Giusti G, Okhunov Z, et al. Percutaneous nephrolithotomy: update, trends, and future directions. *Eur Urol.* (2016) 70:382–96.

12. Smith A, Averch TD, Shahrour K, Opondo D, Daels FP, Labate G, et al. A nephrolithometric nomogram to predict treatment success of percutaneous nephrolithotomy. *J Urol.* (2013) 190:149–56.

13. Baldea KG, Patel PM, Delos Santos G, Ellimoottil C, Farooq A, Mueller ER, et al. Paravertebral block for percutaneous nephrolithotomy: a prospective, randomized, double-blind placebo-controlled study. *World J Urol.* (2020) 38:2963–9. doi: 10.1007/s00345-020-03093-3

14. Desai MR, Kukreja RA, Desai MM, Mhaskar SS, Wani KA, Patel SH, et al. A prospective randomized comparison of type of nephrostomy drainage following percutaneous nephrostolithotomy: large bore versus small bore versus tubeless. *J Urol.* (2004) 172:565–7. doi: 10.1097/01.ju.0000130752.97414.c8

15. Hu H, Qin B, He D, Lu Y, Zhao Z, Zhang J, et al. Regional versus general anesthesia for percutaneous nephrolithotomy: a meta-analysis. *PLoS One.* (2015) 10:e0126587. doi: 10.1371/journal.pone.0126587

16. Moslemi MK, Mousavi-Bahar SH, Abedinzadeh M. The feasibility of regional anesthesia in the percutaneous nephrolithotomy with supracostal approach and its comparison with general anesthesia. *Urolithiasis.* (2013) 41:53–7. doi: 10.1007/s00240-012-0528-5

17. Pu C, Wang J, Tang Y, Yuan H, Li J, Bai Y, et al. The efficacy and safety of percutaneous nephrolithotomy under general versus regional anesthesia: a systematic review and meta-analysis. *Urolithiasis.* (2015) 43:455–66. doi: 10.1007/s00240-015-0776-2

18. Harkouk H, Fletcher D, Martinez V. Paravertebral block for the prevention of chronic postsurgical pain after breast cancer surgery. *Reg Anesth Pain Med.* (2021) 46:251–7.

19. Chen N, Qiao Q, Chen R, Xu Q, Zhang Y, Tian Y. The effect of ultrasound-guided intercostal nerve block, single-injection erector spinae plane block and multiple-injection paravertebral block on postoperative analgesia in thoracoscopic surgery: a randomized, double-blinded, clinical trial. *J Clin Anesth.* (2020) 59:106–11. doi: 10.1016/j.jclinane.2019.07.002

20. Sato M, Shirakami G, Fukuda K. Comparison of general anesthesia and monitored anesthesia care in patients undergoing breast cancer surgery using a combination of ultrasound-guided thoracic paravertebral block and local infiltration anesthesia: a retrospective study. *J Anesth.* (2016) 30:244–51. doi: 10.1007/s00540-015-2111-z

21. Borle AP, Chhabra A, Subramaniam R, Rewari V, Sinha R, Ramachandran R, et al. Analgesic efficacy of paravertebral bupivacaine during percutaneous nephrolithotomy: an observer blinded, randomized controlled trial. *J Endourol.* (2014) 28:1085–90. doi: 10.1089/end.2014.0179

22. Kamble TS, Deshpande CM. Evaluation of the efficacy of Bupivacaine (0.5%) alone or with Clonidine (1mug/kg) versus Control in a single level paravertebral blockin patients undergoing PCNL procedure. *J Clin Diagn Res.* (2016) 10:UC13–7. doi: 10.7860/JCDR/2016/20890.9033

23. Saroa R, Palta S, Puri S, Kaur R, Bhalla V, Goel A. Comparative evaluation of ropivacaine and levobupivacaine for postoperative analgesia after ultrasound-guided paravertebral block in patients undergoing percutaneous nephrolithotomy. *J Anaesthesiol Clin Pharmacol.* (2018) 34:347–51. doi: 10.4103/joacp.JOACP_187_17

24. Liu Y, Yu X, Sun X, Ling Q, Wang S, Liu J, et al. Paravertebral block for surgical anesthesia of percutaneous nephrolithotomy: care-compliant 3 case reports. *Medicine (Baltimore).* (2016) 95:e4156. doi: 10.1097/MD.0000000000004156

25. Yang H, Yu X, Hu J, Peng E, Li C, Cui L, et al. Usage of multilevel paravertebral block as the main anesthesia for mini-invasive PCNL: retrospective review of 45 cases with large stones. *Urol Int.* (2017) 99:326–30. doi: 10.1159/000480094

26. Li C, Song C, Wang W, Song C, Kong X. Thoracic paravertebral block versus Epidural anesthesia combined with moderate sedation for percutaneous nephrolithotomy. *Med Princ Pract.* (2016) 25:417–22. doi: 10.1159/000447401

27. Kaur B, Vaghadia H, Tang R, Sawka A. Real-time thoracic paravertebral block using an ultrasound-guided positioning system. *Br J Anaesth.* (2013) 110:852–3.

28. Naja Z, Lonnqvist PA. Somatic paravertebral nerve blockade. Incidence of failed block and complications. *Anaesthesia.* (2001) 56:1184–8. doi: 10.1046/j.1365-2044.2001.02084-2.x

29. Kotze A, Scally A, Howell S. Efficacy and safety of different techniques of paravertebral block for analgesia after thoracotomy: a systematic review and metaregression. *Br J Anaesth.* (2009) 103:626–36. doi: 10.1093/bja/aep272

30. Dutton TJ, McGrath JS, Daugherty MO. Use of rectus sheath catheters for pain relief in patients undergoing major pelvic urological surgery. *BJU Int.* (2014) 113:246–53. doi: 10.1111/bju.12316

31. Assaf E, Chalhoub K, Lteif E, Aoun R, Ashou R, Jabbour MA. Dynamic anatomical description of the parietal pleura setting safety limits for intercostal percutaneous access. *J Endourol.* (2018) 32:919–22. doi: 10.1089/end.2018.0309

32. Wang Y, Dong W, Mauk K, Li P, Wan J, Yang G, et al. Nurses' practice environment and their job satisfaction: a study on nurses caring for older adults in Shanghai. *PLoS One.* (2015) 10:e0138035. doi: 10.1371/journal.pone.0138035

33. Villareal DT, Aguirre L, Gurney AB, Waters DL, Sinacore DR, Colombo E, et al. Aerobic or resistance exercise, or both, in dieting obese older adults. *N Engl J Med.* (2017) 376:1943–55.

34. Mutlu H, Ertas K, Kokulu K, Sert ET, Diri MA, Gul M. An effective treatment option for pain caused by urolithiasis: a randomised-controlled trial of local active warming with heat-patch. *Int J Clin Pract.* (2021) 75:e13969. doi: 10.1111/ijcp.13969

35. Zhang Y, Tian M, Li SR. [Impact of propofol on the optimal sedative depth in patients undergoing gastroscopy]. *Zhonghua Yi Xue Za Zhi.* (2007) 87:44–7.

36. Krenn H, Deusch E, Jellinek H, Oczenski W, Fitzgerald RD. Remifentanil or propofol for sedation during carotid endarterectomy under cervical plexus block. *Br J Anaesth.* (2002) 89:637–40.

37. Sessler DI, Khanna AK. Perioperative myocardial injury and the contribution of hypotension. *Intensive Care Med.* (2018) 44:811–22.

38. Viljoen A, Byth K, Coombs M, Mahoney G, Stewart D, Royal Australian College of Dental Surgeons, et al. Analysis of oxygen saturations recorded during dental intravenous sedations: a retrospective quality assurance of 3500 cases. *Anesth Prog.* (2011) 58:113–20. doi: 10.2344/09-00001.1

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Exploration of teaching practice of analgesia and sedation in mainland China: CASER experience

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Objective: Analgesia and sedation assessments vary widely in clinical performance. This study investigated the cognition of intensivist and the importance of training for analgesia and sedation through the Chinese Analgesia and Sedation Education & Research (CASER) group training program.

Methods: A total of 107 participants studied the training courses on the "Sedation, Analgesia and Consciousness Assessment of Critically Ill Patients" held by CASER from June 2020 to June 2021. Ninety-eight valid questionnaires were recovered. The content of the questionnaire included the preface, general information of the trainees, students' awareness of the importance of analgesia and sedation evaluation and related guidelines, and professional test questions.

Results: All respondents were senior professionals engaged in the ICU. A total of 92.86% believed that analgesia and sedation treatment were very important parts of the ICU, and 76.5% believed that they had mastered relevant professional knowledge. However, when evaluating the relevant professional theory and practice of the respondents from an objective point of view, it can be seen that only 28.57% of the respondents could reach the passing line in the specific case analysis scenario. Before participating in the training, 42.86% of the medical staff believed that analgesia and sedation treatment should be evaluated in the daily work of the ICU; after participating in the training, 62.24% of the medical staff believed that the evaluation was necessary and believed that they had improved after the training. Moreover, 69.4% of the respondents affirmed the necessity and significance of jointly undertaking the task of analgesia and sedation in Chinese ICUs.

Conclusion: This study revealed that the assessment of analgesia and sedation is not standardized in the ICU in mainland China. The importance and significance of standardized training for analgesia and sedation are presented. The CASER working group thus established has a long way to go in its future work.

KEYWORDS

analgesia, sedation, assessment, training, China

Introduction

Analgesia and sedation have become very important and indispensable components of intensive care specialist treatment. The correct use of sedative and analgesic therapy can reduce the pain and fear of critically ill patients so that patients do not perceive, pay attention, remember or forget their pain during the severe stages and avoid anxiety, agitation and even delirium caused by the pain, which may improve patient condition and prognostic outcomes. Compared with Western countries, China's analgesic and sedative treatment started late but has developed rapidly. In 2006, the Intensive Care Medicine Branch of the Chinese Medical Association released the first edition of the Chinese guidelines for analgesia and sedation for critically ill patients in 2006, and the guidelines were updated in 2018 (1). Following the update of the second edition of the Chinese guideline and the publication of the international PIADS guideline (2), domestic critical care colleagues have carried out different forms of study across the country, including self-study by physicians, department teaching, and promotion of related academic conferences. In the process of these studies, a common problem is exposed, and different readers are particularly prominent in the limitations of their own understanding of the guidelines: In actual clinical work, it was found that the theory and application are seriously disconnected. That is, many physicians have good theoretical basic knowledge, but they have subjective cognition and misjudgment about how to operate and implement related analgesia and sedation. To solve this outstanding clinical problem, the Critical Care Medicine Branch of the Chinese Medical Doctor Association established the China Analgesia and Sedation Education and Research (CASER) group and started special training in June 2020, aiming to improve theoretical understanding of analgesia and sedation. The supplement of clinical practice is helpful for the promotion and application of related concepts. Aiming at the contradiction between the significance and role of analgesia and sedation in critically ill patients and the clinical reality, this study investigated the cognition of bedside doctors and the importance of training for analgesia and sedation.

Materials and methods

Training group formation

The CASER group is entrusted by the Critical Care Medicine Branch of the Chinese Medical Doctor Association, with Professor LJ from the Department of Critical Care Medicine, Xuanwu Hospital, Capital Medical University as the project leader. The first batch of four lecturers was identified (YL, RL, SL, and LS). To ensure the consistency of training, the CASER group had conducted training and centralized learning with four fixed lecturers in advance. Before the formal college training of the trainees, three centralized lecturer trainings were organized beginning in March 2020. The training theme, specific training content, course structure organization and teaching methods were discussed and sorted out. After teacher training, the working group organized an assessment of the lecturers and confirmed the qualifications of the lecturers to ensure the homogeneity and consistency of the training.

Investigation objects

From June 2020 to June 2021, the CASER group held training courses on "Sedation, Analgesia and Consciousness Assessment of Critically Ill Patients" in batches. The training course was open to recruiting students from all over the country, and the main groups were doctors and nurses working in the ICU. There were no more than 20 students enrolled in each training session, and registration automatically stopped when 20 students were reached. The main contents of the training were analgesia and analgesia assessment, sedation and sedation assessment, delirium and delirium assessment, and then there were related case simulations and discussions for a total of 10 cases. From February to March 2022, the working group distributed electronic questionnaires to all 107 trainees who participated in the training courses during the above mentioned year and collected them for analysis. The necessity of training was used as an indicator of sample size calculation. It was calculated that a sample of 81 patients would generate a 95% confidence interval estimate (CI), which is a range of likely values for the population proportion with precision (allowable error) of ±10% based on an estimated sample proportion of 70%. Given an anticipated dropout rate of 10%, the total sample size required was at least 90.

Data collection and pilot testing

The questionnaire consisted of four parts (see **Supplementary material**): (1) Preface, which explained the purpose, significance, sponsoring institution and ethics-related matters of this research to the investigators. (2) General information of the trainees, gender, age, educational background, professional and technical title, work affiliation and medical unit and working years. (3) Students' awareness of the importance of analgesia and sedation evaluation and related guidelines. (4) Professional test questions, including six theoretical questions about analgesia, sedation and consciousness assessment and six clinical case analysis questions, each with five points for a total of 30 points.

The questionnaire was organized and completed by the expert group according to the purpose of this research. The members of the expert group included five doctors from comprehensive ICUs in different provinces (with more than 15 years of work experience), two nurses and one medical statistician. The pilot testing of the questionnaire was completed by 10 trainees who participated in the training, and various data were collected, including the layout, structure, attractiveness, question setting, tolerance of the respondents, and understanding of the questions. SPSS software 20.0 was used for content validity analysis, and the Cronbach's alpha value was 0.812, indicating that the questionnaire was effective.

Results

General characteristics

From June 2020 to June 2021, this project held 4 courses and trained a total of 107 trainees. After the questionnaires were distributed, a total of 98 valid questionnaires were returned. Among them, there were 51 males (52.04%) and 47 females (47.96%). Students aged 31–40 accounted for a maximum of 48 (48.98%). There

were 86 Chinese doctors (87.76%) and 12 nurses (12.24%) among the trainees. Most of the academic qualifications were master's degrees (56, 57.14%). Mainly with intermediate and senior titles, a total of 80 people (81.63%). Most of them worked in the comprehensive ICU of the university hospital (65.31%), and their working years were more than 10 years (58.16%) (Table 1).

TABLE 1 The general characteristics of the survey population.

Characteristic	Total ($n = 98$)
Age range (years), n (%)	
<25	2
25–30	16
31–40	48
41–50	28
>50	4
Gender, n (%)	
Male	51
Female	47
Academic degree, n (%)	
Associate's degree	6
Bachelor's degree	21
Master's degree	56
Doctorate degree	15
Profession, n (%)	
Doctor	86
Nurse	12
Level of professional title, n (%)	
Junior	18
Intermediate	50
Senior	30
Departments, n (%)	
General ICU	64
Specialized ICU	30
Emergency department	2
Anesthesiology department	2
Working years, n (%)	
<5	15
5–10	26
11–15	33
16–20	11
>20	13
Hospital type, n (%)	
Tertiary hospital	93
Secondary hospital	3
Private hospital	2

Cognition of physicians on the clinical assessment of sedative, analgesic, and delirium

This study investigated the familiarity of clinicians with the Sedation and Analgesia Assessment Scale and related guidelines through subjective and objective questions. The results showed that the vast majority of medical workers believed that sedation and analgesia assessment was more important in the daily work of the ICU ($n = 91$, 92.86%). A total of 76.5% ($n = 75$) of medical workers believed that they were not satisfied with the PADIS guidelines and the Chinese guidelines for sedation and analgesia (Figure 1).

To obtain an objective view of the familiarity of medical staff with the assessment of analgesia and sedation, medical staff were surveyed through a test questionnaire. Among them, the theoretical questions and clinical questions were out of 50 points each, with a total score of 100 points. The results showed that 42 people (42.86%) scored more than 30 points on theoretical questions, of which 13 people (13.27%) scored full marks. Twenty-eight (28.57%) of the case analysis questions scored more than 30 points, of which 0 were full marks. A total of 29 students (29.6%) had a total score of more than 60 points, and no student received a full score (Figure 2).

The impact of training on the assessment of analgesia and sedation on the theory and practice of medical staff

The findings showed that training increased medical staff's awareness of the importance of assessment. Before participating in the training, only 42 (42.86%) of medical staff believed that evaluation of analgesia and sedation treatment was necessary in the daily work of the ICU; after participating in the training, 61 (62.24%) medical staff believed that the evaluation was necessary. Our survey results show that 69.4% of medical staff believe that this work should be done by doctors or led by doctors. Among the 12 nurses who participated in the survey, no one believed that the work could be done independently by nurses, and seven nurses believed that doctors should be the lead and that the nurses should cooperate with them. A total of 57 think it can be done by doctors (Figure 3).

Discussion

The study found that the vast majority of medical staff in Chinese ICUs have fully realized the importance of sedation and analgesia for the assessment and treatment of delirium, and the content of analgesia and sedation guidelines is well known. However, the specific content of the evaluation of sedation and analgesia for delirium treatment is generally familiar, and it cannot be used correctly in clinical practice. This is a problem that needs to be considered. In particular, the difference between China and foreign countries is that doctors are involved in more assessments of analgesia and sedation, which puts forward higher requirements for doctors and cooperation between doctors and nurses. Through our training, most doctors further improved their understanding of the importance of analgesia, sedation and delirium treatment evaluation, corrected some blind spots where they lacked understanding, and enriched their theoretical knowledge and clinical practice experience.

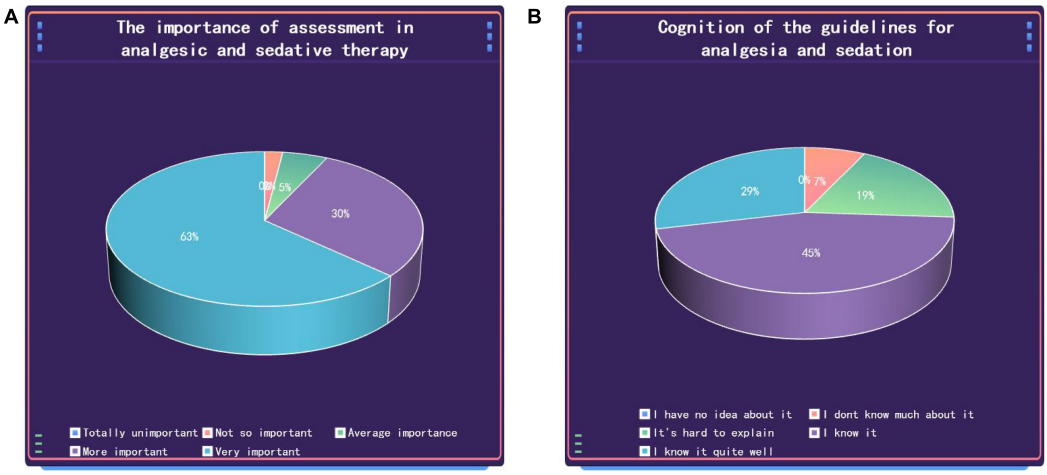

FIGURE 1
Medical staff's understanding of the importance of sedation and analgesia assessment scales **(A)** and related guidelines **(B)**.

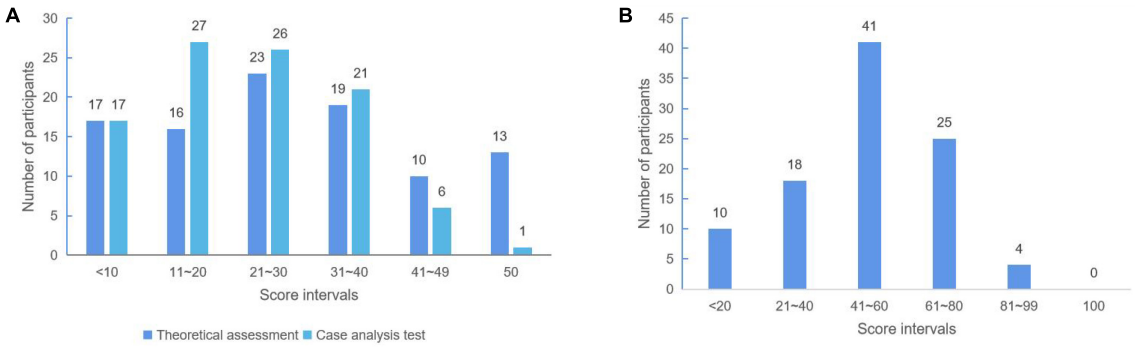

FIGURE 2
The distribution of scores of students' test questions. **(A)** Theoretical assessment and case analysis test score. **(B)** The total score of the test.

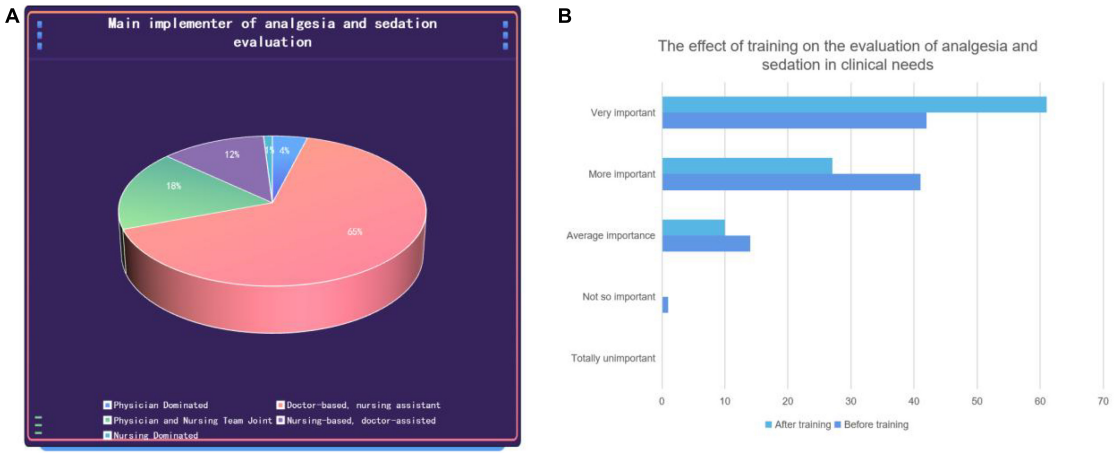

FIGURE 3
The impact of training on the assessment of analgesia and sedation on the theory and practice of medical staff. **(A)** Clinical practice of analgesia and sedation evaluation. **(B)** The effect of training on the doctor's evaluation of analgesia and sedation before and after training.

In addition to the primary disease, critically ill patients in the ICU also suffer from various painful feelings caused by the special environment of the ICU, treatment and nursing and other related operations and suffer from the double blow of the spiritual level, such as the lack of support from relatives around them and the fear of disease and death. Previous studies have shown that 50% of patients who have been in the ICU have painful memories of their experience in the ICU, and approximately 70% of patients

had anxiety, restlessness and fear during their ICU stay (3–5). The Europain study even suggested that our routine movements, such as turning over and sucking sputum, can cause intolerable pain and adverse stimulation to patients (6). As ICU physicians have increasingly recognized the importance of improving the comfort of critically ill patients, analgesia, and sedation are a very important part of the basic treatment in ICU. The American Society of Critical Care Medicine published clinical practice guidelines for adult ICU patients as early as 1995 (7). This guideline was revised in 2002 (8), and the world-renowned PAD Guide was published in 2013 (9). In 2019, the PADIS guidelines were proposed again (2). The publication and update of a series of guidelines fully reflect the understanding of the latest concepts of analgesia and sedation treatment by intensive care physicians, pay more attention to the prevention and assessment of delirium, and further clarify the goal of ICU analgesia-based sedation and general sedation. A light sedation strategy enhances the management of delirium and emphasizes the important role of early activity and sleep. Analgesia and sedation is a subprofessional field, and systematic study and clinical practice are required for this related content to be more accurately grasped and to guide clinical treatment.

Intensive care medicine in mainland China has made great progress in the past 10 years. In particular, COVID-19 has brought some new improvements in the understanding of critical care and changes in clinical behavior. Analgesia and sedation are very important aspects (10). At present, most domestic intensive care physicians have fully realized the importance of analgesia and sedation, and clinical analgesia and sedation have become important treatment methods and means for critically ill patients (11). Through this study, it is believed that the low rate of the correct usage of the sedation and analgesia scale in clinical practice is due to the general familiarity with the assessment of sedation and analgesia treatment. There may be different understandings of the timing of analgesia and sedation, the duration of treatment, and the choice of drugs. The treatment of analgesia and sedation in mainland China is very different and heterogeneous. For example, some ICUs are treated with sedatives only, and some ICUs use deep sedation strategies that cause related complications. Throughout overseas surveys on analgesia and sedation, it was also found that different countries and regions also have very large differences in the choice and use of drugs (12–14). Therefore, the importance of consistent training, especially case-oriented training, and strengthening the application of the clinical application of analgesia and sedation assessment scales for medical staff has important practical significance.

As the saying goes, analgesia and sedation have no evaluation and no treatment. Therefore, the evaluation of analgesia and sedation has become a core issue. Our survey and study found that 75% of the survey respondents indicated that they understood the guidelines for analgesia and sedation, and 91.25% believed that the evaluation of analgesia and sedation was very important. However, the content of analgesia and sedation assessment was generally understood, and only 48.75% were able to achieve basic knowledge. Further examination of the doctor's practical application ability through case analysis questions found that 22.5% of the people could reach 60 points, and only 1 person (1.25%) was able to judge all the differences in the survey correctly. This fully shows that practitioners have a clear understanding of the problem of analgesia and sedation, but the actual application is not ideal. If the evaluation cannot be accurately evaluated, then we cannot talk about the accuracy of the treatment. Therefore, in the evaluation of analgesia and sedation, relevant training needs to be strengthened, especially related operational practice, which is the cornerstone of analgesia and sedation treatment and the focus of this research.

Relevant training for medical staff was carried out in a targeted manner. After the training, 38.75% of medical staff needed to evaluate analgesia and sedation in their daily work in the ICU, and 60% of medical staff start related clinical practice. A total of 91.25% of the trainees believed that the training improved their awareness of the importance of analgesia and sedation evaluation and enriched their theoretical knowledge and clinical practice experience. In addition, more than 60% of Chinese surveyors for analgesia and sedation believed that the dominance lies with doctors, which is different from foreign nurse-led analgesia and sedation (2). Medical staff in China believe that it should be led by doctors and coordinated by nurses. Therefore, medical staff believe that cooperation between medical staff and nurses is essential in clinical work. Doctors provide feedback with nurses through bedside assessment and adjust strategies for care and treatment, which requires a deeper understanding of both doctors' and nurses' cognition of analgesia and sedation and is necessary to strengthen the popularization of relevant knowledge and understanding. The highlight of our training is the establishment of a group, first of all, a unified understanding of the lecturer team, the development of teaching materials, and an audience of doctors and nurses. The practice part is added to the training, especially through the workshop part. The real evaluation process can be seen, and it is no longer a rigid description in the textbook, which avoids misunderstandings. This lays the foundation for future training courses and systems.

In summary, we hope to improve in the following aspects. Firstly, a stable training core tutor team was established to regularly prepare lessons and study, and update new progress of analgesic and sedative treatment. Secondly, the practical courses based on theoretical basis, in addition to providing some standard teaching videos to display the evaluation method, are to build a simulated scenario for offline teaching and learning, or use more advanced virtual reality technology assistance. Third, establishing an assessment and evaluation system. In addition to the assessment of knowledge, we should investigate the form and content of teaching in order to improve the efficiency of teaching. Finally, a training textbook for Chinese national conditions is formed, combining analgesic and sedative teaching with the specific *status quo*, highlighting practicality, and analyzing common issues in targeted.

Conclusion

Although the survey content is limited, it is not difficult to see from the data that Analgesia and sedation in China still need to strengthen training to unify professional understanding and achieve homogeneity in the management and treatment of analgesia and sedation in patients. The first step in training is to achieve an assessment of analgesia and sedation, which are key to laying the groundwork for subsequent treatment. CASER was established in compliance with this purpose. In the future, it will be committed to the promotion, application and research of knowledge of sedation and analgesia in China and will strengthen international exchanges and cooperation, as well as introduce the latest knowledge and concepts related to analgesia and sedation to China. Of course, more diversified teaching experiments and research will be carried out by CASER in the future.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions. The original data can be obtained from the corresponding author. Requests to access these datasets should be directed to LJ, casergroup@aliyun.com.

Author contributions

LS and LJ conceived and designed this study. SL, RL, and YL organized this survey. HZ performed statistics. 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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1010964/full#supplementary-material

References

1. Society of Critical Care Medicine CMA. [Guideline for analgesia and sedation for patients in intensive care unit, China (2006)]. *Zhonghua Wai Ke Za Zhi.* (2006) 44:1158–66.

2. Devlin J, Skrobik Y, Gelinas C, Needham D, Slooter A, Pandharipande P, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* (2018) 46:e825–73. doi: 10.1097/CCM.0000000000003298

3. van de Leur J, van der Schans C, Loef B, Deelman B, Geertzen J, Zwaveling J. Discomfort and factual recollection in intensive care unit patients. *Crit Care.* (2004) 8:R467–73. doi: 10.1186/cc2976

4. Gupta A, Ashburn M, Ballantyne J. Quality assurance and assessment in pain management. *Anesthesiol Clin.* (2011) 29:123–33. doi: 10.1016/j.anclin.2010.11.008

5. Duran-Crane A, Laserna A, Lopez-Olivo M, Cuenca J, Diaz D, Cardenas Y, et al. Clinical practice guidelines and consensus statements about pain management in critically ill end-of-life patients: A systematic review. *Crit Care Med.* (2019) 47:1619–26. doi: 10.1097/CCM.0000000000003975

6. Puntillo K, Max A, Timsit J, Vignoud L, Chanques G, Robleda G, et al. Determinants of procedural pain intensity in the intensive care unit. The Europain(R) study. *Am J Respir Crit Care Med.* (2014) 189:39–47. doi: 10.1164/rccm.201306-1174OC

7. Shapiro B, Warren J, Egol A, Greenbaum D, Jacobi J, Nasraway S, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. *Crit Care Med.* (1995) 23:1596–600. doi: 10.1097/00003246-199509000-00021

8. Jacobi J, Fraser G, Coursin D, Riker R, Fontaine D, Wittbrodt E, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med.* (2002) 30:119–41. doi: 10.1097/00003246-200201000-00020

9. Barr J, Fraser G, Puntillo K, Ely E, Gelinas C, Dasta J, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* (2013) 41:263–306. doi: 10.1097/CCM.0b013e3182783b72

10. Yang X, Hu B, Shang Y, Liu J, Zhong M, Shang X, et al. Expert consensus on management of analgesia and sedation for patients with severe coronavirus disease 2019. *Chin Med J (Engl).* (2020) 133:2186–8. doi: 10.1097/CM9.0000000000001034

11. Liu X, Xiong J, Cheng Y, Liu Y, Wang D. [Current state of sedation, analgesia and blood glucose management in intensive care units of county hospitals: a multicenter cross-sectional survey in Guizhou Province of China]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* (2019) 31:108–11. doi: 10.3760/cma.j.issn.2095-4352.2019.01.021

12. Martin J, Parsch A, Franck M, Wernecke K, Fischer M, Spies C. Practice of sedation and analgesia in German intensive care units: results of a national survey. *Crit Care.* (2005) 9:R117–23. doi: 10.1186/cc3035

13. Richards-Belle A, Canter R, Power G, Robinson E, Reschreiter H, Wunsch H, et al. National survey and point prevalence study of sedation practice in UK critical care. *Crit Care.* (2016) 20:355. doi: 10.1186/s13054-016-1532-x

14. Daverio M, von Borell F, Ramelet A, Sperotto F, Pokorna P, Brenner S, et al. Pain and sedation management and monitoring in pediatric intensive care units across Europe: an ESPNIC survey. *Crit Care.* (2022) 26:88. doi: 10.1186/s13054-022-03957-7

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Leadership during airway management in the intensive care unit: A video-reflexive ethnography study

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Effective leadership is crucial to team performance within the intensive care unit. This novel study aimed to explore how staff members from an intensive care unit conceptualize leadership and what facilitators and barriers to leadership exist within a simulated workplace. It also aimed to identify factors that intersect with their perceptions of leadership. This study was underpinned by interpretivism, and video-reflexive ethnography was chosen as the methodology for the study. The use of both video recording (to capture the complex interactions occurring in the ICU) and team reflexivity allowed repeated analysis of those interactions by the research team. Purposive sampling was used to recruit participants from an ICU in a large tertiary and private hospital in Australia. Simulation groups were designed to replicate the typical clinical teams involved in airway management within the intensive care unit. Twenty staff participated in the four simulation activities (five staff per simulation group). Each group simulated the intubations of three patients with hypoxia and respiratory distress due to severe COVID-19. All 20 participants who completed the study simulations were invited to attend video-reflexivity sessions with their respective group. Twelve of the 20 participants (60%) from the simulations took part in the reflexive sessions. Video-reflexivity sessions (142min) were transcribed verbatim. Transcripts were then imported into NVivo software for analysis. The five stages of framework analysis were used to conduct thematic analysis of the video-reflexivity focus group sessions, including the development of a coding framework. All transcripts were coded in NVivo. NVivo queries were conducted to explore patterns in the coding. The following key themes regarding participants' conceptualizations of leadership within the intensive care were identified: (1) leadership is both a group/shared process and individualistic/hierarchical; (2) leadership is communication; and (3) gender is a key leadership dimension. Key facilitators identified were: (1) role allocation; (2) trust, respect and staff familiarity; and (3) the use of checklists. Key barriers identified were: (1) noise and (2) personal protective equipment. The impact of socio-materiality on leadership within the intensive care unit is also identified.

KEYWORDS

leadership, intensive care unit, airway, video reflective ethnography, intubation, simulation

1. Introduction

Effective leadership in healthcare is important as it is known to optimize team performance (1–3). This is especially crucial in the complex environment of the intensive care unit (ICU) (3, 4). Existing evidence that underpins our understanding of leadership in the ICU is commonly discussed in an individualist fashion, similar to how it is conceptualized in the broader healthcare literature (4). Leadership within the healthcare environment has been conceptualized in different ways, with four discourses of leadership being described: individualist; relational; contextual; and complexity (1). In this way, leadership may be defined by the actions and styles of individuals (individual discourse), the leader-follower relationship (relational discourse), or how a context determines the behavior of leaders (contextual discourse). Finally, an emergent process of leadership can be described within an adaptive system (complexity discourse) (1).

Healthcare leadership has also been described by different dimensions, defined as leadership conceptualizations (1). A recent integrative review of the literature exploring leadership in the ICU identified two dominant discourses (individual and relational) and nine central dimensions (4). Dimensions such as role allocation, clinical skills, and communication skills defined leadership within the ICU as well as leader behaviors such as decision-making, being calm in a crisis, or being approachable, and traditional hierarchies (4). This integrative review highlighted a significant lack of literature relative to leadership and followership within the ICU, recommending that future research fill the gap by exploring ICU members' experiences of leadership, as well as the key facilitators and barriers of leadership within this environment (4). This research could allow a richer understanding of how leadership is enacted in the context of an ICU. It may also facilitate further research into improving specific patient or staff-related outcomes attributed to leadership within this environment.

The ICU environment is unique, and the leadership dimensions may differ from other environments. Critically unwell patients are cared for by multi-disciplinary teams in an environment which can be very busy and often chaotic due to inadequate staffing or a life-threatening emergency or an elective procedure with adequate staff and time for preparation and planning. The COVID-19 pandemic has also had a significant impact on this environment, through the increased utilization of personal protective equipment (PPE), changes to the physical ICU environment, as well as the need for additional staff training and new team dynamics (5). Leadership within this complex environment is known to also face the challenges of certain historical influences, particularly those of hierarchy and gender (4, 6). Disciplinary hierarchies describe the traditional power imbalance between doctors and nurses or between senior and junior staff within the medical profession, which can make any collaborative approach to leadership more challenging (7). The role of gender in medical leadership has also been broadly discussed in the literature. This has not only been limited to emergency and crisis leadership, but also in formal leadership positions within the ICU (6). Leadership styles of men and women may be different, with male leadership associated with a more traditional authoritative style and female leadership being associated with more inclusiveness (8). The latter may be less likely to be recognized by medical teams as 'leadership' (8).

Currently, little is known about how ICU staff conceptualize leadership within the ICU and what dimensions, such as gender and hierarchy, impact leadership and followership in this context. Furthermore, whether particular barriers or enablers to leadership exist within this complex environment is also unknown. To our knowledge, no studies report the impact of the ICU environment on leadership and followership among ICU teams. In particular, how socio-materiality impacts leadership (see Table 1 for a glossary of key qualitative and theoretical terms), whereby socio-materiality describes how human beings, physical objects, and physical environments interact (13).

Ethnography is a qualitative research method which involves the observational study of people in their own environment. Video-reflexive ethnography *(VRE)* refers to the practice of filming professionals at work and using the footage to allow scrutiny and discussion about their work and behaviors at reflexive sessions (14). This interpretive tool has been shown to improve staff understanding of their behaviors, as well as to allow further improvement in their practice to enhance patient safety (14–16). VRE can therefore be used as an interpretive method to understand the environment and how staff behave. VRE has been used previously in this way to study staff communication in the clinical ICU setting, and as an interpretive research tool exploring leadership within broader healthcare (9, 17). It has yet to be utilized to look at leadership within ICU teams. The use of VRE by ICU teams as a research tool requires video of their practice within the ICU environment. However, in the face of the COVID-19 pandemic, video of real-life situations in the ICU has been challenging.

Simulation can be used as a surrogate to facilitate VRE to better understand staff performance in the ICU. Simulation-based staff training in healthcare has shown improvements in procedural performance, teamwork, and communication (18). Within the ICU, simulation-based team training has been demonstrated to facilitate clinical learning and positively alter staff behaviors (19). During the recent COVID-19 pandemic, the use of simulation-based team-training for airway management in ICU was ubiquitous, with one study demonstrating its use in 97% of Australian and New Zealand ICUs (20). Simulation training

TABLE 1 Glossary of qualitative and theoretical terms.

Term	Meaning
Video-reflexive ethnography *(VRE)*	A research methodology that is both "ethnographic, in that video captures participants in their 'natural' working environment, and is 'reflexive', in that it involves participants exploring as a group what was captured on the video footage" (9).
Socio-materiality	A "focus on materials as dynamic and enmeshed with human activity in everyday practices" (10).
Interpretivism	An understanding through research that "looks for culturally derived and historically situated interpretations of the social life-world" (11).
Abductive coding	A coding process in qualitative research by which researchers "start with a deductive codebook and through the process of coding, build the codebook and, by extension, build theory by developing data-driven inductive codes" (12).

often occurs within a designated simulation training center, which aims to replicate the environment of a clinical space. However, *in-situ simulation* refers to simulation training done within the actual clinical space, potentially providing improved fidelity, cost-effectiveness, and staff familiarity with devices and their environment (21, 22).

This study was designed to video the simulations of airway management within a busy ICU and use VRE to further investigate leadership within the ICU.

It aims to address the following research questions (RQs):

1. How do ICU staff members conceptualize leadership through their reflections on the simulated ICU?
2. What are the ICU staff members' perceptions of facilitators/barriers to leadership within the simulated ICU?
3. What factors intersect with the ICU staff members' perceptions of leadership in the simulated ICU?

2. Materials and methods

2.1. Study design

This study was underpinned by interpretivism, understanding that multiple perspectives of reality exist which the research will investigate. VRE was chosen from an interpretive perspective as the methodology for the study to answer the RQs (23). Given that leadership is complex and enacted through dynamic interactions underpinned by communication (24), our research is grounded in social constructionism, where knowledge and experiences of leadership are created through relationships and shared social experiences (25). Therefore, we accept that complex and multiple truths exist, and we aimed to use VRE to understand them to address our RQs.

The use of both video recording (to capture the complex interactions occurring in the ICU) and team reflexivity (which provides further social interactions among participants) provides opportunities for repeated analysis of those interactions by the research team. VRE makes the complex environment of the ICU and the relationships for which leadership depend upon visible to the research team and the participants. It also allows for detailed and repeated analysis by the participants to drive understanding of their environment and work practices (14, 26).

Ethics was obtained from the hospital Human Research Ethics Committee (06–04–03-21).

2.2. Sampling and recruitment

Purposive sampling was used to recruit participants from an ICU in a large tertiary and private hospital in Melbourne, Australia. Simulation groups were designed to replicate the typical clinical teams involved in airway management within the ICU. Twenty-two ICU staff were invited *via* email to participate in this study. Twenty staff consented (91%) and participated in the four simulation groups (five staff per simulation group). Written consent was obtained by the lead author for: 1. Video recording during simulation; 2. Use of video and photos from the simulation for publication purposes; and 3. Participation in the video-reflexivity sessions. All invited participants were provided with specific participant and relevant ethics information and signed consent forms for participation. All 20 participants who completed the study simulations were invited to attend video-reflexivity sessions with their respective group. Twelve of the 20 participants (60%) from the simulations took part in the reflexive sessions.

Nurses were defined as "senior" when having greater than 7 years of ICU nursing experience, whereas junior nursing staff were categorized as those with less than 7 years of ICU nursing experience. All consultant ICU medical staff had completed fellowship training with the College of Intensive Care Medicine (CICM) of Australia and New Zealand. Trainee medical staff had yet to complete fellowship training. The composition of three groups (in relation to seniority of staff) reflected "in-hours practice" (groups 1, 3, and 4). One team reflected "after-hours" practice (group 2). Descriptions of the individual participants are in Table 2.

Four groups of ICU staff were assembled to complete a total of 12 *in-situ* simulations, where each group completed simulations of three different contexts/phases of airway management within the ICU.

2.3. Data collection

The first author, who is a practicing intensive care specialist from within the workplace where the study was undertaken, collected all data. Data were collected in two phases: video observation phase and video-reflexivity phase (see Figure 1 for an overview of data collection phases).

2.3.1. Video-observation phase

Each group simulated the intubations of 3 patients with hypoxia and respiratory distress due to severe COVID-19 (see Supplementary material 1). All participants wore airborne PPE including goggles/glasses, masks, gloves, gowns, and face shields, consistent with normal clinical practice during all simulations. The simulations occurred inside a busy working ICU both outside and inside a negative pressured room. Each group completed simulations involving three phases of airway management representing different clinical activities and contexts:

1. Planning and preparing for airway management (occurring outside the simulated patient's room).
2. Performance of a routine intubation procedure (occurring inside the simulated patient's room) *immediately* following phase 1.
3. Management of an unexpected crisis (occurring inside the room) *filmed a few minutes after* the start of 1 and 2.

The unexpected crises simulated included one of the following:

1. A power failure inside the room (groups 2 and 3)
2. Conscious collapse of a medical practitioner responsible for intubation during the procedure (prior to its safe completion) (group 4)
3. Failure of a safe completion of the intubation procedure (group 1)

All simulations were recorded on two separate video cameras. One was a fixed camera in the corner of the simulated patient's room. The other was a roving GoPro camera controlled by the first author. In total, 114 min of simulated activities was recorded. The first author chose 16 video clips (see Table 3) to use for the four VRE sessions, sharing four clips with each group (see Table 3 for details). Clips were chosen by the first author and confirmed after review, by a second author (WB) who is also a senior intensive care clinician-researcher. Clips were chosen in this way to take an interpretive approach to the research study; to maximally understand the data relevant to the RQs. Clips were also

TABLE 2 Participant information.

Participant	Profession	Seniority	Gender
Group 1			
N1	Nurse	Senior	Female
N2	Nurse	Senior	Female
N3	Nurse	Junior	Female
D1	Doctor	Consultant	Male
D2	Doctor	Trainee	Male
Group 2			
N4	Nurse	Senior	Female
N5	Nurse	Senior	Female
N6	Nurse	Senior	Female
D3	Doctor	Trainee	Female
D4	Doctor	Trainee	Female
Group 3			
N7	Nurse	Senior	Female
N8	Nurse	Senior	Female
N9	Nurse	Junior	Female
D5	Doctor	Consultant	Male
D6	Doctor	Trainee	Female
Group 4			
N10	Nurse	Senior	Female
N11	Nurse	Senior	Female
N12	Nurse	Junior	Male
D7	Doctor	Consultant	Female
D8	Doctor	Trainee	Male

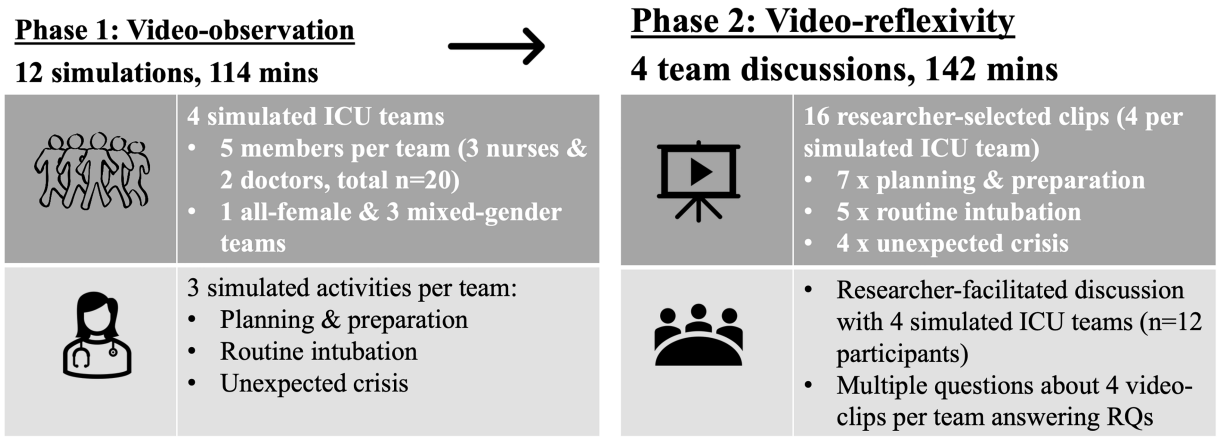

FIGURE 1
Overview of data collection.

chosen to represent diversity across the three activity phases of the scenarios (including different clinical contexts) and were identified as good trigger materials for discussions about leadership, thereby helping to answer the study RQs (see Figures 2–4).

2.3.2. Video-reflexivity phase

The 12 participants at the four discrete reflexive sessions were asked to watch the selected video clips from their simulations and discuss them as a group with respect to the overarching RQs. Due to ongoing

TABLE 3 A summary of video clips used for reflexivity.

Group	Clip	Clinical phase/ context	Duration (seconds)	Summary
1	1	Planning	48	Team meet outside room and agree to plan an intubation. Roles are allocated by senior doctor (D1) and senior nurse (N1). Staff attempt to put on PPE.
	2	Planning	56	Team huddle in PPE to read a checklist before entering the simulated patient's room.
	3	Procedure	40	Intubation is performed by junior doctor (D2) with assistance of senior nurse (N2) and direction of senior doctor (D1) (allocated role of team leader). Senior doctor (D1) helps complete the intubation task.
	4	Crisis management (Crisis scenario 3)*	66	Unexpected failure of intubation by junior doctor (D2). Team advised by senior doctor (D1) for junior doctor to abandon attempts at intubation and change to "plan B" and insert laryngeal mask airway device to rescue ventilate the simulated patient.
2	5	Planning	45	Team meets outside room and agree to plan an intubation. Roles are allocated by junior doctor (D3) and senior nurse (N4). Checklist is read by group.
	6	Planning	35	Role allocation and planning continues to occur in a group forming a circle around a checklist. Second junior doctor (D4) speaks up to acknowledge a lack of confidence with the scenario given her perceived lack of experience.
	7	Procedure	52	Difficult procedure where first attempt at intubation is unsuccessful by the junior doctor. Same junior doctor (D3) decides to insert laryngeal mask airway (LMA) device to allow time to oxygenate the patient and think about her next steps.
	8	Crisis management (Crisis scenario 1)*	62	Unexpected power failure within the ICU (lights go out) while team member attempts intubation. Junior doctor (D3) leads team in assembling battery powered lighting for the room and completing the task of intubation and rescue the crisis.
3	9	Planning	66	Team meets outside room to plan an intubation. Roles are allocated by senior doctor (D5) only and clarified by the others. Staff are standing in a circle and all wearing PPE.
	10	Planning	42	Team discuss plan for intubation one more time inside the simulated patient's room while setting up equipment. Senior doctor (D5) answers questions from junior doctor (D6) about tasks required for the procedure.
	11	Procedure	44	Routine intubation procedure commences. Tasks shared between senior doctor (D5) and senior nurse (N7).
	12	Crisis management (Crisis scenario 1)*	60	Unexpected power failure within the ICU (lights go out) while team attempting intubation. Senior doctor (D5) and senior nurse (N7) instruct team to assemble battery powered lighting for the room and complete the intubation task.
4	13	Planning	60	Team huddle in a circle (all in PPE) and read through checklist and discuss procedure. Junior doctor (D8) begins leading the process but senior doctor (D7) takes over leading the process during the verbalizing of the plan for the procedure by the junior doctor (D8).
	14	Procedure	53	Team starts the intubation attempt. Lots of dialogue between junior and senior doctors (D8 and D7). Junior and senior nursing staff are busy preparing equipment (N11 and N12). Team members have to re-position multiple pieces of equipment either obstructing the action or out of position (including the bed, video laryngoscope monitors and oxygen apparatus) as they attempt to start oxygenation and make the environment safer to work in.
	15	Procedure	43	Team pause after the start of the procedure to clarify one final time the next steps in the procedure. Senior doctor (D7) clarifies everyone is ready to continue to the next step. Junior doctor (D8) verbalizes the plan while simultaneously also oxygenating the patient with a self-inflating resuscitation bag and mask.
	16	Crisis management (Crisis scenario 2)*	39	Junior doctor (D8) responsible for intubation collapses with chest pain just after patient receives paralyzing drugs but before intubation can be attempted. Senior nurse (N11) abandons task to attend to junior doctor on floor. Senior doctor (D7) takes over the procedure and re-allocates roles to other staff to safely complete the procedure.

Crisis scenario 1 = power failure; Crisis scenario 2 = Conscious collapse of a medical practitioner; and Crisis scenario 3 = failure of intubation.

COVID-19 restrictions, the video-reflexivity sessions were conducted on Zoom *(Zoom Video Communications Inc., California, USA, 2016)*. The sessions were facilitated by the first author. These reflexivity sessions were audio-recorded. During these semi-structured sessions, participants were asked various questions including:

1. What do you see in this clip?
2. How is leadership / followership enacted and why is it this way? What makes you think that?
3. How do you feel leadership/followership in this clip relates to leadership in the ICU in general?

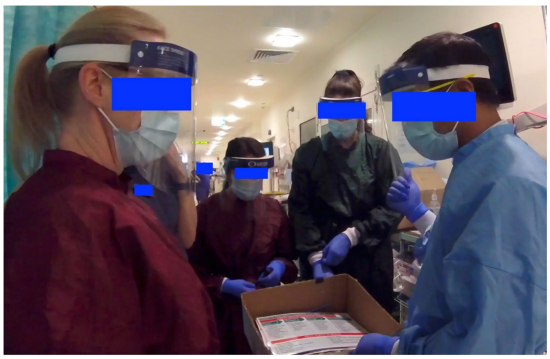

FIGURE 2
Photo of simulated planning by group 3 (From left to right N7, N8, N9, D6, D5).

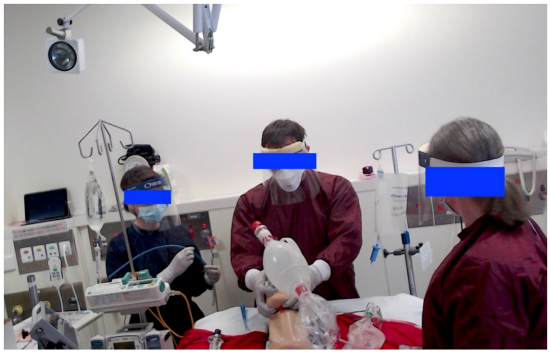

FIGURE 3
Photo of simulated procedure by group 4 (From left to right: N11, D8, D7).

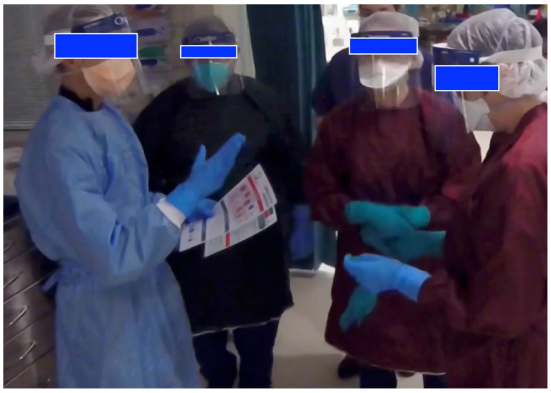

FIGURE 4
Role allocation occurring during clip 2 (referred to in quote 19).

4. What (if any) were the barriers to leadership in this clip?
5. What (if any) were the facilitators to leadership in this clip?
6. Does this clip relate to any of your past experiences of leadership in the ICU? Please describe.
7. Is there anything else you want to say about leadership in this clip?

Free conversation between participants relevant to the research questions was encouraged. Reflexivity sessions ranged in duration from 30 to 42 min, with an average of 35.5 min across the four groups. This provided a total of 142 min of video-reflexivity sessions that were transcribed verbatim. Transcription was initially conducted by Otter.ai software *(Otter.ai, Los Altos California, 2022)*, then checked (with errors

corrected) by the lead author. Transcripts were then imported into NVivo software version 12 *(QSR International Pty Ltd, Version 12, 2018)* for analysis.

2.4. Data analysis

The study employed a thematic analysis approach drawing on a previously developed coding framework, while maintaining openness to new themes based on the data.

The five stages of framework analysis were used to conduct thematic analysis of the video-reflexivity focus group sessions (27).

Familiarization. All transcripts were read by the first author (DB). One of the transcripts was read by each of four other authors (WB, LG, MS, CR).

Development of coding framework. This study used an abductive approach to develop a coding framework (28). Using a previous inductively developed coding framework as a starting point (4), further development of that coding framework was done (on the basis of the data and our study research questions). The first author (DB) identified additional themes in all transcripts to add to the previously published coding framework specific to leadership within the ICU (4). These themes were recorded and then sorted into codes and added to the coding framework. Four other authors (WB, LG, MS, and CR) read one transcript each to also identify additional themes to allow quality assurance of the new coding processes. This framework (see Supplementary material 2, with new codes highlighted) was imported into the NVivo software to help facilitate the analysis of the VRE transcripts.

Indexing. All transcripts were coded in NVivo by the lead author and a selection of coding was checked by the second author (JB).

Charting. NVivo queries were conducted to explore patterns in the coding. NVivo provides counts of the number of quotations coded to each theme/sub-theme, so it was possible to first identify the dominance of certain themes/sub-themes across the whole dataset, plus identify the dominance of themes based on specific participants' contributions (junior/trainee versus senior staff, medical or nursing staff) or based on reflection on certain phases of the simulated scenarios (e.g., planning and preparation, versus routine procedures versus unexpected crises). Hierarchical charts demonstrated the distribution of coding frequencies within the coded quotations from the VRE transcripts. This enabled the researchers to identify key themes relevant to our RQs. Analysis of tabulated coding frequencies was done in NVivo with heat mapping. This was used to further explore which themes were identified as more relevant to certain contexts and/or from the responses of specific participants.

The co-occurrence of themes was explored using matrix coding queries, which demonstrated the intersections between coded quotations for themes/sub-themes and different participants or clinical contexts.

Interpretation. Themes were summarized and presented in quotations, hierarchical charts, and tables. Within tables, color coding of frequencies or coded quotations (heat maps) were used. Heat maps show varying density of data when comparing themes/sub-themes by groups. These were discussed among the research team during interpretation. Key themes are presented in narrative form with illustrative quotes, allowing us to answer the RQs.

2.5. Team reflexivity

Team reflexivity acknowledged differences among our six researcher backgrounds, theoretical positioning and experiences. Our team included four males and two females, three intensive care specialists (all with research experience in airway management), one physiotherapist with 10 years of ICU experience. One of us has a background in psychology. Three of us are health professionals and education researchers with expertise in qualitative and/or leadership research. Two of us have previous experiences employing VRE as a methodology and one of us has experience video-recording *in-situ* simulations. This

TABLE 4 Illustrative quotes (conceptualizations of leadership).

D5 (consultant doctor, group 3, clip 10)	*"But I think at the nitty gritty, it would be a shared role with people bouncing off each other."* *(Quote 1)*
N5 (experienced nurse, group 2 final comment, no specific clip)	*"Somebody needs to be leading. It is a collaborative thing, but it's not a leadership community. It's one person."* *(Quote 2)*
N5 (experienced nurse, group 2 final comment, no specific clip)	*"Obviously, a lot of it is clear communication. And it's, and when I say communication, it's knowing when to shut up as well."* *(Quote 3)*
N2 (experienced nurse, group 1, clip 1)	*"He (D1) is always very clear about what he wants done. In a clear, calm, concise way."* *(Quote 4)*
D3 (trainee doctor, group 2, clip 7)	*"My experience is that men are naturally perceived as the leader."* *(Quote 5)*
D3 (trainee doctor, group 2, clip 7)	*"In other departments, a junior male will often be sought after over a senior female to lead a scenario. Gender plays heavily and I think … females must really work on performance in order to be perceived as the leader."* *(Quote 6)*
N5 (experienced nurse, group 2, clip 7)	*"I think sometimes we feel a bit more comfortable with the women team leaders because we feel like they are more likely to include us…"* *(Quote 7)*

diversity allowed for rich debate on the meaning of the data that was captured and analyzed, as well diversity contributed to ensuring the rigor of the study.

3. Results

Codes were added to the coding framework (see abductive coding framework in Supplementary material). Most notably, some new codes referred to the role of socio-materiality in the ICU. The significance of these interactions was noted initially by the researchers in their viewing of the simulations, as a theoretical/philosophical construct, and subsequently in their analysis of the transcripts of the reflexivity sessions.

Individual quotations ($n = 380$) from video-reflexivity session transcripts were coded to various codes across the dataset. These quotations were identified from a relatively evenly distributed number of reflections by medical and nursing staff (47% vs. 53%) and in reference to the three scenario activity phases (phase 1 = 31%, phase 2 = 32% and phase 3 = 37%). Senior staff were responsible for most of the quotations (73%), comprising 10 of the 12 participants in the reflexive sessions.

TABLE 5 Intensive care unit (ICU) staff members' perceptions of key facilitators and barriers to leadership.

Key facilitators	Role allocation
	Trust, respect and staff familiarity
	Checklists
Key barriers	Noise
	PPE

The following key themes to leadership within the ICU were identified to answer the overarching RQs:

3.1. RQ1: How do ICU staff members conceptualize leadership through their reflections on the simulated ICU?

Leadership within the ICU was conceptualized by the participants in a variety of ways during the reflexive sessions. The most dominant themes are presented below and in Tables 4–7.

3.1.1. Leadership is both a group/shared process and individualistic/hierarchical

The two dominant themes identified were leadership as a *group process* and as *hierarchy*. We found these leadership dimensions to be context-dependent. Differences in attitudes to leadership were reported from the planning phase before performing intubation, which was often referred to as a group process (quote 1), to the unexpected crisis management, more frequently described as individualistic (quote 2). During discussion of the crisis management, a more hierarchical and individualistic leadership model (of the most senior doctor taking charge) was described (predominantly by nursing participants). Hierarchy occurs most commonly in reference to a doctor leading a team of nursing staff and represents the most common individualistic leadership model described.

The participants described group leadership as a shared and distributive model, whereby multiple team members make decisions (including role allocation and clinical decisions) at the same time to prevent cognitive overload on one individual. This is most commonly described as occurring when a senior nurse and a doctor share the leadership.

TABLE 6 Illustrative quotes (facilitators of leadership).

D3 (trainee doctor, group 2, clip 5)	*"You need to be very clear as the leader and the team gains confidence from clear role allocation. So, it's your responsibility as the leader to ensure that that's done properly. There's no confusion."* *(Quote 8)*
N5 (experienced nurse, group 2, clip 5)	*"When it's done well, it's one person allocating"* *(Quote 9)*
D1 (senior doctor, group 1, clip 1)	*"A pretty privileged position, having N1 and N2 (who are) very senior nursing staff that I have worked with a lot and trust and know their capabilities. That really helps as a leader."* *(Quote 10)*
D5 (senior doctor, group 3, clip 9)	*"I would say the familiar environment and familiarity with the staff. Because we have known each other we know each other's skills and strengths. So that makes it easier."* *(Quote 11)*
N1 (senior nurse, group 1, clip 1)	*"I think respect has a lot to do with enabling multiple leaders."* *(Quote 12)*
N10 (senior nurse, group 4, clip 15)	*"Checklists have been very important in making sure things aren't getting missed and that everything is done as safely as possible for the patient."* *(Quote 13)*
D5 (senior doctor, group 3, clip 11)	*"So you just go through the checklist, make sure I've got everything here, and everyone knows what they are doing."* *(Quote 14)*
N10 (senior nurse, group 4, clip 13)	*"And there was the checklist that was read slowly and deliberately, which allowed time for team members to speak up if needed to clarify any issues."* *(Quote 15)*

TABLE 7 Illustrative quotes (barriers to leadership).

N10 (senior nurse, group 4, clip 14)	*"Noise is always a potential barrier to leadership. Obviously, just with all of the beeps of the machines, if you add in people talking elsewhere, as well, it can become quite difficult for leadership to be maintained, and for control of the situation to stay with the leader."* *(Quote 16)*
D5 (senior doctor, group 3, clip 10)	*"And the same issue with the noise, the phone ringing, lots of distractions in terms of leadership."* *(Quote 17)*
N2 (senior nurse, group 1, clip 2)	*"I was a bit distracted by trying to get my gloves on."* *(Quote 18)*
N1 (senior nurse, group 1, clip 2)	*"I think one of the big major barriers, obviously, in that situation is the PPE. [commenting on planning phase and role allocation – see Figure 4] It makes it very, it makes it harder to hear, you do not see their (the leader's) facial expressions… you cannot lip read if there's background noise."* *(Quote 19)*

3.1.2. Leadership is communication

All groups reflected on communication as a key dimension of leadership. Many participants reflected on the need for communication to be clear and concise (quotes 3 and 4), as well as the need for silence from followers (quote 3). As a dimension, it was the third most abundant theme we identified.

3.1.3. Gender is a key dimension within the ICU

One group (the all-female group) reflected on how their gender impacted past experiences of leadership. Note that gender as a key leadership dimension was not discussed in the other three (mixed-gender) groups. This all-female group discussed their past experiences in the ICU of male staff being perceived as the leader (quotes 5 and 6) in preference to female staff, with female leaders reportedly being more inclusive of other female team members in decision-making processes (quote 7). Further to this, this group acknowledged the struggles of females to be allocated and/or assume leadership roles within the ICU (quote 6).

3.2. RQ2: What are the ICU staff members' perceptions of facilitators/barriers to leadership within the simulated ICU?

3.2.1. Facilitators of leadership

3.2.1.1. Role allocation

Quote 8 highlights understanding role allocation as both a key leadership behavior and a key facilitator to team performance. The act of allocating roles was seen by many participants as a leadership behavior and usually done by one person (quote 9). Followers also felt more confident in their performance when allocated a clear role.

3.2.1.2. Trust, respect, and staff familiarity

All groups identified team trust and familiarity as key facilitators of leadership in the ICU. Knowing each other, and respecting others' skills and knowledge was seen to create the platform for leadership (quotes 10 and 11). Respect was also seen as a key facilitator to distributed leadership occurring (quotes 12).

3.2.1.3. Checklists

Participants indicated that the use of checklists to guide clinical decision-making was vital as a facilitator of leadership during airway management within the simulated ICU. Checklists were seen by the staff as a tool for ensuring patient safety (quote 13) and helping to familiarize staff with the correct processes and equipment to use (quote 14). They were also thought to be a tool allowing the team to stop, talk through a procedure, and allow followers to speak up if they had concerns or needed clarification of the process (quote 15).

3.2.2. Barriers to leadership

3.2.2.1. Noise

Participants identified noise as the most significant barrier to leadership, referring to noise from other staff (quote 16), as well as beeping machines and monitors (quotes 16 and 17). Participants in all groups commented on the competing chatter of sub-groups within the simulation scenarios, the ambient noise of ICU and the noise from equipment (such as alarms and the continuous beeping noise of the simulated patient monitor's pulse oxygen saturation).

3.2.2.2. PPE

PPE was commented on by staff to be a profound barrier to communication and leadership within the ICU. Participants described the distraction of having to put on their PPE during role allocation and planning (quote 18), as well as the clothing being a significant barrier to both verbal and non-verbal communication (quote 19).

3.3. RQ3: What factors intersect with the ICU staff members' perceptions of leadership in the simulated ICU?

Matrix coding allowed for identification of how the above findings intersected with either the staff involved or the situational context. We found that:

Perceptions of leadership, being a *shared or individual process*, were context driven. The shared model was most discussed after watching video clips of simulated planning for a procedure, whereas individual and hierarchical leadership was described in reference to video clips of airway management during a crisis.

Role allocation was the most identified facilitator to leadership mentioned across all three phases of the scenarios and by all staff (both medical and nursing participants, as well as senior and junior staff). Role allocation is seen to be the key leadership act in all scenarios that allowed followers to feel confident in their performance.

Calm and *clear communication* was seen as most important during the performance of a procedure or management of crisis.

In terms of barriers to leadership, *noise from other staff* as a barrier to leadership was most identified primarily by senior nursing staff. However, all staff (senior, junior, medical, and nursing) referred to the noise of machines as a major barrier to leadership.

PPE was most frequently reported to be a barrier to leadership during reflection on the planning phases of airway management. It seemingly distracted staff during the role allocation process and inhibited them from understanding (both verbal and non-verbal) communication.

4. Discussion

This study used both *in-situ* simulation and VRE to better understand ICU staff members' conceptualizations of leadership within the complex environment of their ICU. Through an interpretive lens, we found that participants largely spoke about leadership as group (shared) and hierarchy (individual) processes when triggered by different phases/contexts of the scenario (e.g., during the team planning or time critical performance of airway management respectively). The results of this study, therefore, demonstrate that leadership in the ICU is not viewed in a *one-size-fits-all* way by ICU staff. Indeed, context varies understandings of leadership. Group or shared leadership was described across all contexts of the simulations but was perhaps more likely to occur during the planning phase and the traditional individualistic hierarchal leadership model became more noticeable in crisis management. Calm and clear communication was also seen as an important leadership dimension within the ICU, especially during the performance of a procedure or in the context of managing a crisis. Female staff also reported that gender was a key underlying dimension to leadership within the ICU, with female doctors finding it more difficult to be perceived as leaders in the presence of male counterparts.

The dichotomy of leadership we have described within the ICU, being both a shared and individual process, is well described in other healthcare literature (1). However, our findings are new and important in the context of the ICU. Gender is known to be a significant issue within the ICU medical workforce (6). Albeit from one group of all-female staff, we also found that gender has been a key theme in some previous negative experiences relevant to leadership among female staff in the ICU, both medical and nursing. In particular, our female staff in this group reported leadership to be more difficult to be granted or accepted in the presence of male medical staff. Furthermore, as suggested in the previous literature based on research within the operating room, this study highlights that some female staff within the ICU have also experienced more inclusive leadership from female leaders (8).

Whichever leadership dimension is at the forefront of ICU clinicians' minds, participants felt that key facilitators to leadership occurred across individual, relational, and organizational levels. At the individual level, role allocation was the most widely discussed facilitator of leadership. Clear role allocation was seen as a positive leader behavior and gave followers confidence to complete their tasks. Trust, respect, and familiarity with other staff was also reported to be a key relational facilitator to leadership in the ICU setting. Finally, organizational endorsement of checklists was another important perceived leadership facilitator by the staff.

The ICU environment is perhaps the greatest barrier to leadership. Machines and equipment were reported to be key causes of distraction, through noise, as well as the physical environment crowded with so many people. After the COVID-19 pandemic, a new barrier to leadership (i.e., PPE) is significant, especially in its effects on both verbal and non-verbal communication. According to the reflections of our participants, noise was seen as a significant distractor. Noise from machines, the background noise of a busy ICU and noise related to the conversation of other staff are all seen as marked barriers to team performance within the ICU. Noise within the ICU has previously been linked to negative outcomes, in particular poor sleep (29, 30). However, to our understanding, it has not been reported as a barrier to leadership within the ICU. These findings, both the facilitators and barriers to leadership within the ICU, have not to our knowledge been previously described within the literature.

4.1. Methodological strengths and challenges

There are many strengths to the innovative methodology of this study. A rigorous approach to team-based analysis of VRE data was employed using NVivo software. As a working specialist from within the ICU where the study was undertaken, the primary author (and data collector) had insider knowledge of the study environment. This facilitated comfort within the study environment and understanding of the language used by participants (31). The primary author also had the trust of the research participants. This may be reflected in the excellent response rate to the study invitation (91%). The familiarity of the staff with each other may have allowed them to feel safe in sharing their reflections and led to a vigorous discussion, helping the researchers to answer the RQs. The location of the *in-situ* simulations, being within the actual workplace of the participants, may have optimized the fidelity of the simulations and created a more realistic example of a clinical encounter. Finally, leadership practices were examined in a safe (simulated) setting, so research did not interfere with actual patient care.

There are a few limitations to our study to discuss. First, with this interpretive study, the sample size of the participants, the amount of data and diversity of the sample should be acknowledged as a limitation; influencing adversely the transferability of the findings to other contexts. However, efforts were made to select a sample of participants with a balance of clinical experience and gender that reflects the typical ICU workforce in Australia. Furthermore, the participants invited were aimed to reflect the balance of the allocated roles within the usual clinical workplace. Second, simulation data, despite however many efforts are made to maintain high fidelity, are still not real clinical practice. However, this was unavoidable given the research restrictions placed upon us by the COVID-19 pandemic. Third, our inclusion of pre-existing teams of participants, with established relationships and hierarchies, might mean that our study findings are not transferable to other ICU contexts, whereby airway teams are assembled in an impromptu fashion without established relationships and hierarchies. Fourth, the VRE methodology used for this study was through an interpretative lens only. Viewing the actions of a group by the participants themselves stimulated discussion among that group. Analysis of their reflexive discussions was done by the researchers to better understand leadership within the ICU. Further observations of the simulated videos and discussion by

non-participants (ethical approval and participant consent permitting) may have identified additional leadership themes. Finally, as the study was conducted at only one hospital, there will always be concerns for transferability (as mentioned above). Given this study was undertaken at a large, private, metropolitan, and tertiary ICU, transferability of results to smaller or rurally located ICUs may be challenging. However, they should be transferable to other large Australian tertiary hospitals, which make up the majority of ICUs. Also, our participants work in other ICUs (public and private) further adding to the transferability of the results.

4.2. Future research

VRE was used in this study employing an interpretive lens, and further interpretivist research is needed to explore these issues in different contexts (e.g., smaller, rurally located ICUs), and in different countries with different educational systems in critical care. Moreover, further research using VRE in this area may choose to come from a critical inquiry perspective (23). This would allow researchers to determine if the knowledge gained from VRE could lead to changes in outcomes, either through altered staff performance and behaviors or patient-centered outcomes.

The effects of the ICU environment, particularly socio-materiality impacts, on leadership within ICU were significant. Noise, machines, PPE, and checklists all significantly affect leadership practices. A critical inquiry study could look at how to minimize the effect of perceived barriers and enhance the effects of any enablers on leadership.

Different leadership approaches, particularly an individualistic hierarchical style and a distinctly different shared or group interprofessional approach, were reported by participants in this study. This dichotomy of leadership approaches was described in different clinical contexts, including the planning phase prior to undertaking an intubation, as well as during the chaos and stress of an unexpected airway management crisis. The outcomes of either approach within the ICU need further research. Finally, the role of gender and its effects on both leadership approaches and staff confidence in enacting leadership could be further explored within the ICU setting.

This study has highlighted that VRE can enable ICU staff to visualize their leadership practices within their workplace. Simulation was realistic and participants' experiences were consistent with real life. Future research should adopt a more critical inquiry approach to see if video and reflection could also improve their leadership practices.

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 Cabrini Hospital Research Governance (06–04–03-21). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Data collection was done by DB and JB. DB conducted coding framework development and checked by CR, WB, MS, and LG. Coding of transcripts was done by DB and results were discussed by all authors. DB was the primary author for the manuscript preparation. All authors contributed to the study design. 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.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1043041/full#supplementary-material

References

1. Gordon, LJ, Rees, CE, Ker, JS, and Cleland, J. Dimensions, discourses and differences: trainees conceptualising healthcare leadership and followership. *Med Educ*. (2015) 49:1248–62. doi: 10.1111/medu.12832

2. Blumenthal, DM, Bernard, K, Bohnen, J, and Bohmer, R. Addressing the leadership gap in medicine: residents' need for systematic leadership development training. *Acad Med*. (2012) 87:513–22. doi: 10.1097/ACM.0b013e31824a0c47

3. West, M, Armit, K, Loewenthal, L, Eckert, R, West, T, and Lee, A. *Leadership and Leadership Development in Healthcare: The Evidence Base*. London: The Kings Fund (2015).

4. Brewster, DJ, Butt, WW, Gordon, LJ, and Rees, CE. Leadership in intensive care: a review. *Anaesth Intensive Care*. (2020) 48:266–76. doi: 10.1177/0310057X20937319

5. Brewster, DJ, Chrimes, N, Do, TB, Fraser, K, Groombridge, CJ, Higgs, A, et al. Consensus statement: safe airway society principles of airway management and tracheal intubation specific to the COVID-19 adult patient group. *Med J Aust*. (2020) 212:472–81. doi: 10.5694/mja2.50598

6. Modra, LJ, and Yong, SA. Towards gender balance in the Australian intensive care medicine workforce. *Med J Aust*. (2019) 211:300–302.e1. doi: 10.5694/mja2.50330

7. Lingard, L, Vanstone, M, Durrant, M, Fleming-Carroll, B, Lowe, M, Rashotte, J, et al. Conflicting messages: examining the dynamics of leadership on interprofessional teams. *Acad Med*. (2012) 87:1762–7. doi: 10.1097/ACM.0b013e318271fc82

8. Minehart, RD, Foldy, EG, Long, JA, and Weller, JM. Challenging gender stereotypes and advancing inclusive leadership in the operating theatre. *Br J Anaesth*. (2020) 124:e148–54. doi: 10.1016/j.bja.2019.12.015

9. Gordon, L, Rees, C, Ker, J, and Cleland, J. Using video-reflexive ethnography to capture the complexity of leadership enactment in the healthcare workplace. *Adv Health Sci Educ Theory Pract*. (2017) 22:1101–21. doi: 10.1007/s10459-016-9744-z

10. Fenwick, T. Sociomateriality in medical practice and learning: attuning to what matters. *Med Educ*. (2014) 48:44–52. doi: 10.1111/medu.12295

11. Crotty, M. *The Foundations of Social Research. Meaning and Perspective in the Research Process*. London: SAGE (2003).

12. Vila-Henninger, L, Dupuy, C, Van Ingelgom, V, Caprioli, M, Teuber, F, Pennetreau, D, et al. Abductive coding: theory building and qualitative (re)analysis. *Sociol Methods Res*. (2022):004912412110675. doi: 10.1177/004912412110675

13. Orlikowski, WJ. Sociomaterial practices: exploring technology at work. *Organ Stud*. (2007) 28:1435–48. doi: 10.1177/0170840607081138

14. Iedema, R, Mesman, J, and Carroll, K. *Visualising health care practice improvement: Innovation from within*. London: Radcliffe Publishing (2013).

15. Iedema, R. Creating safety by strengthening clinicians' capacity for reflexivity. *BMJ Qual Saf*. (2011) 20:i83–6. doi: 10.1136/bmjqs.2010.046714

16. Iedema, R, Hor, SY, Wyer, M, Gilbert, GL, Jorm, C, Hooker, C, et al. An innovative approach to strengthening health professional infection control and limiting hospital acquired infection: video reflexive ethnography. *BMJ Innov*. (2015) 1:157–62. doi: 10.1136/bmjinnov-2014-000032

17. Carroll, K, Iedema, R, and Kerridge, R. Reshaping ICU ward round practices using video-reflexive ethnography. *Qual Health Res*. (2008) 18:380–90. doi: 10.1177/1049732307313430

18. Okuda, Y, Bryson, EO, DeMaria, S Jr, Jacobson, L, Quinones, J, Shen, B, et al. The utility of simulation in medical education: what is the evidence? *Mt Sinai J Med*. (2009)) 76:330–43. doi: 10.1002/msj.20127

19. Low, XM, Horrigan, D, and Brewster, DJ. The effects of team-training in intensive care medicine: a narrative review. *J Crit Care*. (2018) 48:283–9. doi: 10.1016/j.jcrc.2018.09.015

20. Brewster, DJ, Nickson, CP, McGloughlin, S, Pilcher, D, Sarode, VV, and Gatward, JJ. Preparation for airway management in Australia and New Zealand ICUs during the COVID -19 pandemic. *PLoS One*. (2021) 16:e0251523. doi: 10.1371/journal.pone.0251523

21. Patterson, MD, Blike, GT, and Nadkarni, VM. In situ simulation: challenges and results. In: Henriksen, K., Battles, J.B., Keyes, M.A., and Grady, M.L., editors. *Advances in patient safety: New directions and alternative approaches (Vol. 3: Performance and tools)*. Rockville (MD): Agency for Healthcare Research and Quality (US); (2008) Available from: https://www.ncbi.nlm.nih.gov/books/NBK43682/

22. Monesi, A, Imbriaco, G, Mazzoli, CA, Giugni, A, and Ferrari, P. In-situ simulation for intensive care nurses during the COVID-19 pandemic in Italy: advantages and challenges. *Clin Simul Nurs*. (2022) 62:52–6. doi: 10.1016/j.ecns.2021.10.005

23. Carroll, K, and Mesman, J. Multiple researcher roles in video-reflexive ethnography. *Qual Health Res*. (2018) 28:1145–56. doi: 10.1177/1049732318759490

24. Fairhurst, G, and Uhl-Bien, M. Organizational discourse analysis (ODA): examining leadership as a relational process. *Leadersh Q*. (2012) 23:1043–62. doi: 10.1016/j.leaqua.2012.10.005

25. Gergen, KJ, and Wortham, S. Social construction and pedogogical practice In: KJ Gergen, editor. *Social Construction in Context*. London: Sage (2001). 115–36.

26. Ajjawi, R, Hilder, J, Noble, C, Teodorczuk, A, and Billett, S. Using video-reflexive ethnography to understand complexity and change practice. *Med Educ*. (2020) 54:908–14. doi: 10.1111/medu.14156

27. Ritchie, J, Spencer, L, and O'Connor, W. Carrying out qualitative analysis. *Qual Res Pract*. (2003) 2003:219–62.

28. Timmermans, S, and Tavory, I. Theory construction in qualitative research: from grounded theory to abductive analysis. *Sociol Theory*. (2012) 30:167–86. doi: 10.1177/0735275112457914

29. Maidl-Putz, C, McAndrew, NS, and Leske, JS. Noise in the ICU. *Nurs Crit Care*. (2014) 9:29–35. doi: 10.1097/01.CCN.0000453470.88327.2f

30. Simons, KS, Verweij, E, Lemmens, PM, Jelfs, S, Park, M, Spronk, PE, et al. Noise in the intensive care unit and its influence on sleep quality: a multicenter observational study in Dutch intensive care units. *Crit Care*. (2018) 22:250. doi: 10.1186/s13054-018-2182-y

31. Burns, E, Fenwick, J, Schmied, V, and Sheenan, A. Reflexivity in midwifery research: the insider/ outsider debate. *Midwifery*. (2012) 28:52–60. doi: 10.1016/j.midw.2010.10.018

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China's current situation and development of hospice and palliative care in critical care medicine

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1. Introduction

Hospice and palliative care (HPC) is a novel inter-discipline with a history spanning the last 50 years, during which time, it has become an independent discipline in many countries. In 2000, the American Board of Hospice and Palliative Medicine stated that "palliative medicine is the medical specialty devoted to achieving the best possible quality of life of the patient and the family during the course of a life-threatening illness through the relief of suffering and the control of symptoms" (1). As a discipline focusing on the quality of life of patients with a finite life span, it provides hope in modern medicine, helping illuminate the dark moments of death and providing solutions to many difficult medical scenarios. However, in China, HPC has not yet become a specialized or sub-specialized subject, with a lack of corresponding education for most medical students/nursing students. Accordingly, there is a need to promote the dissemination and popularization of relevant knowledge of HPC in various ways.

2. Ignorance of the demand for HPC in critical care medicine

The therapeutic goal is a "cure" for patients with acute and critical illnesses receiving treatment in the hospital. However, despite a clear diagnosis of diseases with poor prognosis based on the use of assessment tools for prognosis, the need for, and practices of HPC are also seriously ignored in large hospitals guided by the mainstream values of "saving lives" and "resuscitation." For example, according to a survey of two major acute care hospitals, one-third of the patients had HPC needs (2), suggesting an insufficiency of HPC care for these patients (3).

In critical care medicine, the topic related to end-of-life is a problem that cannot be ignored. ICU is an important place where the hospital provides life sustaining treatment for critically ill patients, so as to rebuild and maintain organ functions. The focus of attention in the ICU is "how to live." It seems that talking about "death" means "giving up," which means "medical failure." Despite the continuous development of medical science and technology, the mortality rate in ICU is still as high as 20%−35% (4). The initial treatment provided to patients in ICU might cause more harm than good when patients start to develop organ failure or have no response to that treatment. Doctors in the ICU also have to consider how to cope with the imminent death of patients.

3. The definition of HPC

In 2000, the American Board of Hospice and Palliative Medicine stated that "palliative medicine is a medical specialty devoted to achieving the best possible quality of life for the patient and the family during the course of a life-threatening illness through the relief of suffering and the control of symptoms" (1). HPC is a discipline that can offer assistance to patients with a finite life span caused by serious diseases and their families. It can provide assistance to patients and their families, helping maintain the best possible quality of life by actively evaluating, discovering, and dealing with the patients' holistic suffering, including physical, psychological, spiritual, and social suffering so that they can live out the final stage of life smoothly. Significantly, HPC is available at any time according to the patient's needs, independent of the patient's age or the type of disease.

HPC is a subject that confronts the limitations of medical science and technology and is a subject that faces death. It can offer active assistance for patients and their families to understand the true meaning of life and death at ease. In other words, life has its limits. Death is not a failure of medicine but the law of life. Human beings cannot change this law. On the premise of conforming to this law, human beings should not only "fight" against disease but also timely reconcile with death. The word "timely" is the core and also the difficulty of HPC. Importantly, medicine has never been a technology based on theory only but a combination of science and humanity. Notably, practice in HPC is the most perfect demonstration of medical humanities.

4. Intimate association between critical care medicine and HPC

Seemingly, critical care medicine and HPC are two opposite disciplines. The former wants to "save life," while the latter talks about "death." In addition, in some people's opinion, critical care medicine is "technical medicine" and HPC is "talking medicine."

Really? It will be apparent in a moment's consideration that the two disciplines are full of commonalities and intertwined so harmoniously. Both critical care medicine and HPC are concerned with the care of patients with serious diseases/life threats. The purpose of critical care medicine is to save lives, without excluding the maintenance of the quality of life and with the emphasis on coping with the topics of "death." Simultaneously, HPC aims to maintain quality of life of patients, without excluding life extension and with emphasis spent talking about "how to live well." Both critical care medicine and HPC share consistent values and goals to obtain a higher quality of life and human dignity while maintaining the life cycle. As mentioned in the definition of palliative care (PC) by WHO, all patients shall be provided with PC at the same time when receiving curative treatment. In clinical practice, there is no contradiction between saving/prolonging life and alleviating pain/maintaining the quality of life.

5. Indispensable roles of HPC in ICU

There are many problems to be coped with in ICU, such as patients' painful symptoms, family members' anxiety and depression, difficult decision-making, difficult communication, how to respect patients' autonomy, how to benefit patients rather than injuries, whether to withdraw or not to give a treatment, etc.

The incidence of painful symptoms in critically ill patients reached 27%−75% in ICU, and one-third of patients had delirium (5). In addition to alleviating the physical pain of patients, the medical team should also maintain their dignity and give them respect for life, which can be addressed to some extent by following the concept and practice of HPC. Clinically, besides the suffering of patients, their families are also suffering of which 57% have trauma-related pain and 70%−80% have depression (6).

In addition to coping with all types of suffering of patients and their families, medical staff in ICU also need to distinguish between "death" and "reversible deterioration" in the treatment process, which are generally difficult to discriminate. Medical staff will also have many psychological, moral, and ethical pressures under the aforementioned difficult situations. Medical staff who have not received adequate training for HPC are often powerless. In view of the above, it is important to carry out HPC-related assessments as well as early prediction and intervention for patients entering the ICU to reduce the suffering of many people.

Previous research has confirmed that the involvement of the HPC team can promote the early initiation of family meetings in the ICU, shorten the length of stay in the ICU, and the total length of stay in the hospital (7). As proposed by the latest guidelines for sepsis, it is suggested that PC should be taken into account in sepsis and septic shock according to the patient's situation (8). HPC Medical team in Peking Union Medical University Hospital, established in 2012, has begun and address the HPC of critically ill patients and has achieved good results.

6. The content of HPC in ICU

The core of HPC is to take care of critically ill patients in the ICU, control symptoms, and discuss the goals of care.

Part of the daily work of medical staff in the ICU is to comfort the patients receiving treatment in ICU physically, such as alleviating pain and improving symptoms such as thirst, anxiety, sleep disorders, and dyspnea. However, due to the limited energy of the medical staff and the therapeutic goal of "cure," this part of the work may not be fully paid attention to and implemented in the clinical practice.

Discussing the goals of care is important for the treatment of critically ill patients. Meanwhile, the therapeutic goal should not be formulated by the medical team unilaterally but is the result of the joint decision-making of the multi-disciplinary team (MDT), the patient, and family members.

It is crucial that the goals of care are discussed with the patient themselves or the patient's family members. Following the principle of autonomy among the four basic principles of medical ethics, it is extremely important to respect the wishes of patients. Hence, patients are allowed to express their wishes and care goals. It is, however, not fully emphasized in China, and there is a long way to go compared with current international practices. The patient's serious illness is frequently not truthfully informed to the patient or their family, and even the medical staff regard this "white deception and lies" as "great love" and "filial piety." Under the influence of the so-called love and filial piety, even if the patient himself/herself has decision-making ability and willingness, there is no opportunity for the patient to make decisions. In many cases, patients are delivered into ICU

unwittingly, with corresponding autonomy completely disrespected. Advance care planning (ACP) is a method widely used abroad to express wishes. In China, there is also the text of "My Five Wishes" of the Living Will Promotion Association and the promotion based on the website, WeChat official accounts, and offline activities of the Association. If there is an opportunity, we can know the wishes of patients by communicating ACP or "My Five Wishes," which, unfortunately, is extremely difficult to implement.

When patients do not have the opportunity to express their wishes, doctors generally communicate with their families about the therapeutic goals. There will be a great difference between the conclusions drawn by the families from the best interests of patients or their feelings when determining the goals. Some families may make some decisions based on the interests and wishes of the patients, e.g., "My father once said that he should not be intubated, he should go with dignity." However, at present in China, more family members of patients make decisions from the perspective of "the common practice of the society," "what others will think of me," and "I don't want to leave any regrets." Consequently, the wishes and feelings of patients are ignored to some extent. As reported by previous studies, in some cases, the family members were not really given such decision-making opportunities but were just informed by the medical team that had made decisions already.

Therefore, discussing the therapeutic goals is an important ability of doctors in the ICU. It is the routine work of the ICU and should also be regarded as an important part of the competency of doctors in the ICU. The content of HPC in the ICU should include discussing the therapeutic goals repeatedly at any time, providing patients with physical, psychological, social, and spiritual support, and family members with emotional and decision-making support, as well as self-pressure regulation of team members, in addition to the relief of physical symptoms. In the process of decision-making, it is the basic skill of doctors in the ICU to discuss with patients/families and team members not to give or withdraw a certain treatment.

7. Specific practice of HPC in ICU

It is a great challenge to help patients in the ICU get holistic care. Before the concept of emergence and intervention of HPC, we should make up our minds about the facts that life is limited and death may be coming, which is the biggest difficulty. In addition, it is also a great difficulty to balance the wishes of patients/families, doctors' therapeutic strategies, and patients' wishes.

From the perspective of international practice, there are two modes for ICU to practice HPC. The first is the integration mode (9), which allows medical staff in the ICU to learn the concept and knowledge of HPC, so as to promote a direct application of the concept of HPC to the specific practice such as the control of patients' painful symptoms, psychological, social, and spiritual support of patients, support of family members, family meetings, and joint decision-making. In other words, this mode allows the medical staff of critical care medicine to be responsible for the work of primary HPC. The other is consultation mode. HPC professionals are allowed to participate in the consultation of the ICU, with symptom control as the main content and with additional attention paid to spiritual care simultaneously. Nevertheless, the disadvantage of this consultation mode is that HPC professionals are insufficient to meet all the needs of HPC in the ICU. Moreover, excessive reliance on HPC consultation may imbalance the therapeutic relationship between doctors and patients in ICU, resulting in a fragmented medical mode. In addition, the implementation of HPC consultation will reduce the demand for doctors in ICU to learn PC skills and knowledge. HPC consultation can be initiated when the HPC concept has not been integrated into the knowledge system of doctors in the ICU.

Therefore, it is recommended currently to combine the integration mode with the consultation mode. It has been documented that the practice of the mixed mode can improve the quality of life of patients, improve the signing rate of ACP and the utilization rate of HPC institutions, and reduce the utilization rate of ineffective life maintenance treatment (10).

8. HPC skills required by doctors in ICU

To provide good services for HPC of critically ill patients, doctors in the ICU need to have the following abilities:

8.1. The ability to improve the professional ability of intensive care to accurately control the disease

Doctors of critical care medicine are required to have professional quality and ability. It not only contributes to the determination of the patient's condition and severity at the first time but also can make an appropriate and accurate judgment on the treatment response. Based on this ability, doctors can apply appropriate treatment according to patients' conditions, rather than "overtreatment."

8.2. Ability to predict and fully inform

The doctors in ICU should have the ability to predict (e.g., painful symptoms, pain, thirst, anxiety, etc.) what the patients will experience during their stay in the ICU, the state of the patients after entering the ICU, the possible therapeutic effect, possible outcome, the possible cost of treatment in ICU, ways for family members to visit and accompany patients, post-ICU syndrome, and the experience and common reactions of family members such as psychological and physical pain, depression, and post-traumatic syndrome and fully communicate with the patients/families. The key lies in that in addition to communicating with the patients/families about "the necessity and possible benefits of treatment in ICU," it is important to fully explain "the painful situation of patients in ICU, the proportion of poor prognosis, high costs, and many other unfavorable details." Based on this, the patient can make the important decision of "whether to stay in the ICU or not." In many cases, doctors in ICU are busy with their work in emergency situations and fail to inform the patients/families of the latter details.

8.3. Ability to hold family meetings and do shared decision-making

Family meetings are the work that doctors in ICU deal with every day. It is challenging for doctors to make better

joint decisions at any time based on a family meeting. Among them, the communication contents and technical points involved generally in the family meetings of critically ill patients include not giving or withdrawing a certain treatment, available options at the end of life, the purpose of treatment, the methods to reduce pain, the wishes of patients, the arrangement of things after death, and the peace of mind of family members are the talking contents and technical points often involved in family meetings for severe patients.

8.4. Ability to communicate well with families

Both patients and their families prefer honest, respectful, and sympathetic communication with the feeling of being listened to. Previous research has revealed that the way the doctors in the ICU guide conversations would affect the therapeutic relationship between doctors and patients and the acceptance of their families (11). A planned communication framework is as important as the specific content of communication, e.g., being able to find out the key family members who can promote communication and the people who are more willing to discuss the end-of-life topics in the family of the patients, being able to detect and deal with the complex emotions of the patients/families, such as anxiety, fear, anger, entanglement, and reluctance, and being able to carry out discussion on the topics related to ethics clearly and methodically, i.e., respecting patients' autonomy, being beneficial, not harmful, patients' decision-making ability, and determining entrusted agents.

8.5. Ability to effectively deal with patients' physical, psychological, social, and spiritual pain

This ability involves non-drug pain relief methods and the use of analgesic and sedative drugs. The ability to pay attention to and care for psychological, social, and spiritual pain is also quite important in ICU, in addition to the ability to control the physical symptoms of the patients. It has been reported that dignity therapy, life review, personal narration, and wish fulfillment (12) are all available methods with significant effects. It is particularly worth emphasizing that the aforementioned contents need to be prepared and intervened as soon as possible. According to multiple clinical cases, it is time-consuming to prepare for death! It needs to be proposed early! It is not recommended to discuss this issue only a few hours or minutes before death.

8.6. Ability to self-learning

Currently, many resources and tools are available to assist doctors in critical care medicine to learn about primary PC (13).

9. Obstacles to the integration of critical care medicine and HPC

Obstacles to the integration of critical care medicine and HPC mainly include the following two parts: (1) it is mistakenly believed that the treatment in ICU and HPC are related in time and thought that HPC can be carried out after there is nothing to deal with in ICU, without recognizing the coexisting and complementary relationship between them; and (2) the medical team and family members have unrealistic expectations for treatment and worry that the implementation of HPC is to give up the patients or even hasten the death. All these views may lead to insufficient training of the medical team in HPC skills.

The aging of the population accelerates the occurrence of death. With the development of the social economy and the improvement of the level of civilization, there is a constant improvement in the public's requirements for quality of life, including the rigid demand for a good ending and peace between life and death. All medical staff should have the ability to help patients die well. In particular, the medical staff of critical care medicine bears a more important mission. It is critical to maintaining the balance between life and death, which embodies the difficulty and responsibility of the clinical practice of the medical staff in critical care medicine more significantly.

10. Prospective future

China's critical care medical treatment has just begun, and much data is still blank. The focus and core of our work lie in how to balance the boundaries of intensive care and palliative care. This requires intensivists to know the content of HPC in the ICU and master HPC skills and perform special practice in the daily work at the same time. In the future, China will accelerate into aging, and the role of HPC in the ICU is about to be highlighted. It is necessary to speed up training and improve the perception of employees.

Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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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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References

1. Lamba S, Mosenthal AC. Hospice and palliative medicine: a novel subspecialty of emergency medicine. *J Emerg Med.* (2012) 43:849–53. doi: 10.1016/j.jemermed.2010.04.010

2. Gardiner C, Gott M, Ingleton C, Seymour J, Cobb M, Noble B, et al. Extent of palliative care need in the acute hospital setting: a survey of two acute hospitals in the UK. *Palliat Med.* (2013) 27:76–83. doi: 10.1177/0269216312447592

3. Kelley AS, Meier DE. Palliative care–a shifting paradigm. *N Engl J Med.* (2010) 363:781–2. doi: 10.1056/NEJMe1004139

4. Angus DC, Truog RD. Toward better ICU use at the end of life. *JAMA.* (2016) 315:255–6. doi: 10.1001/jama.2015.18681

5. Puntillo KA, Arai S, Cohen NH, Gropper MA, Neuhaus J, Paul SM, et al. Symptoms experienced by intensive care unit patients at high risk of dying. *Crit Care Med.* (2010) 38:2155–60. doi: 10.1097/CCM.0b013e3181f267ee

6. McAdam JL, Dracup KA, White DB, Fontaine DK, Puntillo KA. Symptom experiences of family members of intensive care unit patients at high risk for dying. *Crit Care Med.* (2010) 38:1078–85. doi: 10.1097/CCM.0b013e3181cf6d94

7. Braus N, Campbell TC, Kwekkeboom KL, Ferguson S, Harvey C, Krupp AE, et al. Prospective study of a proactive palliative care rounding interventionin a medical ICU. *Intensive Care Med.* (2016) 42:54–62. doi: 10.1007/s00134-015-4098-1

8. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. *Crit Care Med.* (2021) 49:e1063–143.

9. Nelson JE, Bassett R, Boss RD, Brasel KJ, Campbell ML, Cortez TB, et al. Models for structuring a clinical initiative to enhance palliative care in the intensive care unit: a report from the IPAL-ICU project (improving palliative care in ICU). *Crit Care Med.* (2010) 38:1765–72. doi: 10.1097/CCM.0b013e3181e8ad23

10. O'Mahony S, McHenry J, Blank AE, Snow D, Eti Karakas S, Santoro G, et al. Preliminary report of the integration of a palliative care team into an intensive care unit. *Palliat Med.* (2010) 24:154–65. doi: 10.1177/0269216309346540

11. Bloomer MJ, Endacott R, Ranse K, Coombs MA. Navigating communication with families during withdrawal of life-sustaining treatment in intensive care: a qualitative descriptive study in Australia and New Zealand. *J Clin Nurs.* (2017) 26:690–7. doi: 10.1111/jocn.13585

12. Cook D, Swinton M, Toledo F, Clarke F, Rose T, Hand-Breckenridge T, et al. Personalizing death in the intensive care unit: the 3 wishes project: a mixed-methods study. *Ann Intern Med.* (2015) 163:271–9. doi: 10.7326/M15-0502

13. Jeffrey E, Louis V, Judith N. Ten key points about ICU palliative care. *Intensive Care Med.* (2017) 43:83–5. doi: 10.1007/s00134-016-4481-6

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