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Insights in intensive care medicine and anesthesiology 2023

Edited by
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Published in
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-8325-6075-4
DOI 10.3389/978-2-8325-6075-4

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Insights in intensive care medicine and anesthesiology: 2023

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Citation
Kaynar, A. M., ed. (2025). *Insights in intensive care medicine and anesthesiology: 2023*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-6075-4

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 08 June 2023
DOI 10.3389/fmed.2023.1194005

OPEN ACCESS

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RECEIVED 26 March 2023
ACCEPTED 22 May 2023
PUBLISHED 08 June 2023

CITATION
Sun L, Wei X, Wang K and Zhou J (2023) Research trends from 1992 to 2022 of acupuncture anesthesia: a bibliometric analysis. *Front. Med.* 10:1194005. doi: 10.3389/fmed.2023.1194005

Research trends from 1992 to 2022 of acupuncture anesthesia: a bibliometric analysis

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Background: Acupuncture anesthesia is a significant technical development that originated in China in 1958 and was introduced to the West in the early 1970s. Due to its relative novelty, it has been the subject of intense scrutiny and contestation. Since the early 1970s, the use of acupuncture as a complementary treatment for opioid analgesics has been accepted. Research on acupuncture anesthesia has helped to reduce clinical opioid abuse. However, only a few articles have focused on previous publications that reflect the trend of the study, the main investigators, reciprocal collaboration, and other information in this field. In view of this, we utilized bibliographic analysis methods to objectively analyze current trends and research hotspots in this field, aiming to provide a foundation and reference for future studies.

Methods: The Web of Science database was searched for publications related to acupuncture anesthesia between 1992 and 2022. The CiteSpace and VOSviewer were used to analyze the annual publications, authors, Co-cited authors, and their countries (regions) and institutions, co-occurrence keywords, burst keywords, Co-citation references and Co-citation journals.

Results: A total of 746 eligible publications were retrieved from the database for the analysis, including 637 articles and 109 reviews. And the trend of annual publications continued to grow. Aashish J. Kumar, Daniel I. Sessler, Baoguo Wang, and Paul F. White published the most papers in this field (7), and all authors, had a very low centrality (<0.01). China (252) and the University of California System (21) were the most productive country (region) and institution, respectively, while the United States (0.62) and University of California System (0.16) had the highest centrality. After removing keywords related to the search strategy, the three most frequent were pain (115), electroacupuncture (109), and stimulation (91). The six most recent burst keywords were recovery, transcutaneous electrical acupoint stimulation, systematic review, quality, general anesthesia, and surgery. Wang et al.'s article had the highest co-citation count (20), whereas Zhang et al.'s articles had the highest centrality (0.25). The Journal of *Anesthesia and Analgesia* was the most influential one (408 co-citations).

Conclusion: This research provides valuable information for the study of acupuncture anesthesia. In recent years, frontier topics in acupuncture anesthesia research have been the promotion of perioperative rehabilitation, anesthesia management, and quality improvement.

KEYWORDS

acupuncture, anesthesia, bibliometric analysis, CiteSpace, VOSviewer

1. Background

Acupuncture anesthesia refers to the use of acupuncture to obtain or strengthen anesthesia by following meridians, identifying evidence, or localizing points of acupuncture according to different diseases and surgical sites (1). It is a unique anesthesia method in China that uses acupuncture therapy to assist in surgery. Acupuncture anesthesia is a new exploration of anesthesiology and an original research field in the history of Chinese medicine (2, 3). It perfectly combines the ancient acupuncture technique with the modern anesthesia technique in the surgical field and is a typical case of the integration of traditional Chinese and Western medicine (4).

During President Nixon's historic visit to China in 1972, members of his delegation observed thyroidectomy and lobectomy surgeries performed under acupuncture anesthesia. This event marked the beginning of a global surge in interest and research into acupuncture anesthesia (5, 6). It is well known that surgery occupies an unshakable position in Western medicine, and traditional Chinese acupuncture can be combined with surgery, which has promoted acupuncture therapy worldwide. Multiple clinical studies demonstrated that combining acupuncture with anesthesia leads to improved patient outcomes, including decreased preoperative anxiety, less stress response during surgery, improved immune function, and fewer postoperative side effects (7–11). The indications for acupuncture anesthesia are also expanding, not only for various surgical procedures (12) but also for gynecological procedures such as abortion (13) and cesarean section (14), as well as local trauma-assisted examinations such as peritoneal dialysis (15) and gastroscopy (16). These advancements have significantly contributed to the improvement of individuals' overall health.

In recent years, the number of research papers on acupuncture anesthesia published in high-level domestic and international journals has increased rapidly, and acupuncture anesthesia research is progressing in a scientific and standardized manner (17). However, despite enthusiasm in the clinical and research fields (18, 19), no studies conducted to systematically organize and deeply analyze research trends in acupuncture anesthesia, which to some extent restricts the advancement of the general research of acupuncture anesthesia (20). Therefore, an in-depth study of this field using bibliometric analysis is highly warranted.

Bibliometric analysis is a method of evaluating and quantifying information in the literature using mathematical and statistical methods, which helps to gain a complete understanding of research progress in a scientific field (21, 22). This analysis has been applied to several fields of acupuncture, including acupuncture for cardiac disease and postoperative analgesia, and many research results have been accumulated (23–25). The bibliometric approach was applied in this study to analyze the literature on acupuncture anesthesia over the last 31 years from multiple perspectives, such as authors, institutions, countries, keywords, co-cited references, and co-cited journals. And the results were presented in the form of scientific knowledge maps by using the CiteSpace software; then the maps were further interpreted and analyzed to gain an intuitive and comprehensive understanding of the research in the field, identify research hotspots, and provide new research ideas (26, 27).

2. Materials and methods

2.1. Data sources and search strategy

All data for this study were obtained from the Web of Science (WoS) Core Collection database. Relative to general databases such as Scopus, Derwent, China National Knowledge Infrastructure (CNKI), and the Chinese Social Sciences Citation Index (CSSCI), WOS includes more scientific publications and provides overall data sources for bibliometric software. Thus, WOS is the most frequently used database in bibliometric research (28, 29). The terms "acupuncture" and "anesthesia" were used in the MeSH search.[1] Data retrieval strategies were established by referring to the Mesh terms tree and related literature for additional information (25, 30, 31). Timespan: 01-01-1992 to 31-12-2022. (Retrieved on January 30, 2023). Seven hundred and eighty-eight documents were obtained. Only the type of article and review document was retained, which were formally published and had comprehensive research data. There were no restrictions on the language or type of research. Duplicate records were removed. Finally 746 documents were included in the analysis. Specific search strategies and results are shown in Table 1.

2.2. Bibliometrics and visualization analysis

We exported retrieved articles in plain text format with full records and references, named "download_XXX.txt" and then imported into CiteSpace (version 6.1.R6 64-bits). CiteSpace combined with Excel was applied for data organization, the centralities calculations, and visual analysis, including: (1) statistical and descriptive analysis: for parameters such as annual publication volume, authors, countries, and institutions; (2) collaborative network analysis: mainly for the three dimensions of countries (regions), institutions and authors; (3) co-occurrence analysis: for keywords; (4) citation burst analysis: mainly for keywords; (5) co-citation analysis: for authors, references and journals.

The VOSviewer (version 1.6.19) was used to optimize and supplement the unaesthetic map. The different nodes represent different items, while the size of the circle, determined by the weight

1 https://www.ncbi.nlm.nih.gov/mesh

TABLE 1 The topic search query for web of science.

Set	Results	Search query
#1	28,384	TS = (Acupuncture OR Pharmacopuncture OR Acupressure OR Acupuncture Therapy OR Acupuncture Point* OR acupunct* OR needl* OR Electroacupuncture OR Transcutaneous Electrical Acupoint Stimulation OR Ear Acupuncture OR Auricular acupuncture OR Laser Acupuncture OR meridian* OR acupoint*)
#2	207,332	TS = (Anesthesia* OR anesthesia* OR anesthetic* OR "Hypnosis Anesthetic" OR Anaesthetization OR Narcosis* OR Narcotism* OR "Nerve Block" OR Cryoanesthesia)
#3	788	#1 AND #2

of the item, reflects productivity. The lines between items represent links. Scimago Graphica 1.0.26[2] was used to visualize country distribution and partnerships. MapEquation[3] is used to produce a keyword alluvial diagram. Thicker lines mean stronger links and closer cooperation. The impact factor (IF) and the H-index[4] were added to the table for a comprehensive and scientometric result analysis.

The specific parameters for the visualization analysis were set as follows: The threshold of "Top N% per slice" was 50 for all calculations. The time span was from January 1992 to December 2022, and the time slice setting for all analyzes conducted with CiteSpace was "1 year per slice." The clustering labels were extracted using the LLR algorithm (21). When mapping visualization knowledge figures, we followed the main procedural steps of CiteSpace, including time slicing, thresholding, modeling, pruning, merging, and mapping (32). Central concepts of CiteSpace include burst detection, betweenness centrality, and heterogeneous networks, which can help to timely visualize the research status, hot spots, and frontiers.

2 https://graphica.app/
3 https://www.mapequation.org/apps/AlluvialGenerator.html
4 http://www.scimagojr.com/countryrank.php

2.3. Charts interpretation

CiteSpace generates maps composed of nodes representing the objects under analysis (e.g., authors, institutions, or keywords). The diameter of these nodes corresponds to the frequency of the analyzed objects, for instance, the output or citation frequency. The color of the nodes varies according to the year of publication, and

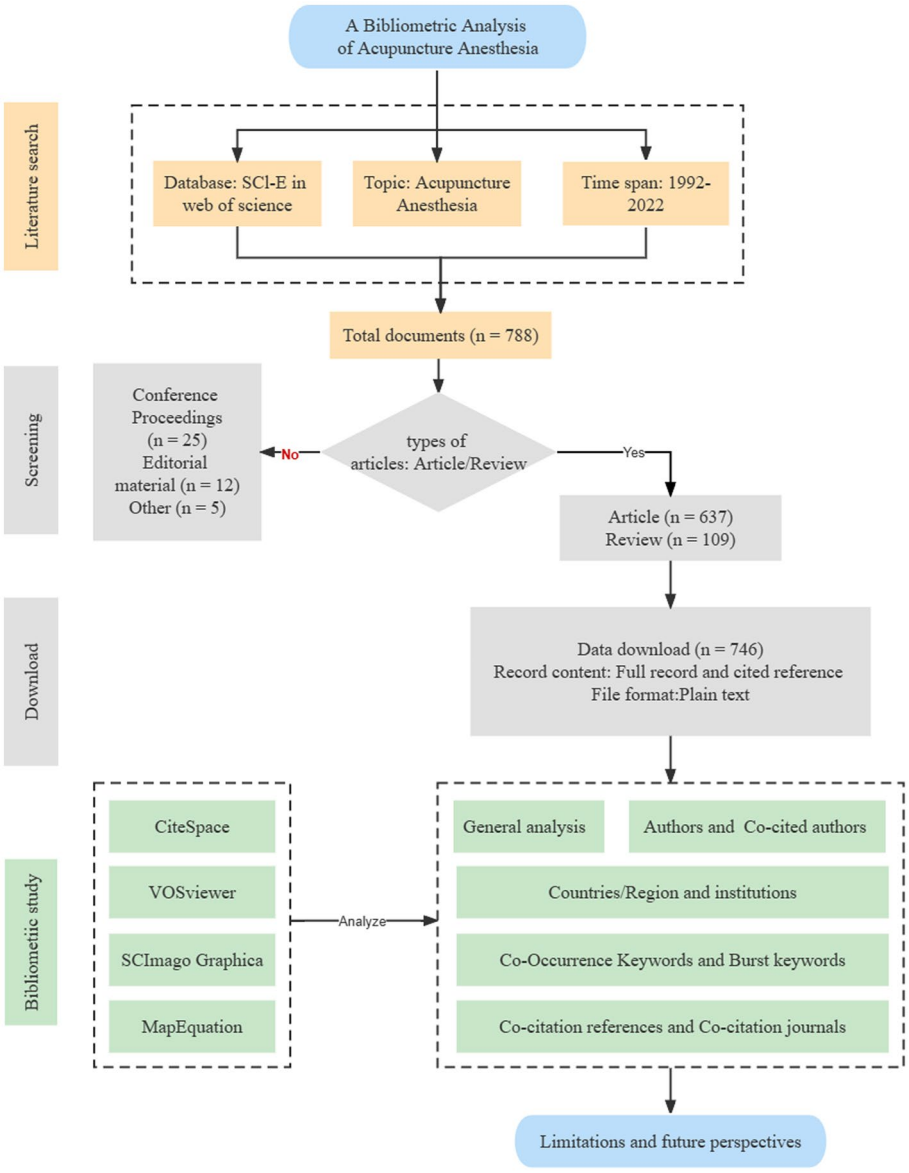

FIGURE 1
Flow chart indicating the selection process for this bibliometric analysis.

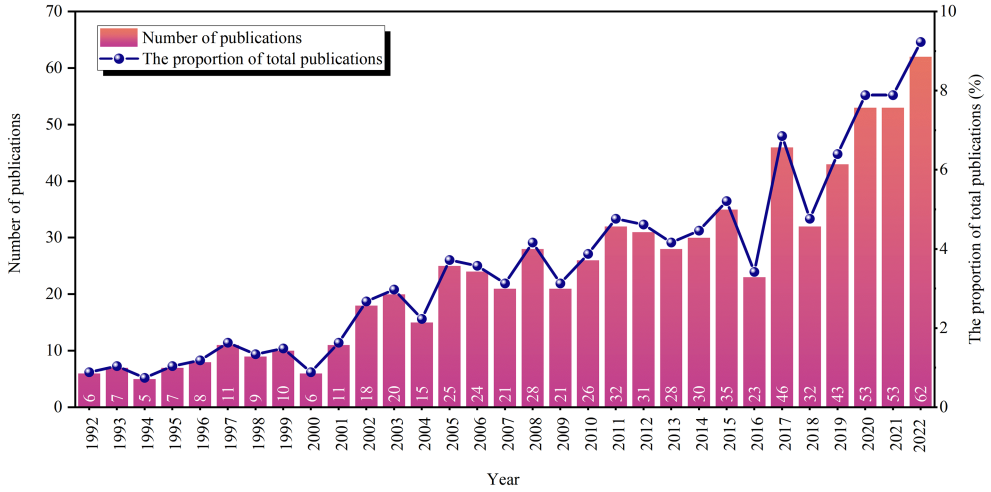

FIGURE 2
Annual trend of publications.

the lines connecting them represent collaborations or co-occurrences. The color of the lines indicates the time of the first collaboration, while the thickness of the lines reflects the strength of the collaboration (33).

3. Results

3.1. Search results and study characteristics

After duplicating removal function in CiteSpace software and manually cleaning the merged data, 746 studies were finally identified. Amid these document types, the Article and the Review had the percent of 85.39 and 14.61%, respectively. A flowchart of the screening process is presented in Figure 1.

3.2. Annual publications and trends

In the field of acupuncture anesthesia, there has been a steady increase in the number of publications over the past 31 years, with some fluctuations ranging from 5 to 62 publications. Notably, from 2016 to 2017, the number of related publications increased the most with 23 publications. This increase in publication indicates growing interest from researchers in this field. Please refer to Figure 2 for the number and trend of annual articles.

From 2005 to 2016, there was a stable trend in the publication of articles, with an average of around 27 articles per year. However, in 2017, there was an increase in the number of publications to 46. After a temporary decline, the period from 2018 to 2022 saw a sustained and significantly accelerated increase in publication rates. The average number of publications during this period was over 52 per year, which is the highest recorded over the past 31 years.

To facilitate a quick look at representative articles, the top ten cited articles and their features and findings are in Supplementary material.

3.3. Analysis of countries/region and institutions

In total, 746 references were published by 51 countries or regions. To improve visual clarity, this study used VOSviewer and Scimago Graphica to select 30 countries or regions with more than two articles, resulting in 6 clusters and 83 links (Figure 3A). The thickness of the line between countries indicates the level of cooperation (Figure 3B). Co-occurrence map analysis of institutions reveals that China cooperates with a wide range of countries, with 16 having published ten or more papers. China ranked first in the number of publications (252 papers), followed by the United States, South Korea, Germany, Japan, Brazil, and the United Kingdom, etc.

The United States exhibited the highest centrality (0.62), indicating relevance and strong cooperation in this field. China, although the top publisher, had a centrality of only 0.25. This finding highlights that China and the United States play critical roles in research in this field, but academic exchanges between the two countries remain limited. As the birthplace of acupuncture anesthesia, China should seek more international cooperation to promote the global use of acupuncture anesthesia. The top 10 countries/regions and institutions are listed in Table 2.

A total of 953 research institutions were involved, and 114 institutions with more than 3 papers were chosen for visualization. We performed the co-occurrence analysis of institutions using VOSviewer, resulting in 42 clusters and 135 links (Figure 4). Our analysis found a relatively low level of centrality, indicating that collaboration among institutions is not well-established. The top 10 institutions in terms of the number of publications were the University of California System (21), Capital Medical University (20), Kyung Hee University (16), China Academy of Chinese Medical Sciences (13), China Medical University (13), Air Force Medical University/Fourth Military Medical University (12), Guangzhou University of Chinese Medicine (12), Yale University (11), Chengdu University of Traditional Chinese Medicine (10), and Peking University (9). In the future, greater academic exchange and cooperation among universities and research institutions could promote the further development of acupuncture anesthesia.

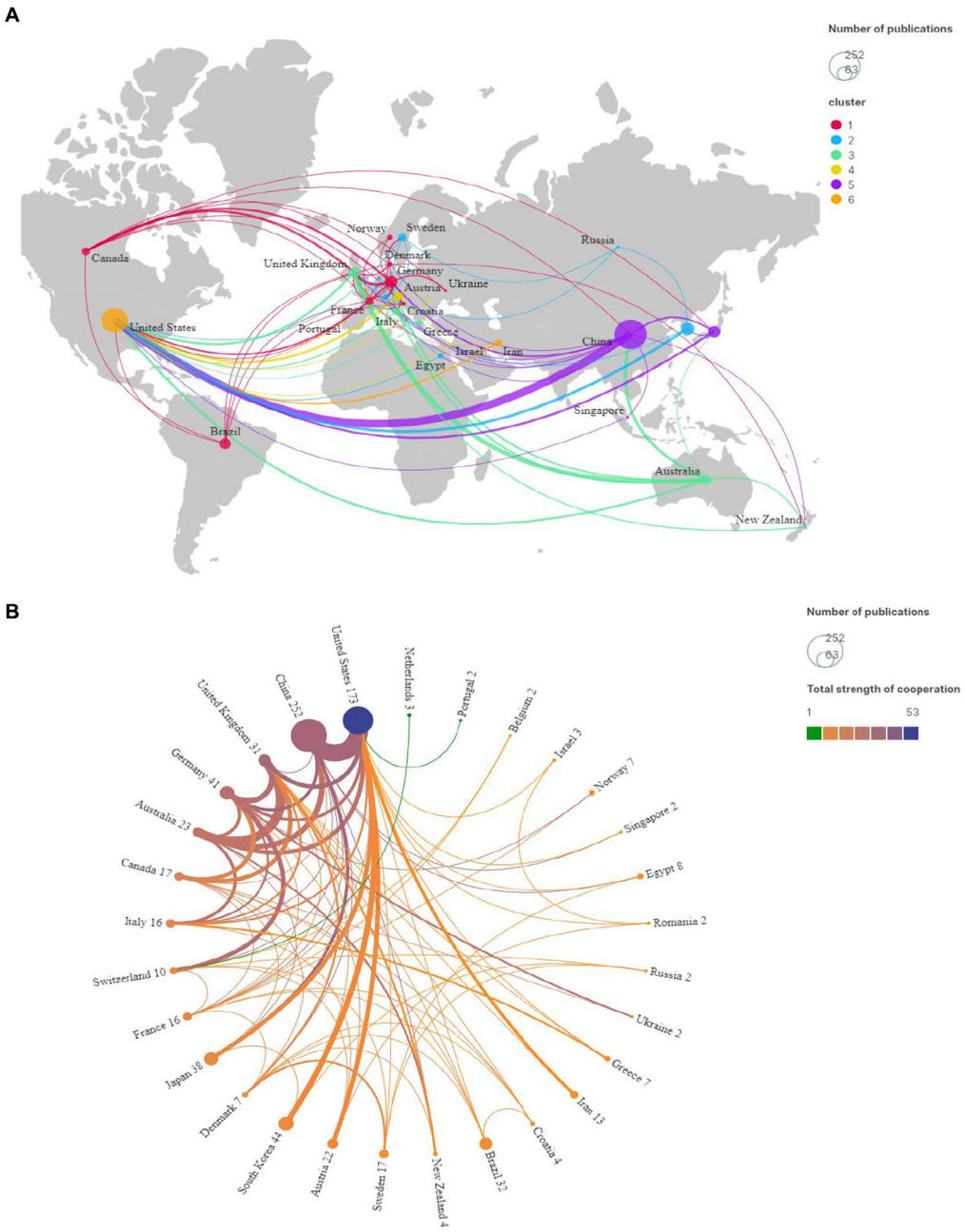

FIGURE 3
(A) Map of the geographic location of countries/regions. **(B)** Chord chart of the strength of countries/regions cooperation.

3.4. Analysis of authors and co-cited author

A total of 3,466 authors contributed to these articles; we selected 363 ones with more than two papers for better visualization. We performed the co-occurrence analysis of authors using VOSviewer, resulting in 97 clusters and 687 links (Figure 5A). The relationships between authors can also be observed on this map. In the top 10 authors listed in Table 3. The co-authorship network shows prolific authors and the collaboration among them. The largest number of papers was 7 (Aashish J. Kumar, Daniel I. Sessler, Baoguo Wang and Paul F. White), followed by 6 (Taras I. Usichenko and Qiang Wang). Although many authors have published relevant articles, there was little collaboration among them. Furthermore, the centrality of the authors was relatively low, suggesting that more large-scale, high-quality collaborations are needed in the future.

Fifteen thousand nine hundred seventy-seven co-cited authors contributed to these articles; we selected 252 ones with more than 10 papers for better visualization. The Collaboration map of Co-cited Authors consisted of 22 clusters and 10,940 links, and we chose to visualize the largest connected component only (Figure 5B).

TABLE 2 Top 10 countries and institutions with the highest frequency and centrality on acupuncture anesthesia.

Rank	Country	Publications	Centrality	Institution	Publications	Centrality
1	China	252	0.25	University of California System	21	0.16
2	United States	173	0.62	Capital Medical University	20	0.15
3	South Korea	44	0.02	Kyung Hee University	16	0.05
4	Germany	41	0.13	China Academy of Chinese Medical Sciences	13	0.14
5	Japan	38	0.02	China Medical University	13	0.08
6	Brazil	32	0.13	Air Force Medical University (the Fourth Military Medical University)	12	0.02
7	United Kingdom	31	0.13	Guangzhou University of Chinese Medicine	12	0.06
8	Australia	23	0.08	Yale University	11	0.01
9	Austria	22	0.06	Chengdu University of Traditional Chinese Medicine	10	0.03
10	Turkey	19	<0.01	Peking University	9	0.06

University of California System (University of California System) includes University of California, Irvine (9 publications), University of California, Los Angeles (6 publications), and other campuses.

DUNDEE, JW, from the Department of Anesthetics at Queen's University of Belfast in Northern Ireland is the author with the highest number of citations (228). As early as 1990, Garwin and his colleagues combined the clinical findings of P6 (Neiguan) stimulation for postoperative sickness with the literature to provide evidence supporting the use of acupuncture for all types of vomiting (34). The top 10 authors and Co-cited authors are listed in Table 3.

3.5. Analysis of co-occurrence keywords

Co-occurrence refers to the phenomenon in which two or more keywords appeared in other literature at the same time. The 746 publications on acupuncture anesthesia brought of 661 keywords together. A total of 661 nodes and 2,415 links (density = 0.0111) comprised the merged co-keyword network. When "Pathfinder" and "pruning sliced networks" were applied, a co-occurrence map of keywords, Figure 6A, was generated. The alluvial diagram of the changes from year to year in keywords for acupuncture anesthesia is shown in Figure 6B. The 20 most frequent co-occurrences refer to the phenomenon in which two or more keywords appear together in the literature. Table 4 lists the 20 most frequently co-occurring keywords. Undoubtedly, "acupuncture" and "anesthesia" were the two most frequent, with 202 and 141 publications, respectively. Keywords related to the retrieval strategy were removed and the top 10 keywords were, in descending order of frequency, pain, electroacupuncture, stimulation, surgery, management, analgesia, postoperative nausea and prevention. "acupuncture" had the highest centrality (0.22), followed by "anesthesia" (0.17) and "pain" (0.16).

3.6. Analysis of burst keywords

"Burst keywords" refer to keywords cited frequently over some time, thereby indicating the frontier areas. Figure 7 shows twenty burst keywords sorted by the "begin year." As displayed, the related investigation heat from the keyword "metoclopramide" and "children" has lasted for more than 10 years. And then, "droperidol" became popular among researchers from 1997 to 2005, with the highest strength (8.45) among these 25 burst keywords. Currently, six keywords had become burst and have lasted until now: recovery, transcutaneous electrical acupoint stimulation, systematic review, quality, general anesthesia, and surgery.

3.7. Analysis of co-citation references and co-citation journals

It is believed that the citation rate can not only measure the impact or importance of a certain work but also reflect its recognition within the scientific community. Therefore, identifying highly cited papers can help recognize the papers or topics in acupuncture anesthesia that have received the most recent attention from the scientific community. Considering that citations accumulate over time, we present the top 10 highly cited papers during the last decade based on the average citations per year in Table 5.

A total of 864 nodes and 2,611 links (density = 0.007) comprised the co-citation reference network. A total of 864 references were extracted from the 746 articles on acupuncture anesthesia to analyze the cited references (Figure 8A). The first cited literature was published in 1987, and the most recent was published in 2022. Five of these were RCTs, three meta-analyzes, one review, and one guideline. *Transcutaneous electric acupoint stimulation reduces intra-operative remifentanil consumption and alleviates postoperative side-effects in patients undergoing sinusotomy: a prospective, randomized, placebo-controlled trial* (35) by Wang et al., published in 2014, topped the list with 20 citations during the last decade. Written by Zhang et al., Mechanisms of Acupuncture-Electroacupuncture on Persistent Pain (IF: 9.198), published in 2014 had the highest centrality of 0.25 during the last decade.

A total of 768 nodes and 6,083 links (density = 0.0207) comprise the co-citation journal network (Figure 8B). *Anesthesia and Analgesia* (*Anesth Analg*, IF:6.627) topped the list with 408 citations. *Acupuncture and Electro-Therapeutics Research* (*Acupuncture Electro*,

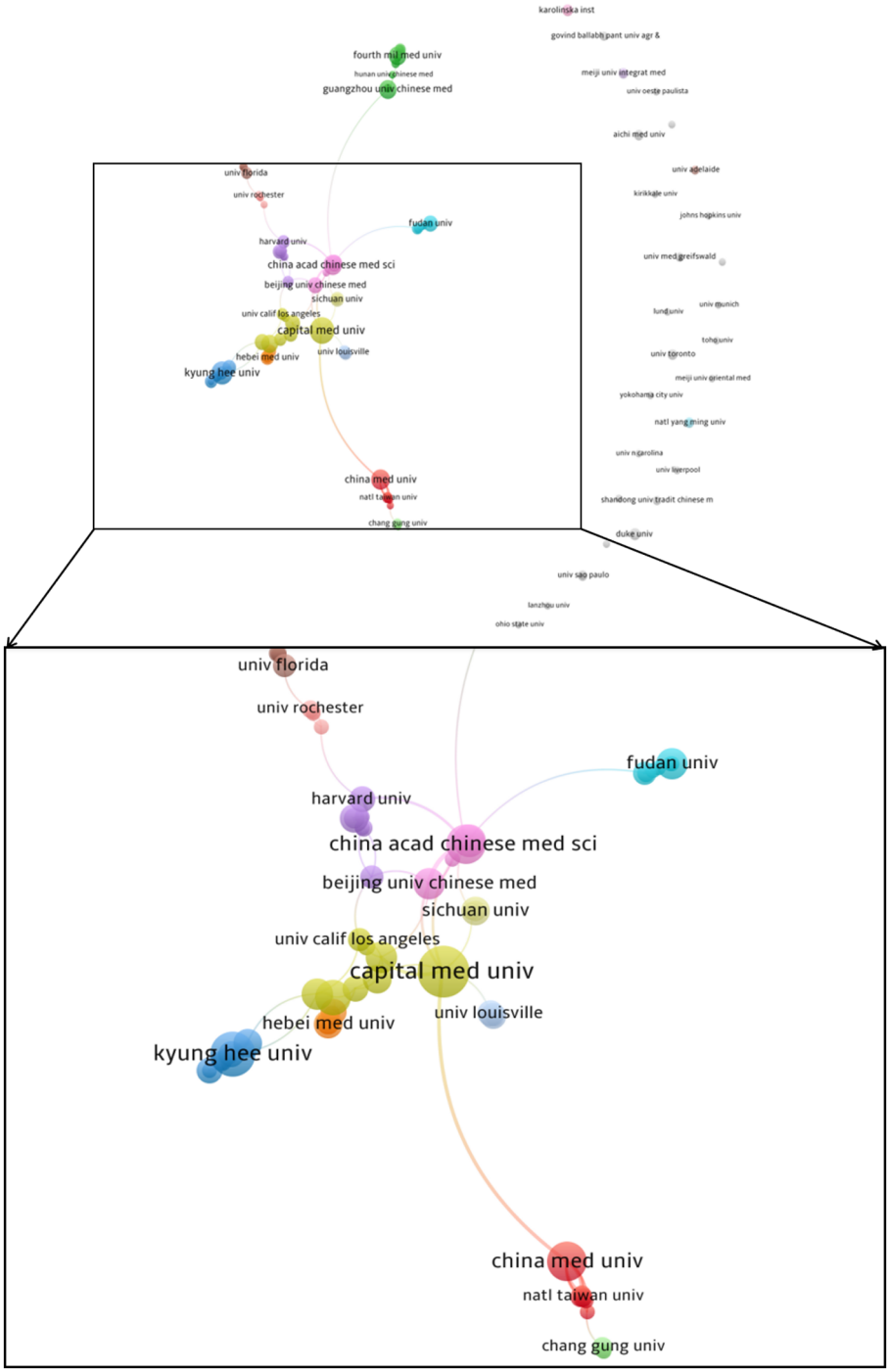

FIGURE 4
Map of institutions with publications in acupuncture anesthesia.

IF: 0.684) had the highest centrality (0.13), with 104 citations. The top 10 co-citation journals listed in Table 6.

4. Discussion

The meridian system, known as jingluo, is a fundamental concept in both physiology and pathology. Acupoints, located over these meridians, are selected sites for acupuncture. Acupuncture points refer to specific sites on the body surface where meridians, qi, and blood gather. These sites serve as stimulation points and therapeutic foundations for acupuncture, as well as sensory and reaction points for physiological functions and pathological changes of internal organs. Acupuncture points are related to immune, neurological, and endocrine regulatory networks, and regulating these acupoints can promote overall bodily regulation for achieving balance and

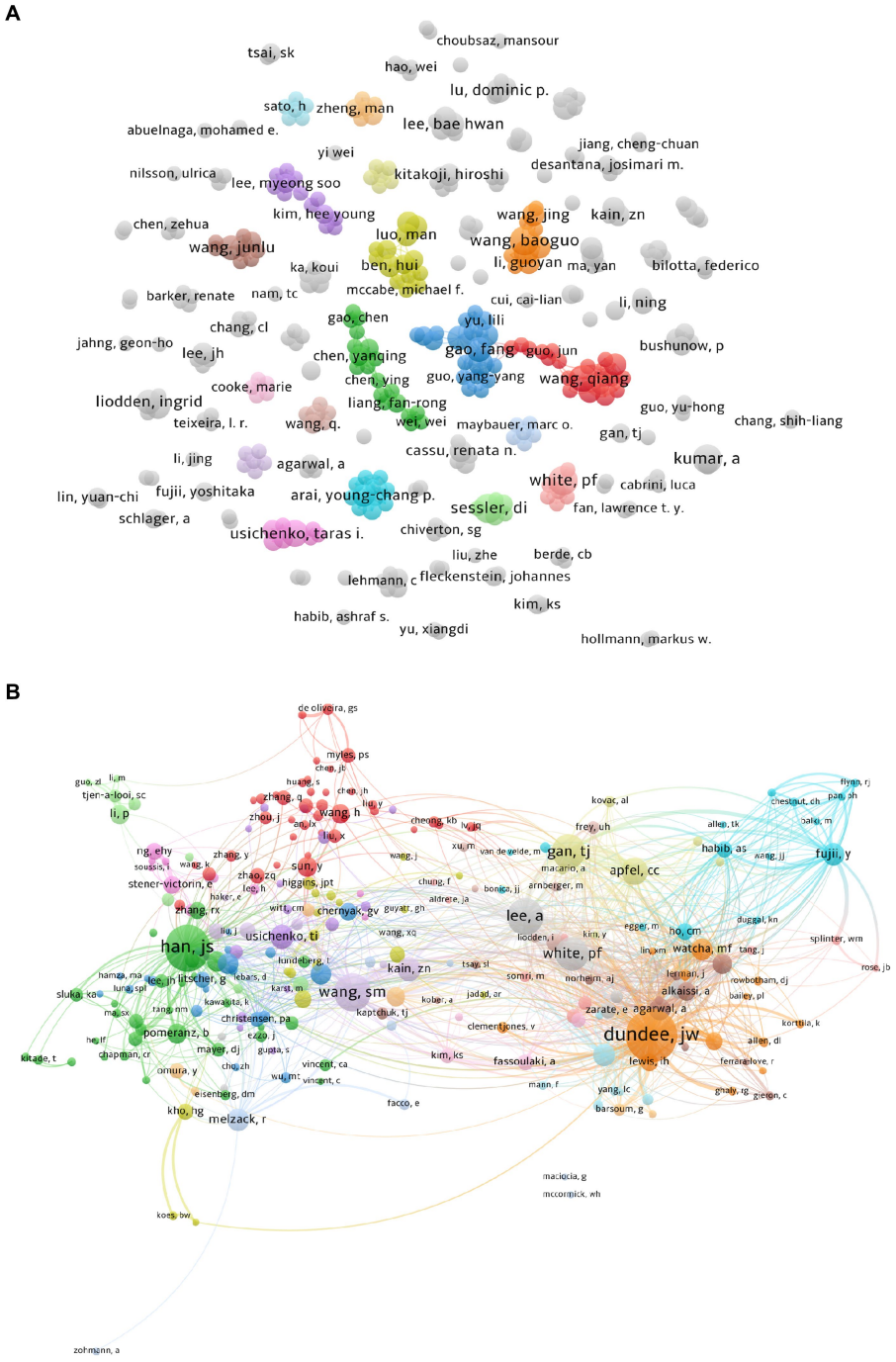

FIGURE 5
(A) Collaboration map of Authors with publications in acupuncture anesthesia. **(B)** Collaboration map of Co-cited Authors with publications in acupuncture anesthesia.

maintenance of harmonious internal and external environments (44). When acupuncture stimulation is applied to acupuncture points, it promotes releases special molecules, like opioid peptide, glutamate, and adenosine calcium, which alleviate pain on particular organs (43). Several clinical studies (11, 19, 45, 46) have demonstrated that acupuncture anesthesia can effectively reduce the dosage of anesthetic drugs and the risk of adverse reactions in surgical applications, with minimal physiological intervention in patients. Adenosine, a neuromodulator with antinociceptive characteristics, is involved in the local analgesic effect of acupuncture and amplifies the rise in acupuncture-induced adenosine and its antinociceptive effect (47). Given its clinical significance, the research, discovery, and innovation of acupuncture anesthesia is a crucial and interesting field of study. This research seeks to produce a more comprehensive and thorough

TABLE 3 Top 10 authors and co-cited authors with the highest frequency in acupuncture anesthesia.

Rank	Author	Publications	Centrality	Co-cited Author	Citations	Centrality
1	Aashish J. Kumar	7	<0.01	DUNDEE, JW	228	0.13
2	Daniel I. Sessler	7	<0.01	HAN, JS	188	0.23
3	Baoguo Wang	7	<0.01	Wang, Shu-Ming	135	0.09
4	Paul F. White	7	<0.01	Lee, Anna	129	0.06
5	Taras I. Usichenko	6	<0.01	Gan, Tong Joo	118	0.06
6	Qiang Wang	6	<0.01	White, Paul F.	111	0.07
7	Fang Gao	5	<0.01	Apfel, CC	82	0.04
8	Bae Hwan Lee	5	<0.01	Usichenko TI	67	0.02
9	Shuqin Li	5	<0.01	Kain, Zeev N	66	<0.01
10	Yanan Li	5	<0.01	Yentis, S. M.	60	0.02

analysis of the development of acupuncture anesthesia in the last three decades using bibliometric data.

Currently, Western culture and science and technology have exerted a significant influence on acupuncture anesthesia's development, resulting in various emerging challenges. However, this phenomenon also represents an opportunity for its growth (48). Notably, a new model of comprehensive perioperative management of acupuncture anesthesia with the characteristics of integrated traditional Chinese and Western medicine has gradually been forming in China (49). To strengthen the practice of acupuncture anesthesia, researchers must promote exchange and cooperation actively. They should absorb and embrace the latest evidence-based concepts, research methods, and techniques to expand the scope of acupuncture anesthesia's application. This approach should take into account the traditional connotations of this method while also acknowledging its limitations critically. To ensure the continued success of acupuncture anesthesia, researchers must follow the law of cross-disciplinary integration and innovative development. By doing so, they can maintain absorption, collaboration, innovation, and continuously improve the quality, vitality, and development of acupuncture anesthesia.

Our study found that in terms of research methods, RCTs, systematic reviews, and meta-analyzes are the mainstream of evidence-based medicine and are widely used in clinical practice. Research hotspots and directions have expanded from theoretical basis, historical evolution, clinical observation, and safety studies to mechanism studies, perioperative analgesia, and enhanced recovery after surgery (ERAS).

Since its first publication in 1992, the field of acupuncture anesthesia has experienced a fluctuation in growth. However, current trend analysis suggests that there will be a continued growth trend and greater development space in the coming years. One significant breakthrough in acupuncture anesthesia occurred in early 20th century Shanghai, China, where a successful case of mitral valvuloplasty was completed under this method and later televised in the BBC documentary *"Alternative Therapy: Acupuncture"* (1, 50). This event marked the re-entry of acupuncture anesthesia into the global spotlight, allowing it to gain international recognition and attention (1). This boom may have influenced the academic community as well, and the inflection points of steady growth in the field of acupuncture anesthesia also occurred after 2005, with an annual publication volume of more than 20.

The country co-occurrence analysis showed that China, the United States, and South Korea contributed the top three in terms of the number of publications, with the United States having the highest intensity of collaboration. This may be related to the historical origin of the belief that China and the United States have shared a common interest in acupuncture anesthesia since the 1970s. China should take advantage of being the birthplace of acupuncture anesthesia to strengthen international cooperation. Furthermore, collaboration between institutions shows a clear cluster character, with clusters being relatively distant and dispersed, which means that there are currently fewer reciprocal ties between institutions, and no global collaboration has yet been formed.

The co-author network map shows that the centrality of the top 10 authors in terms of number of posts is less than 0.01, reflecting the lack of collaboration among authors and the need for improvement. This highlights the pressing need to strengthen international exchange and collaboration in the field of acupuncture anesthesia. There are numerous international scientific research institutions and teams that possess a significant interest in acupuncture anesthesia and are at the forefront of scientific advancements. Therefore, it is important to expand the avenues of international academic exchanges on acupuncture anesthesia. This could be achieved by strengthening the drive to inherit innovation, encouraging researchers, teachers, and students alike to learn new theories, ideas, technologies, and methods, and carrying out and reinforcing cooperative experiments on acupuncture anesthesia. We could also establish international joint research centers and laboratories for acupuncture anesthesia to provide a high-tech platform for the development of acupuncture anesthesia research and innovation. By integrating the resources and strengths of all relevant parties, strengthening exchanges, and promoting mutual progress, we should aim to improve the stakeholder network for acupuncture anesthesia. Through systematic and orderly guidance, stakeholders can jointly promote the development and innovation of a series of high-quality acupuncture anesthesia research studies.

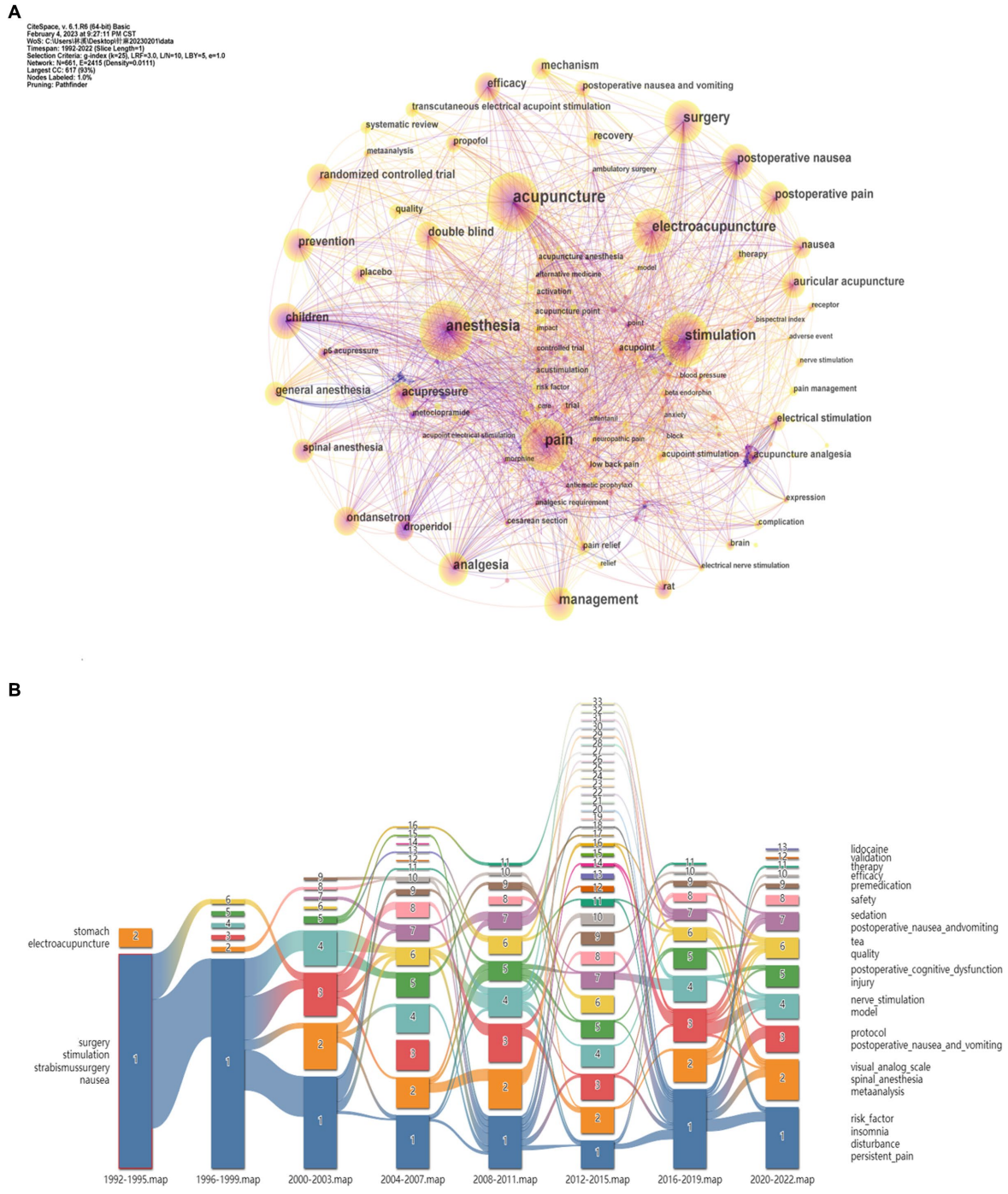

FIGURE 6
(A) Map of keywords with publications in acupuncture anesthesia. **(B)** An alluvial diagram illustrating the emergence of acupuncture anesthesia.

Keywords such as "pain," "electroacupuncture," stimulation," "surgery," "analgesia," and "postoperative nausea" appear early and frequently and were the focus of attention in this field. Since 2006, the emergence of the high-frequency keywords "randomized controlled trial" and "mechanism" suggests that international research has gradually paid attention to quality control and mechanism exploration of studies related to acupuncture anesthesia. In terms of indications, acupuncture anesthesia is being investigated not only for clinical anesthesia management but also for perioperative pain, nausea and vomiting, and other symptoms that can hasten patient recovery (51). In terms of applicable groups, it is being applied to special populations aimed at elderly, children and pregnant women (46, 52, 53). This approach complies with the principles of ERAS (54), an

TABLE 4 Top 20 keywords with the highest frequency in acupuncture anesthesia.

Rank	Keyword	Frequency	Centrality	Year	Rank	Keyword	Frequency	Centrality	Year
1	Acupuncture	202	0.22	1993	11	Postoperative pain	47	0.08	2002
2	Anesthesia	141	0.17	1993	12	Acupressure	46	0.08	1993
3	Pain	115	0.16	1993	13	Children	45	0.11	1992
4	Electroacupuncture	109	0.08	1999	14	Double blind	45	0.09	2001
5	Stimulation	91	0.15	1993	15	General anesthesia	38	0.06	1992
6	Surgery	83	0.05	1993	16	Auricular acupuncture	38	0.07	2003
7	Management	75	0.07	1994	17	Efficacy	36	0.05	2000
8	Analgesia	68	0.14	1992	18	Mechanism	36	0.06	2010
9	Postoperative nausea	49	0.09	1993	19	Ondansetron	35	0.03	2000
10	Prevention	47	0.04	1993	20	Randomized controlled trial	35	0.06	2006

evidence-based, multimodal, and multidisciplinary approach to surgical patient care. ERAS aims to enhance perioperative management and outcomes (55). This is in line with the recommendations of various guidelines, which suggest that opioids should be used sparingly. Reduced opioid use is believed to improve patient outcomes and reduce the risk of addiction and overdose.

The research frontiers were identified by analyzing the burst keywords The five most recent burst keywords were "recovery" "transcutaneous electrical acupoint stimulation" "systematic review" "quality" "general anesthesia" and "surgery." Facilitating rehabilitation anesthesia management and reduction of opioid abuse has been a topic of interest in surgical departments (56–58). Despite progress in research more efforts are needed to understand the characteristics of the role of acupuncture anesthesia in rehabilitation sedation and mechanisms to reduce anesthetic drugs. In contrast transcutaneous electrical acupoint stimulation is widely used in the perioperative period instead of traditional needling because of its ease of operation and noninvasive nature. Quality indicates that the field of acupuncture anesthesia is placing increasing emphasis on the credibility of research and future acupuncture anesthesia research can be speculated to be of higher quality standardized and institutionalized. Clinical trial design standardization of operational procedures and optimization of the scaling of perioperative effects have become popular (7). For example establish a core outcome set to assessing the effectiveness of acupuncture anesthesia and reach a consensus by integrating the opinions of different stakeholder groups (59).

The keyword timeline view describes the chronological sequence of keywords that appear on the horizontal timeline and displays the dynamic time change of clustering keywords. Combined with the alluvial diagram, it can be seen that the research frontier has variability at different time stages, which is related to various factors, such as national policies, the development of medical research, the social environment, the awareness and acceptance of the patient and the inheritance of acupuncture anesthesia techniques. From 1992 to 2004, the research frontier focused on the advancement of effectiveness and the improvement of postoperative nausea and vomiting in the areas of anesthetic drugs, acupuncture points, electrical stimulation, and effectiveness. From 2005 to 2013, the research frontier migrated to mechanisms, double-blind placebo, conventional anesthesia, and postoperative pain (24, 60). From 2014 to 2022, the research frontier includes systematic evaluation, randomized controlled trials, quality, and recovery, with a greater focus on evidence-based integration of outcome indicators and the promotion of multifaceted and multilevel recovery after surgery. Focusing on evidence-based medicine, the researchers optimized perioperative management by reducing the dose of anesthetic drugs to reduce the physiological stress response of surgical patients and promote their recovery. On this basis, Chinese scholars proposed "*perioperative acupuncture medicine*," which is the use of acupuncture techniques to optimize preoperative, intraoperative and postoperative treatment (61).

Based on the above results, we believe that acupuncture anesthesia has accumulated certain clinical research and theoretical basis, and the combination of frontier keywords and related research (48) can predict that acupuncture will have better combinations and advantages throughout the perioperative phase. However, advancements in precision medicine have increased the need for precise population stratification (62), and the effects of needling and anesthesia management are influenced by complex individual characteristics, highlighting the need for more precise research. Furthermore, due to the high heterogeneity of surgical procedures, the nature of the surgical intervention is difficult to reveal, and the multidisciplinary collaboration is more conducive to the development of this discipline. As a result, we should promote collaboration across industries, the mutual benefit of sharing scientific research resources, and cultivating professionals skilled in acupuncture, surgery, and anesthesia. Researchers must harness the synergies of multidisciplinary approaches (59) while actively using big data, MRI (63) and positron emission tomography (PET), systems research and machine learning (64) to clarify the specific roles and mechanisms of acupuncture anesthesia in different surgical procedures, in order to inform future development and preventative strategies (65).

A

Top 25 Keywords with the Strongest Citation Bursts

Keywords	Year	Strength	Begin	End	1992 - 2022
metoclopramide	1992	4.15	1992	2002	
traditional chinese acupuncture	1992	3.81	1992	1997	
children	1992	6.6	1994	2005	
droperidol	1992	8.45	1997	2005	
morphine	2000	4.24	2000	2006	
rat	2002	3.5	2002	2009	
acupoint	1999	3.57	2006	2012	
spinal anesthesia	2002	4.37	2007	2012	
ondansetron	2000	3.62	2008	2016	
stimulation	1993	5.04	2009	2013	
trial	2009	4.82	2009	2016	
randomized controlled trial	2006	4.67	2012	2018	
mechanism	2010	4.18	2015	2017	
postoperative nausea and vomiting	2007	3.71	2015	2017	
postoperative pain	2002	3.48	2015	2018	
recovery	2016	7.49	2016	2022	
metaanalysis	2000	3.86	2016	2017	
double blind	2001	3.54	2016	2018	
transcutaneous electrical acupoint stimulation	2017	6.45	2017	2022	
management	1994	5.6	2017	2019	
systematic review	2017	5.53	2017	2022	
quality	2016	5.41	2018	2022	
electroacupuncture	1999	7.76	2019	2020	
general anesthesia	1992	3.76	2019	2022	
surgery	1993	5.43	2020	2022	

B

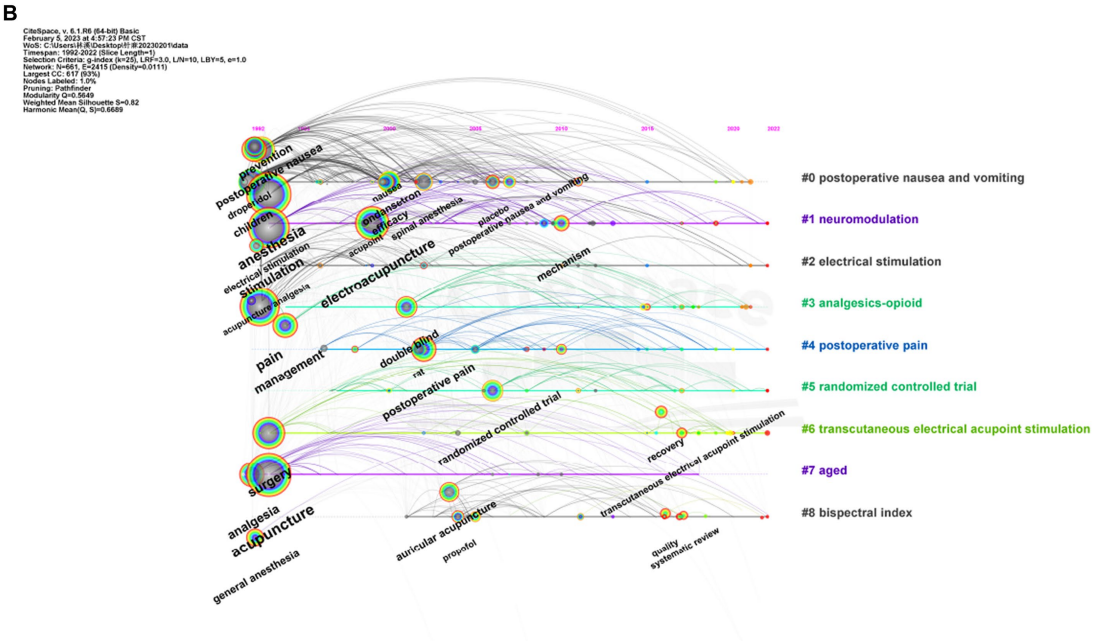

FIGURE 7
(A) Top25 keywords with the Strongest Citation Bursts in acupuncture anesthesia. g-index (*k*=25). gamma=1.0. The discontinuous blue lines represent the timeline, specifically, each small blue rectangle represents 1year, and the red part in the timeline represents the burst duration of the keyword. **(B)** Timeline view of the keywords in acupuncture anesthesia. The top nine clusters were arranged on a horizontal timeline, and the direction of time points to the right from 1992 to 2022. The horizontal lines are timelines, with different color in each cluster. The tree rings represent occurrence of keywords, and the larger rings represent more frequency of occurrence. The camber line above the horizontal line represents the co-occurrence relationship between keywords.

4.1. Highlights and limitations

To our knowledge, this is the first study to use bibliometric analysis to summarize the progress of acupuncture anesthesia, visually presenting authors, institutional collaboration networks, research hotspots and development prospects (22). Future scholars can read this article to understand the current development situation, identify development prospects, and develop research ideas. We hope to further strengthen cooperation and communication through better understanding of the contributions

TABLE 5 Top 10 Co-citation references with the highest frequency in acupuncture anesthesia (within 10 years).

Rank	Representative author (publication year)	Title of reference	Frequency	Centrality	DOI	Journal			Type of research
						Name	IF (2021)	H-index (2021)	
1	Wang et al. (35)	Transcutaneous electric acupoint stimulation reduces intra-operative remifentanil consumption and alleviates postoperative side-effects in patients undergoing sinusotomy: a prospective, randomized, placebo-controlled trial	20	0.04	10.1093/bja/aeu001	British Journal of Anesthesia	11.719	189	RCT
2	Asmussen et al. (10)	Effects of Acupuncture in Anesthesia for Craniotomy: A Meta-Analysis	16	0.08	10.1097/ANA.0000000000000290	Journal of Neurosurgical Anesthesiology	4.01	66	Meta-analysis
3	Gan et al. (36)	Society for Ambulatory Anesthesia. Consensus guidelines for the management of postoperative nausea and vomiting	16	0.08	10.1213/ANE.0000000000000002	Anesthesia and Analgesia	6.627	208	Guideline
4	Wu et al. (37)	The Efficacy of Acupuncture in Post-Operative Pain Management: A Systematic Review and Meta-Analysis	15	0.07	10.1371/journal.pone.0150367	PLoS One	3.752	367	Meta-analysis
5	An et al. (38)	Electro-acupuncture decreases postoperative pain and improves recovery in patients undergoing a supratentorial craniotomy	12	0.07	10.1142/S0192415X14500682	American Journal of Chinese Medicine	6.005	67	RCT
6	Gao et al. (39)	Transcutaneous electrical acupoint stimulation for prevention of postoperative delirium in geriatric patients with silent lacunar infarction: a preliminary study	11	0.01	10.2147/CIA.S183698	Clinical Interventions in Aging	3.829	85	RCT
7	Huang et al. (40)	Effects of transcutaneous electrical acupoint stimulation at different frequencies on perioperative anesthetic dosage, recovery, complications, and prognosis in video-assisted thoracic surgical lobectomy: a randomized, double-blinded, placebo-controlled trial	11	0.07	10.1007/s00540-015-2057-1	Journal of Anesthesia	2.931	49	RCT
8	Lee et al. (41)	Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting	11	< 0.01	10.1002/14651858.CD003281.pub4	Cochrane Database of Systematic Reviews	11.874	292	Meta-analysis
9	Liu et al. (42)	Intraoperative and postoperative anesthetic and analgesic effect of multipoint transcutaneous electrical acupuncture stimulation combined with sufentanil anesthesia in patients undergoing supratentorial craniotomy	11	0.02	10.1136/ACUPMED-2014-010749	Acupuncture in Medicine	1.976	48	RCT
10	Zhang et al. (43)	Mechanisms of Acupuncture-Electroacupuncture on Persistent Pain	10	0.14	10.1097/ALN.0000000000000101	Anesthesiology	9.198	245	Review

RCT: Randomized Controlled Trial.

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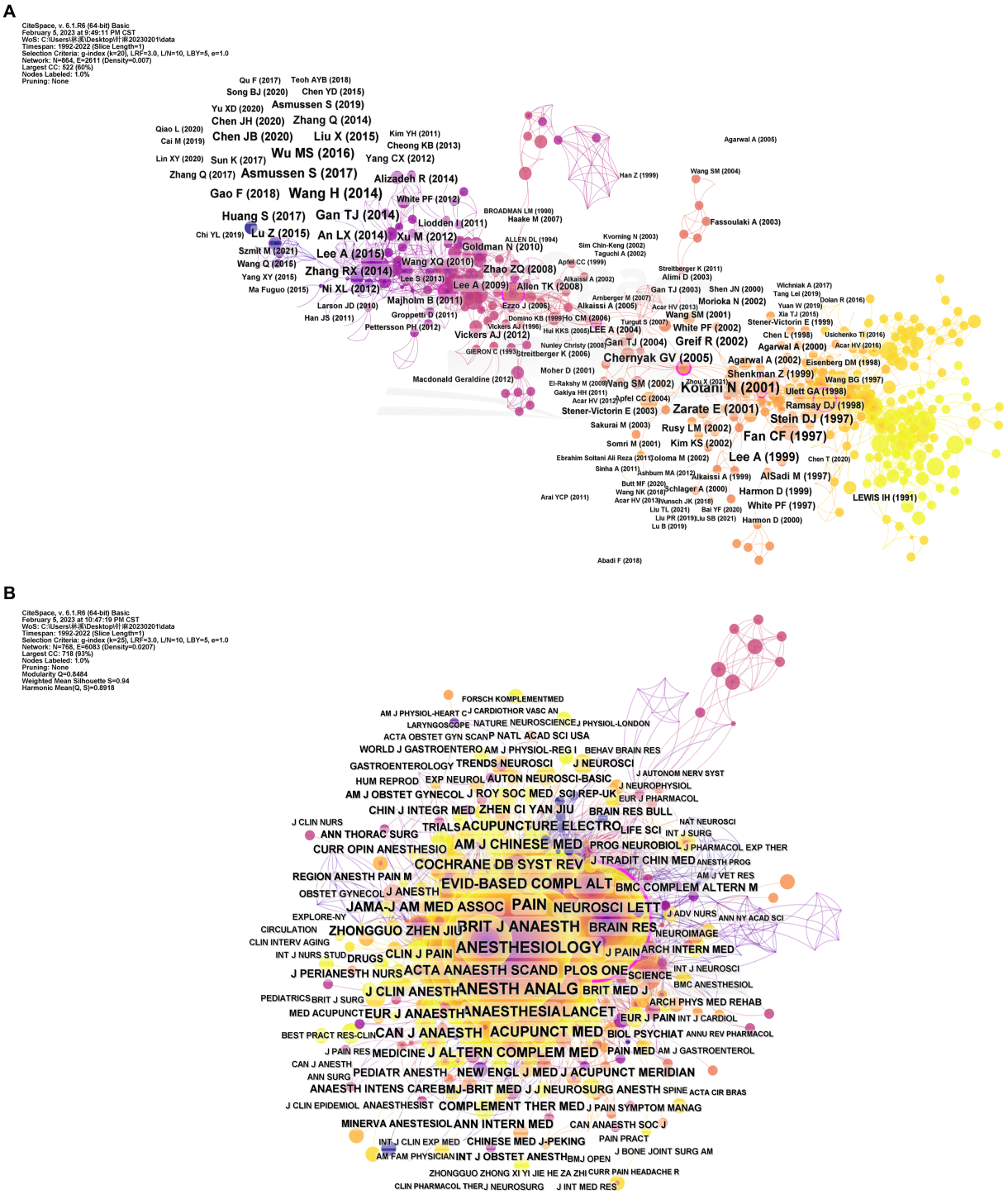

FIGURE 8
(A) Co-occurrence network of co-citation references (threshold=3). **(B)** Co-occurrence network of co-citation journals (threshold=15).

of scholars and institutions with in this field. This study had some limitations. First, owing to the limitations of CiteSpace data analysis, we only collected literature from the WOS core collection database. We did not include studies from Chinese or other English databases. Some original Chinese studies were excluded, which affected the results. Articles may have different citation counts and centrality when searching for different time periods. Therefore, this study only presents results from the past 31 years. Furthermore, due to the purpose and type of research, the specific mechanism of acupuncture anesthesia has not been definitively determined.

TABLE 6 Top 10 Co-citation journals with the highest frequency in acupuncture anesthesia.

Rank	Cited journal	Frequency	Centrality	IF (2021)	H-Index (2021)	Year
1	Anesthesia and Analgesia	408	0.02	6.627	208	1992
2	Anesthesiology	353	0.02	9.198	245	1992
3	British Journal of Anesthesia	337	0.02	11.719	189	1992
4	Pain	266	0.04	7.926	269	1992
5	Anesthesia	232	0.04	12.893	124	1992
6	Acupuncture in Medicine	197	0.07	1.976	48	1996
7	Evidence-Based Complementary and Alternative Medicine	187	0.01	2.65	100	2007
8	Acta Anaesthesiologica Scandinavica	172	0.07	2.274	112	1992
9	Lancet	170	0.06	202.731	807	1992
10	Cochrane Database of Systematic Reviews	158	0.03	11.874	292	2006

5. Conclusion

In this study, we used CiteSpace, VOSviewer, and other visualization software to describe the research progress of acupuncture anesthesia from 1992 to 2022, recent hotspots of concern and exposed problems, provide references to predict future development trends, and make suggestions for reflection. These results indicate a steady increase in international publications related to acupuncture anesthesia after 2005, suggesting a growing research base in this field. With the change in emphasis on the direction of perioperative acupuncture and analgesia, research in this field is developing in a more favorable direction. However, previous studies have faced challenges such as inconsistent theories, unknown mechanisms, and low quality. A core strength of research has yet to develop, and there is a lack of common understanding and cooperation among researchers, as well as a lack of high-quality basic research. Nevertheless, these challenges reflect that research in this field is currently in a transition stage of exploring and integrating disciplinary knowledge more deeply, with a promising future ahead.

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.

Author contributions

KW and JZ conceived and designed and revised manuscripts. LS and XW contributed to data collection, visualization, and manuscript writing. JZ contributed to obtaining funding for the study and project administration. All authors reviewed the manuscript and approved the submitted version.

Funding

The work was supported by the National Natural Science Fund of China (82074163 and 81973940), Shanghai Clinical Research Center for Acupuncture and Moxibustion (20MC1920500), Science and Technology Commission of Shanghai Municipality (21Y31920100), Clinical Key Specialty Construction Foundation of Shanghai (No. shslczdzk04701), Shanghai Municipal Commission of Health and Family Planning (ZY(2021–2023)-0208), Shanghai Shenkang Hospital Development Center (SHDC2022CRS040), and "Training Plan for Key Talents for Clinical Research" of Affiliated Hospital of Shanghai University of Traditional Chinese Medicine (2023LCRC12).

Acknowledgments

The authors would like to express their appreciation to Professor Chaomei Chen for inventing CiteSpace and making it free to use.

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.2023.1194005/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 09 June 2023
DOI 10.3389/fmed.2023.1193514

OPEN ACCESS

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RECEIVED 24 March 2023
ACCEPTED 22 May 2023
PUBLISHED 09 June 2023

CITATION
Kim JG, Ahn C, Kim W, Lim T-H, Jang B-H, Cho Y, Shin H, Lee H, Lee J, Choi K-S, Na MK and Kwon SM (2023) Comparison of video laryngoscopy with direct laryngoscopy for intubation success in critically ill patients: a systematic review and Bayesian network meta-analysis. *Front. Med.* 10:1193514. doi: 10.3389/fmed.2023.1193514

Comparison of video laryngoscopy with direct laryngoscopy for intubation success in critically ill patients: a systematic review and Bayesian network meta-analysis

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Introduction: This review compares the efficacy of video laryngoscopy (VL) with direct laryngoscopy (DL) for successful tracheal intubation in critically ill or emergency-care patients.

Methods: We searched the MEDLINE, Embase, and Cochrane Library databases for randomized controlled trials (RCTs) that compared one or more video laryngoscopes to DL. Sensitivity analysis, subgroup analysis, and network meta-analysis were used to investigate factors potentially influencing the efficacy of VL. The primary outcome was the success rate of first-attempt intubation.

Results: This meta-analysis included 4244 patients from 22 RCTs. After sensitivity analysis, the pooled analysis revealed no significant difference in the success rate between VL and DL (VL vs. DL, 77.3% vs. 75.3%, respectively; OR, 1.36; 95% CI, 0.84–2.20; I^2 = 80%; low-quality evidence). However, based on a moderate certainty of evidence, VL outperformed DL in the subgroup analyses of intubation associated with difficult airways, inexperienced practitioners, or in-hospital settings. In the network meta-analysis comparing VL blade types, nonchanneled angular VL provided the best outcomes. The nonchanneled Macintosh video laryngoscope ranked second, and DL ranked third. Channeled VL was associated with the worst treatment outcomes.

Discussion: This pooled analysis found, with a low certainty of evidence, that VL does not improve intubation success relative to DL. Channeled VL had low efficacy in terms of intubation success compared with nonchanneled VL and DL.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=285702, identifier: CRD42021285702.

KEYWORDS

laryngoscopy, intubation, critical care, randomized controlled trial, network meta-analysis

1. Introduction

Endotracheal intubation (ETI) is important in life-threatening situations involving hypoxia or unconsciousness, including in the management of critically ill or emergency-care patients who require airway protection (1, 2). The Macintosh laryngoscope for direct laryngoscopy (DL) has been the preferred intubation approach for a half-century, and it is frequently used in both in-hospital and prehospital settings (3, 4). However, ETI success rates decrease in association with difficult airways or emergency circumstances (5–8), and intubation failure owing to the placement of the endotracheal tube into the esophagus, for example, can worsen the patient's hypoxia and result in brain death and, eventually, death (9). Therefore, attempts to increase ETI success rates and decrease complications include the use of appropriate sedatives and neuromuscular blockers, skilled and experienced personnel managing difficult airways, simulation-based training, and care bundles (10–12). Nonetheless, ETI failure may occur because of several influencing factors and unpredictable circumstances.

Video laryngoscopy (VL) can be used in clinical practice as an alternative to DL for ETI, wherein indirect assessment of the glottal structure is possible using a small camera mounted to the laryngoscope blade tip, as has been investigated in several studies of VL outcomes and comparisons of VL vs. DL ETI success rates. However, studies investigating various VL devices or different ETI settings, such as prehospital (13–16), emergency rooms (2, 17, 18), intensive care units (3, 10), or operating rooms (19, 20), have generated conflicting findings, especially comparative trials of VL vs. DL for critically ill and emergency-care patients that have contrasted with the findings associated with planned ETI in the operating room (10, 21–23). A previous meta-analysis of several cohort studies and three randomized trials determined considerably higher ETI success rates associated with VL (24), whereas a subsequent meta-analysis of only randomized trials found no significant difference in ETI success between VL and DL (1). The substantial heterogeneity revealed by the above-mentioned review needs attention, as multiple devices were analyzed using one-arm forced integration for the meta-analysis.

Lee et al. used a network meta-analysis (NMA) of various VL devices in patients scheduled to undergo ETI for surgery to identify the most effective devices; however, the comparison of too many devices made it difficult for clinicians to determine the optimal devices (25). Thus, a more comprehensive multi-arm analysis with clustering of similar VL devices may be required to overcome this issue.

Accordingly, in this review, VL devices were categorized according to the laryngoscope blade, and an NMA was conducted to compare VL with DL efficacy in ETI among critically ill or emergency-care patients. The meta-analysis investigated factors potentially influencing VL efficacy.

2. Methods

2.1. Protocol and registration

This review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for reporting NMAs (26). The review protocol was registered with PROSPERO (CRD42021285702 available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=285702).

2.2. Eligibility criteria

Randomized controlled trials (RCTs) were eligible for inclusion if they compared one or more VL devices with DL or compared two or more VL devices without DL for the oral insertion of single-lumen endotracheal tubes in emergency-care or critically ill adult patients. The adequacy of ETI for emergency-care patients was evaluated in both the prehospital and in-hospital settings. In intensive care units, ETI was deemed to have been conducted on critically ill patients. Case reports, reviews, preprints, conference abstracts, observational studies, pediatric patients, cadaveric models, and manikin models were excluded, as were surgical patients requiring ETI for general anesthesia or those requiring urgent surgical airways, supraglottic airways, double-lumen tube installation, or nasal intubation.

2.3. Information sources and search strategy

An electronic search of the MEDLINE, Embase, and Cochrane Library databases yielded relevant literature without language restrictions, including articles published until October 31, 2022. Additional publications were identified by reviewing the reference lists of the identified papers and relevant previously published reviews. The full search strategy is provided in Supplementary Table S1.

2.4. Article selection and data collection

Title and abstract screening were carried out independently by two investigators (CA and JGK). The full texts of all potentially relevant citations were reviewed for eligibility. Articles were included in the review if they fulfilled the eligibility criteria and had data for at least one outcome of interest. Non-English papers deemed possibly relevant were evaluated for inclusion if the full text could be translated. Any disagreements were resolved through discussion. The same two investigators also independently extracted data.

2.5. Outcome measures

The primary outcome was first-attempt ETI success. Data on eligibility criteria, sample size, baseline characteristics of study participants, and devices evaluated were retrieved.

2.6. Assessment of risk of bias

The risk of bias within the included studies was assessed—using RoB 2 (Risk of Bias, version 2, Cochrane, London, UK) (27)—in terms of the following categories: "risk of bias arising

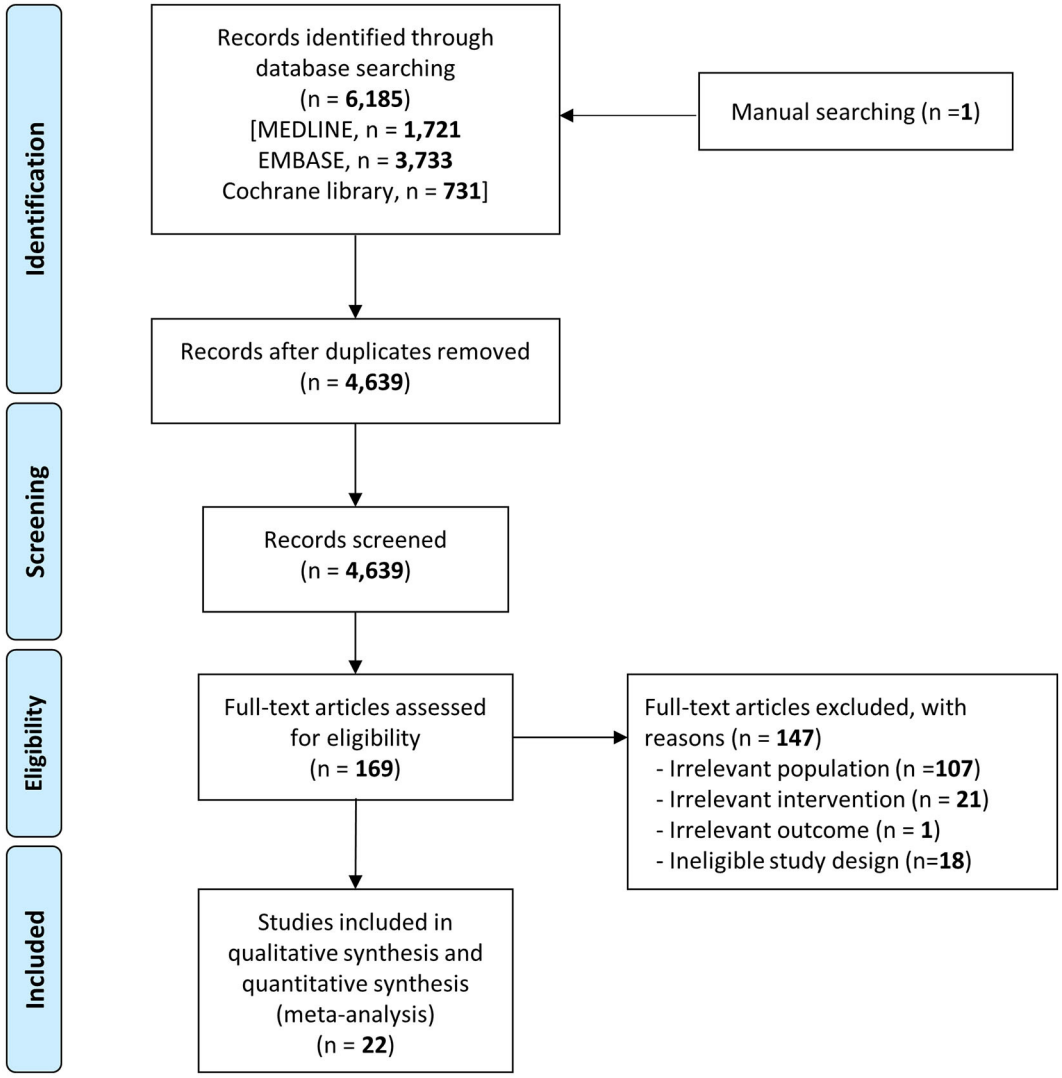

FIGURE 1
PRISMA flow chart depicting the disposition and selection of articles included in this systematic review and meta-analysis.

from the randomization process," "risk of bias due to deviations from the intended interventions," "risk of bias due to missing outcome data," "risk of bias in measurement of the outcome," and "risk of bias in selection of the reported result," with each subcategory rated as "yes," "probably yes," "no," "probably no," or "no information." Based on the overall quality rating standards stated in RoB 2, the risk of bias was classified as "low," "high," or "some concerns." Disagreements, if any, were resolved through discussion. Publication bias across individual articles was examined using funnel plots and Egger's regression test (28).

2.7. Reporting guidelines and certainty of evidence

The modified GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) tool for meta-analyses was used to assess the quality of evidence (29). The following quality levels were assigned to the results: (1) high quality—further research is very unlikely to change the confidence in the estimated effect; (2) moderate quality—further research is likely to have an important impact on the confidence in the estimated effect and may change the estimate; (3) low quality—further research is very likely to have an important impact on the confidence in the estimated effect and is likely to change the estimate; and (4) very low quality, where any estimated effect is highly uncertain. We then used GRADE software (Evidence Prime, Hamilton, ON, Canada) to create a GRADE-evidence profile table to assess these outcomes as high, moderate, low, or very low quality.

2.8. Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated for dichotomous outcomes, and statistically nonsignificant differences were indicated by ORs with 95% CIs

that included 1. For subgroup analysis, continuous variables were converted to dummy variables using the 50% standard as follows: <50% vs. ≥50%. In cases of statistical heterogeneity (I^2 ≥40%) or clinical heterogeneity, sensitivity analysis was performed to investigate potential sources of heterogeneity by sequentially eliminating individual articles using the Baujat plot (30). After excluding an outlier article from the sensitivity analysis, subgroup analyses for the primary outcome were performed based on the following potentially heterogeneous factors: (a) study design: single-center vs. multicenter; (b) study setting: prehospital vs. in-hospital (intensive care unit and emergency room); (c) country: non-Asian vs. Asian; (d) difficult airway proportion: <50% vs. ≥50%; (e) intubators' experience: inexperienced (nonphysician) vs. experienced (physician); (f) rapid sequence intubation: yes vs. no; and (g) the proportion of intubation during cardiopulmonary resuscitation (CPR): <50% vs. ≥50%. The experienced group for ETI was classified by the intubators' experience based on the standard criterion of physicians with sufficient ETI experience. The inexperienced group included students, paramedics, nurses, residents, and fellow trainees. Supplementary Table S2 contains more information on these factors; articles with missing data were excluded from the subgroup analysis. Meta-regression was conducted for two potentially heterogeneous factors: study recruitment start dates and sample sizes.

In the NMA of VL devices, DL with a Macintosh blade was designated as the control, and VL devices were classified into three categories according to their blades: nonchanneled Macintosh devices, nonchanneled angular devices, and channeled devices.

The reference management software Endnote 20 (Clarivate Analytics, Philadelphia, PA, USA) was used to organize all identified articles from the literature search. Meta-analyses, including the risk of bias assessment, sensitivity and subgroup analyses, and meta-regression, were performed for the comparison of VL and DL using R, version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and the following R packages: *meta, metafor,* and *rmeta*. A Bayesian NMA was performed using the *gemtc* R package (31). A random-effects model was used when impact size was pooled. The deviance information criteria and I^2 heterogeneity were used to assess the inconsistency of the Bayesian NMA model (32). The best NMA model was obtained by minimizing deviance information criteria and I^2 using Markov chain Monte Carlo simulation. The rank probability was used to rank each device's effectiveness and select the best device for an outcome. Rank probabilities range from 0 to 1; the closer an intervention's rank probability is to 1, the more likely it ranks first among available treatment options (33).

3. Results

3.1. Article selection and characteristics

In total, 4,639 articles were included after eliminating duplicates. After the titles and abstracts were reviewed, a total of 169 papers were included for full-text review, after the exclusion of documents that did not meet the objectives of this review (Supplementary Table S3). The qualitative synthesis included 22 relevant articles (Figure 1) (2, 3, 10, 13, 15–18, 23, 34–46).

Table 1 shows the characteristics of the included articles comparing VL with DL, published from 2011 through 2021, with sample sizes ranging from 40 to 623 participants. Of the 22 studies included in this analysis, 4 were multicenter RCTs, while the others were single-center studies. Six studies were conducted in the prehospital setting, while the remaining 16 were carried out in the intensive care unit or emergency department, representing an in-hospital setting. ETI was performed by experienced operators in 11 of the studies, while ETI was mainly conducted by inexperienced operators in the remaining 11 studies. Sixteen studies used rapid sequence intubation with sedatives or narcotics and neuromuscular blockades during the intubation process. The following nine VL devices were evaluated in this review: Airtraq (Prodol, Vizcaya, Spain), Airwayscope (Nihon Kohden, Tokyo, Japan), C-MAC (Karl Storz, Tuttlingen, Germany), Glidescope (Verathon, Bothell, WA, USA), King Vision (Ambu, Copenhagen, Denmark), McGrath (Medtronic, Dublin, Ireland), Olympus Video Bronchoscope (Olympus, Tokyo, Japan), UEScope (UE Medical Corp., Zhejiang, China), and VivaSight (ETView Ltd., Misgav, Israel) (Supplementary Figure S1).

In the NMA comparing DL with VL, three VL device types, based on their blades, were included: nonchanneled Macintosh blades (C-MAC, McGrath, and UE scope), nonchanneled angular blades (Glidescope), and channeled blades (Airtraq, Airwayscope, and King Vision). The King Vision was only employed as a channeled device in the included studies. However, the VivaSight included in Grensemann's 2018 article was excluded from the NMA based on blade type because of its single-lumen tube with an integrated video camera that could not be categorized according to the criteria used in this review. The articles by Janz et al. (39) and Macke et al. (16) were excluded from the NMA because the VL devices could not be classified by the blade type (Supplementary Table S2).

3.2. Risk of bias within studies

Regarding the overall risk of bias in each included study, 11 studies had low risk of bias, seven studies were categorized as *some concerns*, and four studies had high risk. In the detailed assessment of all subcategories, the *randomization processes* of nine studies were rated as *some concerns* or *high risk of bias* because detailed descriptions of the randomization processes were omitted. Additionally, the *deviations from intended interventions* of three studies were classified as *some concerns* because it was unclear whether the exclusions of some members of the study populations occurred before or after randomization. Details of the quality assessments of the included studies are shown in Supplementary Figure S2.

3.3. Publication bias across studies

Supplementary Figure S3 presents a funnel plot indicating that the first-pass success comparison between VL and DL was balanced. Egger's regression test revealed no significant bias across studies ($p = 0.28$).

TABLE 1 Characteristics of the studies included in the review and meta-analysis.

References	Study design	Setting	Country	Recruitment period	Patients, N	Laryngoscope (blade)	Difficult airway	Intubators' experience	Sedatives in RSI	Muscle relaxants in RSI	Intubation during CPR
Trimmel et al. (34)	sRCT	Prehospital	Austria	2008–2009	212	Airtraq (C) vs. DL	<50%	Experienced	Used	Used	<50%
Griesdale et al. (35)	sRCT	ICU	Canada	2009–2011	40	Glidescope (A) vs. DL	<50%	Inexperienced	Used	Used	<50%
Yeatts et al. (36)	sRCT	ER	US	2008–2010	623	Glidescope (A) vs. DL	Unknown	Inexperienced	Used	Used	<50%
Arima et al. (37)	sRCT	Prehospital	Japan	2012–2013	118	Airwayscope (C) vs. DL	<50%	Experienced	Not used	Not used	≥50%
Ahmadi et al. (38)	sRCT	ER	Iran	2011	97	Glidescope (A) vs. DL	≥50%	Inexperienced	Unknown	Unknown	<50%
Silverberg et al. (3)	sRCT	ICU	US	2012–2013	117	Glidescope (A) vs. DL	<50%	Inexperienced	Used	Used	<50%
Driver et al. (18)	sRCT	ER	US	2011–2013	198	C-MAC (M) vs. DL	<50%	Inexperienced	Used	Used	<50%
Goksu et al. (23)	sRCT	ER	Turkey	2013–2014	150	C-MAC (M) vs. DL	Unknown	Inexperienced	Used	Unknown	<50%
Janz et al. (39)*	sRCT	ICU	US	2014–2015	150	McGrath (M), Glidescope (A), and Olympus bronchoscope** vs. DL	<50%	Inexperienced	Used	Used	<50%
Kim et al. (17)	sRCT	ER	South Korea	2011–2013	140	Glidescope (A) vs. DL	Unknown	Experienced	Not used	Not used	≥50%
Sulser et al. (2)	sRCT	ER	Switzerland	2014–2015	147	C-MAC (M) vs. DL	<50%	Experienced	Used	Used	<50%
Trimmel et al. (15)	mRCT	Prehospital	Austria Norway	2011–2012	326	Glidescope (A) vs. DL	<50%	Experienced	Used	Used	≥50%
Ducharme et al. (40)	mRCT	Prehospital	US	2014–2016	82	KingVision (C) vs. DL	<50%	Inexperienced	Not used	Not used	≥50%
Lascarrou et al. (10)	mRCT	ICU	France	2015–2016	365	McGrath (M) vs. DL	<50%	Inexperienced	Used	Used	<50%
Abdelgalel et al. (41)	sRCT	ICU	Egypt	2016–2017	120	Airtraq (C) vs. Glidescope (A) vs. DL	Unknown	Experienced	Used	Used	<50%
Gao et al. (42)	sRCT	ICU	China	2014–2016	163	UEScope (M) vs. DL	<50%	Experienced	Used	Not used	<50%
Grensemann et al. (43)*	sRCT	ICU	Germany	2016–2018	53	VivaSight*** vs. DL	Unknown	Experienced	Used	Used	<50%
Kreutziger et al. (13)	mRCT	Prehospital	Austria	2017–2018	514	McGrath (M) vs. DL	<50%	Experienced	Used	Used	≥50%
Dey et al. (44)	sRCT	ICU	India	2017–2018	218	C-MAC (M) vs. DL	Unknown	Experienced	Used	Used	<50%
Macke et al. (16)*	sRCT	Prehospital	Germany	2017–2019	152	C-MAC (M or A) vs. DL	≥50%	Experienced	Unknown	Unknown	≥50%
Ilbagi et al. (45)	sRCT	ER	Iran	2016–2018	70	Glidescope (A) vs. DL	<50%	Inexperienced	Used	Used	<50%
Sanguanwit et al. (46)	sRCT	ER	Thailand	2015–2016	158	Glidescope (A) vs. DL	<50%	Inexperienced	Unknown	Unknown	<50%

The meta-analysis and network meta-analysis included all of the listed articles except those indicated with asterisks (*). The network meta-analysis compared video laryngoscope blades investigated in the studies.

*These studies were excluded from the network meta-analysis because the video laryngoscopes used could not be classified according to blade type.

**Could not be classified by blade because a fiberoptic video bronchoscope was used.

***Could not be classified by blade because an endotracheal tube with an integrated camera at the tip was used.

sRCT, single-center randomized controlled trial; mRCT, multicenter randomized controlled trial; ER, emergency room; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; RSI, rapid sequence intubation; A, nonchanneled angular blade; C, channeled blade; M, nonchanneled Macintosh blade; DL, direct laryngoscope.

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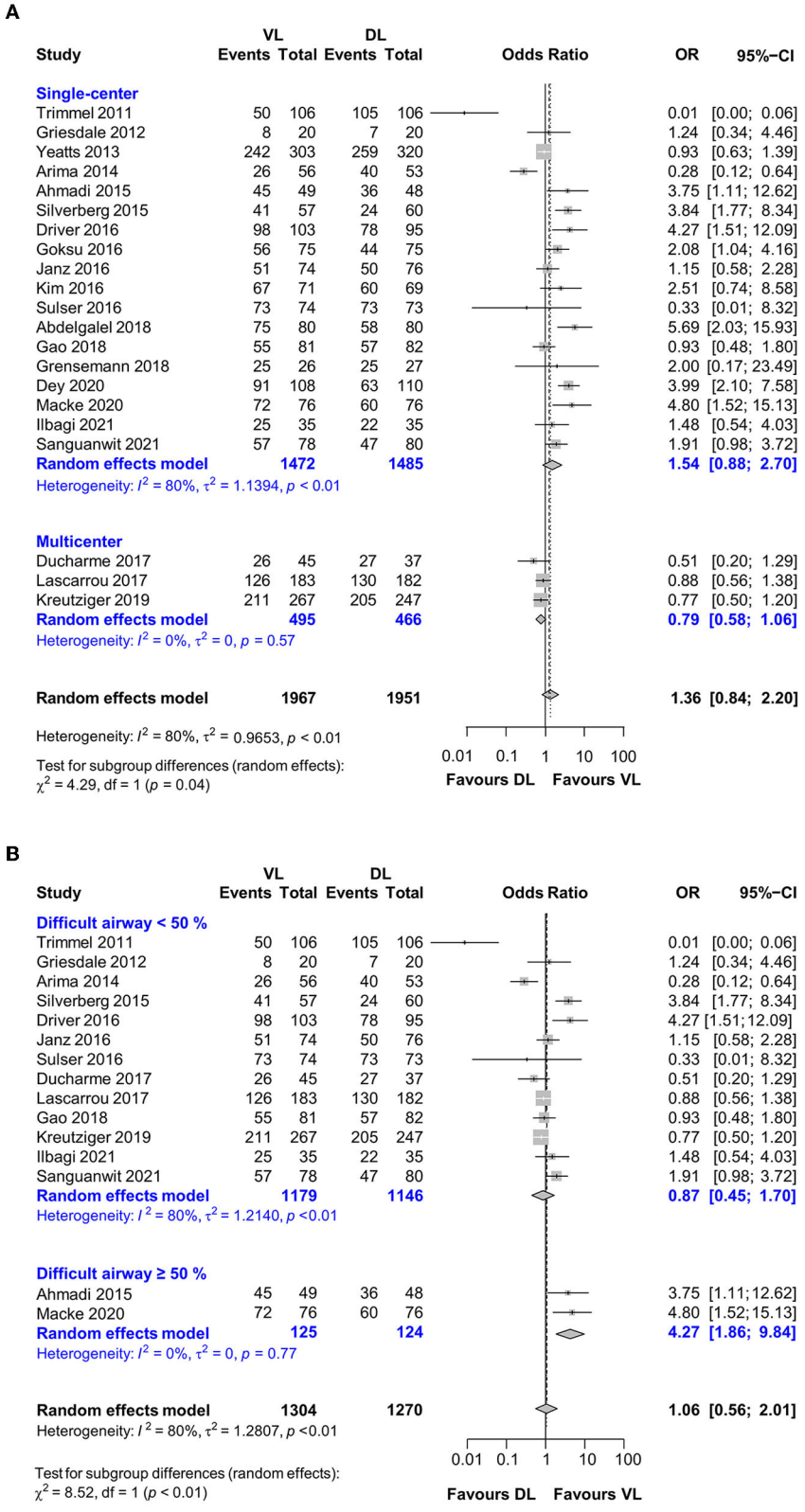

FIGURE 2
Forest plot depicting the subgroup analysis for **(A)** study design and **(B)** difficult airway.

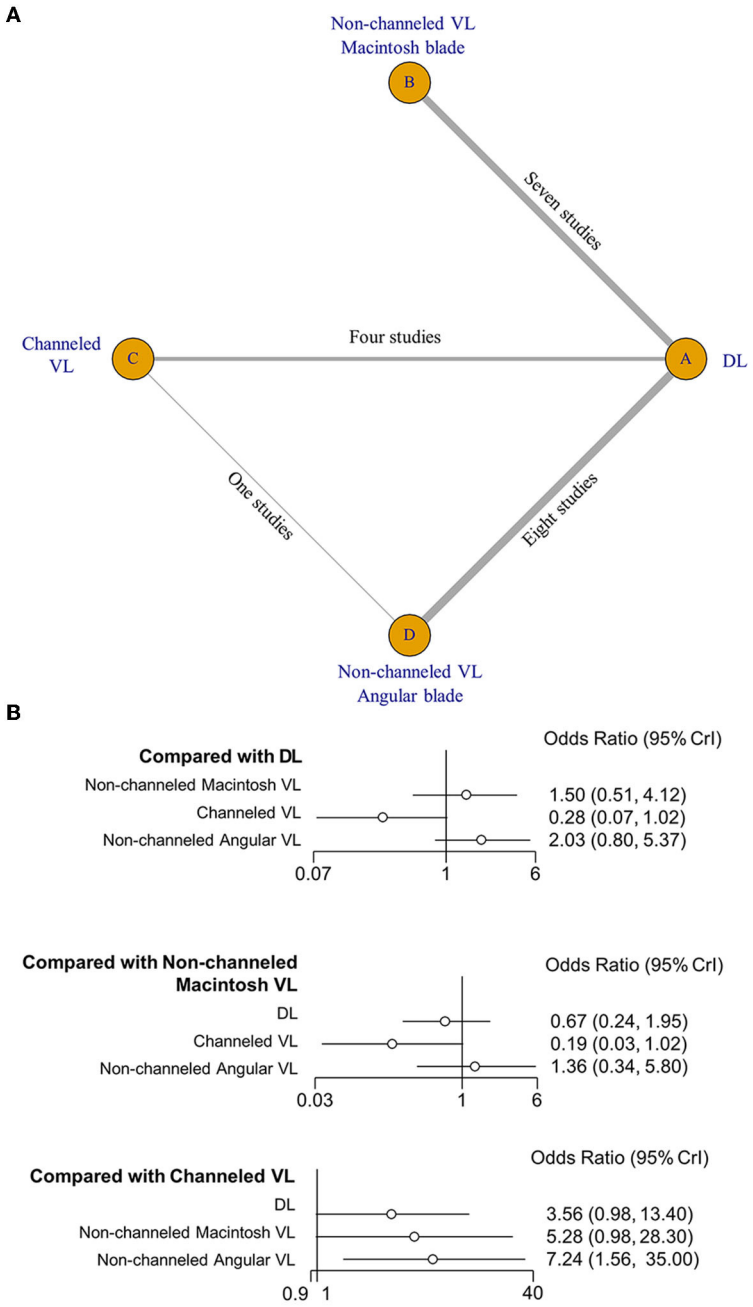

FIGURE 3
Network map **(A)** and forest plot **(B)** of the network meta-analysis of first-attempt intubation success.

3.4. Synthesis of first-attempt success results

Data on first-attempt success rates were provided for all 22 included studies. A pooled analysis revealed no statistically significant difference in the first-attempt success rates between VL and DL (22 studies; OR, 1.16; 95% CI, 0.66–2.03; $n = 4{,}244$; $p = 0.62$), with significant heterogeneity among studies ($p < 0.01$; $I^2 = 85\%$; Supplementary Figure S4).

3.5. Sensitivity analysis

An outlier article by Trimmel et al. (34) caused the most heterogeneity and, in comparison with most of the other articles, the article by Trimmel et al. (34) yielded considerably dissimilar outcomes, with lower VL success rates and higher DL success rates. Pooled analysis revealed no significant difference in the first-attempt success rate between VL and DL after eliminating the outlier study from the sensitivity analysis (21 studies; success rate,

VL vs. DL, 77.3% vs. 75.3%, respectively; OR, 1.36; 95% CI, 0.84–2.20; $n = 3{,}918$; $p = 0.20$; low-quality evidence), with significant study heterogeneity ($p < 0.01$; $I^2 = 80\%$; Supplementary Figure S4).

3.6. Subgroup analyses

After sensitivity analysis, 21 studies underwent subgroup analyses to compare first-attempt intubation success between VL and DL. Significant heterogeneity within studies was only apparent in terms of two factors: study design and difficult airway proportion. The heterogeneity-producing effect of study design was compared between single-center studies (18 studies; $n = 2{,}957$; OR, 1.54; 95% CI, 0.88–2.70; low-quality evidence) and multicenter studies (three studies; $n = 961$; success rate, VL vs. DL, 73.3% vs. 77.7%, respectively; OR, 0.79; 95% CI, 0.58–1.06; high-quality evidence; Figure 2A). This showed that the pooled outcome of multicenter RCTs was more consistent than that of single-center RCTs (I^2 heterogeneity: single center vs. multicenter, 80% vs. 0%, $p = 0.04$). After excluding six articles that did not report the proportions of difficult airways, the subgroup analysis for difficult airways included 15 studies, with a significant heterogeneity effect in the comparison of difficult airway proportions between <50% and ≥50% ($p < 0.01$). Most studies included <50% difficult airways, and the pooled results showed that VL had the same success rate as DL (13 studies; $n = 2{,}325$; OR, 0.87; 95% CI, 0.45–1.70; $I^2 = 80\%$; low-quality evidence). In contrast, pooled results from studies including ≥50% difficult airways showed a higher success rate for VL than DL (two studies; $n = 249$; success rate, 93.6% vs. 77.4%; OR, 4.27; 95% CI, 1.86–9.84; $I^2 = 0\%$; moderate-quality evidence; Figure 2B).

Other factors suspected of causing heterogeneity were intubators' experience (inexperienced vs. experienced, $p = 0.48$), rapid sequence intubation (yes vs. no, $p = 0.32$), and the proportion of intubation during CPR (<50% vs. ≥50%, $p = 0.45$). VL was associated with a higher success rate than DL, with moderate-quality evidence, when used by inexperienced nonphysicians (11 studies; $n = 2{,}050$; success rate, 75.8% vs. 70.4%; OR, 1.54; 95% CI, 1.04–2.26; $I^2 = 64\%$) or in-hospital settings (16 studies; $n = 2{,}849$; success rate, 80.1% vs. 72.1%; OR, 1.86; 95% CI, 1.32–2.64; $I^2 = 65\%$).

In the analysis using meta-regression, the recruitment start dates and sample sizes were not significant (21 studies; recruitment period, $p = 0.11$; sample size, $p = 0.40$; Supplementary Tables S4, S5).

3.7. NMA by blade type

The effect of VL blade type for the first-attempt intubation success was evaluated using Bayesian NMA (18 studies; $n = 3{,}563$) for three VL blade types: nonchanneled Macintosh VL vs. nonchanneled angular VL vs. channeled VL; DL as a reference treatment). The best Bayesian NMA model in this comparison was obtained to minimize inconsistency (deviance information criterion $= 72.2$; $I^2 = 6\%$).

TABLE 2 Rank probability of laryngoscope blade efficacy.

Laryngoscope blade	Rank probability			
	1st	2nd	3rd	4th
DL	0.017	0.238	**0.727**	0.018
Nonchanneled Macintosh VL	0.311	**0.472**	0.195	0.022
Nonchanneled Angular VL	**0.669**	0.278	0.050	0.003
Channeled VL	0.003	0.012	0.028	**0.958**

DL, direct laryngoscope; VL, video laryngoscope. The bold values are the highest value among the each column.

The network graph for first-pass success revealed that three types of VLs and DL could be directly compared. There was only one indirect comparison between channeled VL and nonchanneled angular VL in the VL intercomparison (Figure 3A). Figure 3B shows that the nonchanneled Macintosh and angular blades of nonchanneled VL had an intubation success rate similar to that of DL (nonchanneled Macintosh VL, OR, 1.50; 95% CI, 0.51–4.12; nonchanneled angular VL, OR, 2.03; 95% CI, 0.80–5.37). However, channeled VL had a relatively lower intubation success rate than DL (OR, 0.28; 95% CI, 0.08–1.02). In a VL intercomparison, nonchanneled angular VL had a significantly higher intubation success rate than channeled VL (OR, 7.24; 95% CI, 1.56–35.0).

According to the rank probability test results in Table 2, the nonchanneled angular VL had the best outcome (0.669), the nonchanneled Macintosh VL was ranked second (0.472), and DL third (0.727). The fourth-ranked treatment (0.958) was channeled VL.

4. Discussion

This pooled analysis found, with a low certainty of evidence, that VL, compared with DL, does not improve ETI success in critically ill or emergency-care patients. This finding was supported by pooled results from multicenter RCTs with a high certainty of evidence via sensitivity and subgroup analyses. Using a subgroup approach, we found that VL outperformed DL in association with difficult airways, inexperienced practitioners, and in-hospital settings, with a moderate certainty of evidence. The patient's airway status, intubator experience with laryngoscopes, and intubator surroundings were all significantly associated with ETI success in the evaluation of VL efficacy. In the selection of VL for ETI, this study revealed that channeled VLs had a lower efficacy of ETI success compared with nonchanneled VLs and DL.

VL has advantages for use in the intubation of patients with difficult airways; however, in this review, only a few studies had a high proportion (>50%) of difficult airways, and most of the included studies included a relatively low number of difficult airways (Figure 2), which is the main reason for the equivalent results of VL and DL. Moreover, it might be challenging to include mainly patients who have difficult airways with a high risk of ETI failure in each RCT. Thus, the pooled result of this review may have differed if more studies with high proportions of difficult airways were included.

This review did not demonstrate that differences in ETI providers' levels of experience could affect the success of laryngoscopy (test for subgroup difference in Supplementary Figure S5; experienced vs. inexperienced group, $p = 0.48$). VL showed equal ETI performance in the experienced group (success rate: VL, 745/945 (78.8%); DL, 746/923 (80.8%); OR, 1.00; 95% CI, 0.33–3.09; $I^2 = 87\%$), but outperformed DL in the inexperienced intubator group, with a moderate certainty of evidence [success rate: VL, 775/1,022 (75.8%); DL, 724/1,028 (70.4%); OR, 1.54; 95% CI, 1.04–2.26; $I^2 = 64\%$]. The similarities in the ETI success rates of DL and VL in the total population and experienced group were possibly attributable to an imbalance in ETI experience between VL and DL providers. This implies a significant gap between DL providers' sufficient ETI experience and VL providers' insufficient experience. Most of the included studies revealed that ETI experience for VL providers was limited to manikin training rather than actual patients (Supplementary Table S2) (34, 42, 44). This disparity in ETI experience may cause the DL-associated ETI success rate to be higher than the VL-associated success rate. Some studies with high heterogeneity in the Baujat plot demonstrated this effect, wherein experienced intubators performed ETIs in the prehospital setting, resulting in an apparently higher rate of ETI success with DL than with VL (Supplementary Figure S4) (15, 34, 37). When interpreting the pooled results of this meta-analysis, consideration of the hidden disparity in ETI experience, rather than an exclusive focus on statistical results, is crucial.

Channeled VL had a lower success rate in an NMA relative to nonchanneled VLs and DL. The obvious structural difference between channeled VL and DL could be the primary reason for the lower success rate of channeled VLs. Nonchanneled VL has structural similarities to DL, as well as the use of a stylet in combination with the endotracheal tube. However, ETI using channeled VL can be unfamiliar because it is an alternative ETI procedure without stylet use. The channeled VL blade is slightly thicker than that used in DL to guide the advancement of the tracheal tube during ETI, and this likely increases the difficulty of ETI in patients with narrow or restricted oral cavities (37, 47). Given the intubators' considerable familiarity with DL, the unfamiliar structure and lack of VL experience could be the primary reasons for the channeled VL's lower ETI performance.

There was no statistical difference in ETI between VL and DL in the total population (OR 1.16, CI 0.66–2.03), and heterogeneity was high ($I^2 = 85\%$); thus, the certainty of evidence was low. Sensitivity analysis, subgroup analysis, and meta-regression were used to reduce heterogeneity and obtain more consistent results.

In the sensitivity analysis, omitting the 2016 article by Trimmel et al. (15) significantly reduced the heterogeneity of the pooled results (up to $I^2 = 80\%$, $p < 0.01$). The study by Trimmel et al. (15) contributed the most heterogeneity, according to the Baujat plot, indicating that this study was a significant outlier and demonstrating DL's higher success rate relative to that of VL (Supplementary Figure S4). Thus, the greater experience of practitioners in Trimmel's 2016 study (a mean of 7 years of anesthesiology experience) compared with other included studies, as well as the ground and air ambulance prehospital settings wherein ETI was performed, were the main reasons for its role as a significant outlier.

We anticipated that the intubator surroundings would affect VL efficacy. VL performed similarly to DL in the prehospital setting, but it outperformed DL in the in-hospital setting. Despite the fact that this subgroup categorization was not associated with statistical significance ($p = 0.10$), differences in intubator surroundings could affect ETI performance. Most prehospital studies reported the following unique reasons for ETI failure in VL: impaired sight due to ambient light, fogged camera lenses, and monitor problems. Furthermore, these studies revealed a high rate of arrest, ETI during CPR, oral contamination, and cervical immobilization in trauma patients (13, 34, 40). We predicted that these characteristics of prehospital surroundings would be more detrimental to VL than DL.

Sensitivity analysis, subgroup analysis, and meta-regression did not significantly help reduce heterogeneity, mostly owing to the high rate of single-center RCTs. Differences between recruited hospitals, such as the severity of patients' conditions, hospital size or capacity, and clinicians' skill or experience, may have influenced the results of the pooled analysis. The pooled analysis of multicenter RCTs showed consistent results with a high certainty of evidence (three studies; $n = 961$; OR, 0.79; 95% CI, 0.58–1.06; $I^2 = 0\%$; Figure 1, Supplementary Table S4). Thus, more multicenter RCTs are needed to obtain reliable results.

This meta-analysis yielded the same conclusion as a previous meta-analysis by Jiang et al.: VL was not related to a higher success rate compared with DL in the total population (1). Jiang et al. also reported that prehospital intubation is worsened by VL use even when it is performed by experienced operators. However, this pooled result differed from our analysis. By adding more recently completed studies, we demonstrated VL to be equally successful as DL in the prehospital ETI or experienced intubator group (1), possibly due to the definition of an experienced intubator.

Regarding ETI experience among intubation providers, Jiang et al. included inconsistent criteria for experienced operators (including certified anesthesiologists, emergency medical technicians with >3 years of clinical experience, personnel who performed >50 ETIs, or according to the judgment of the study investigators), and these were primarily related to DL and did not depend on experience with ETI using VL. In contrast to the study conducted by Jiang et al. (1), experienced intubators in the present analysis were designated as physicians with sufficient experience, whereas the inexperienced group included students, paramedics, nurses, residents, and fellow trainees. Although this definition did not completely standardize the difference in intubator experience between DL and VL providers in each of the included studies, it likely lessened the significant heterogeneity of analysis caused by ambiguous criteria defining experienced intubators.

Vargas et al. recently published a systematic review and meta-analysis demonstrating that VL increased the rate of successful

ETI on the first attempt relative to the rate achieved with DL (RR 1.04, 95% CI, 1.01–1.08, I^2 = 79%) (48). Vargas et al. reported that VL outperformed DL in overall results, but their study included a different population than our review because they included surgical patients but excluded those who needed prehospital ETI or ETI during CPR. Therefore, the population differences between these studies may have affected the pooled results (49). During CPR, the camera view of a VL may frequently become obscured due to fogging, secretions, blood, or emesis present in the oropharynx. Consequently, the success rate of ETI using a VL during CPR may be considerably lower in comparison to that achieved using a DL (50). Moreover, in the prehospital setting, where airway management procedures may be conducted outdoors, the presence of sun glare can also impede the successful ETI (51). It is, therefore, plausible that these differences among the studies may have influenced the pooled results.

We believe that this study revealed a scarcity of articles demonstrating the true efficacy of VL because there was a significant gap in ETI experience between VL and DL. The lack of experience for VL is strongly related to the current status of VL, which is only used as a rescue device in difficult airways. This is seriously impeding the accumulation of VL intubating experience (52). This study's VL inexperience is synthesized as a lack of training, familiarity, confidence as a result of occasional use, and knowledge of ETI indication. Because the factors mentioned are significantly associated with insufficient years of ETI experience, years of ETI experience is regarded as the most important factor for ETI success. We also believe that the absence of support from a well-trained technician or nurse outside of the hospital is a major factor impeding overall ETI success. To address this issue, some recent articles suggest that a shift from DL to VL as a legal standard of care is necessary, which can help increase ETI success rates as well as VL's rapid accumulation of experience (50, 51). In this context, future trials by expert clinicians with sufficient real-world experience in both VL and DL, such as non-channeled angular VL showing the best performance in the rank probability test, can thus demonstrate the true efficacy of VL in difficult airways.

Several previous studies have reported that VL improves the first-pass success rates and reduces the risk of ETI failure in patients with difficult airways (50, 51). In the subgroup analysis of the present meta-analysis, which included only two studies, the pooled results of studies with ≥50% difficult airways demonstrated a higher success rate for VL than for DL. In the rank probability of laryngoscope blade efficacy, two VL (nonchanneled angular VL and nonchanneled Macintosh VL) was ranked first and second devices respectively, in contrast, DL was ranked third devices. VL has been shown to be advantageous in managing difficult airways by providing better visualization of the airway structures, which can result in more successful ETI and fewer complications. Although in the ETI trial, VL may have been designated as a backup device, the results of our analysis suggest that VL could be considered as one of the primary tools for ETI in patients with predicted difficulty airway.

There are several limitations to this review and meta-analysis. First, our study aimed to establish a strict standard for ETI experience to minimize heterogeneity; however, this standard did not entirely eliminate the heterogeneity results. The measures of ETI experience, such as manikin training, clinical department experience, and ETI times threshold, varied among the included studies for both DL and VL. Furthermore, in the context of VL experience, a shortage of training time with VL and the use of manikins during training may have contributed to the lower success rate observed with VL. To improve the outcomes and heterogeneity of future RCTs, it is necessary to resolve these potential confounding factors. Second, rather than a fixed model, we used a random-effects model to account for the diverse medical resources or environments; however, a random-effects model cannot completely resolve hidden heterogeneity issues, including information gaps and selection bias. Third, most of the studies included in this meta-analysis did not provide sufficient information regarding the patients' disease, therefore, the assessment of the severity of their condition was not evaluated in this meta-analysis. Although time to ETI was not the primary outcome in this meta-analysis, it may be a crucial factor in patients with poor oxygen reserves or high oxygen demands, such as those with sepsis. In these patient populations, who present with physiological challenges, selecting the laryngoscope device that offers the highest success rate and the shortest time to ETI should be chosen. Finally, the population included in this study exhibits a substantial degree of heterogeneity, characterized by variations in disease severity, difficult airway, ETI location (pre-hospital or in-hospital), ETI during CPR, the presence of additional support during ETI such as a nurse, and the type of laryngoscopes employed. This diversity is reflected in the calculated heterogeneity. the quality of evidence supporting the comparison of multiple devices is considered low. Given these limitations of this study, the findings of the meta-analysis should be interpreted with caution.

5. Conclusion

This pooled analysis showed, with a low certainty of evidence, that VL does not improve intubation success compared with DL; however, VL outperformed DL in the contexts of difficult airways, inexperienced ETI providers, and in-hospital settings, with a moderate certainty of evidence. Channeled VL had the least efficacy for intubation success compared with nonchanneled VLs and DL.

Data availability statement

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

Author contributions

JK, CA, and WK developed the concept, performed the data analysis, and drafted the manuscript. JK and B-HJ performed data acquisition. CA and WK performed the statistical analysis. All authors approved the final version.

Funding

This research was supported by Hallym University Research Fund 2021 (HURF-2021-47) and a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (HI22C155300).

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.2023.1193514/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 14 June 2023
DOI 10.3389/fmed.2023.1200033

OPEN ACCESS

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RECEIVED 04 April 2023
ACCEPTED 19 May 2023
PUBLISHED 14 June 2023

CITATION
Tao X, Zhang X, Wang J, Chen Y and Liu X (2023) The relationship between the PICC tip position and weight gain, length growth of premature infants under ultrasonography: a correlation analysis study.
Front. Med. 10:1200033.
doi: 10.3389/fmed.2023.1200033

The relationship between the PICC tip position and weight gain, length growth of premature infants under ultrasonography: a correlation analysis study

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Objective: This study aimed to analyze the correlation between PICC tip position and weight/length changes in preterm infants in different positions using ultrasonography.

Methods: The study is a prospective before and after self-control clinical trial. The study analyzed the distance between the PICC tip and the entrance of the heart under ultrasonography for premature infants who underwent PICC insertion. The infants were positioned and tracked weekly, and their weight and length were recorded. The Spearman rank correlation test was used to analyze the relationship between the displacement distance of the PICC tip under ultrasonography in different positions and weight/length changes.

Results: A total of 202 premature infants were included in the study, and 100% of them experienced changes in the PICC tip position. During the first week, 134 (66.33%) cases in a flexed position and 153 (75.74%) cases in a straight position showed displacement of the catheter toward the heart. The displacement distance of the tip during catheter retention was significantly correlated with weight change ($r_s = 0.681/0.661$, $P < 0.05$) and length change ($r_s = 0.629/0.617$, $P < 0.05$). In the third and fifth weeks, weight increased by 451 ± 178 and 750 (715–975) g, length increased by 1.50 (1.00–2.12) and 3.00 (2.00–3.70) cm, the catheter moved 1.27 ± 0.89 and 2.23 ± 0.95 cm, respectively, in a flexed position.

Conclusion: The PICC tip position in preterm infants is influenced by weight and length changes. It is crucial to use ultrasonography to track and locate the catheter within the first week of placement and to increase the frequency of catheter localization starting from the third and fifth weeks. The flexed position is recommended during catheter localization.

KEYWORDS

ultrasonography, location, premature infant, peripherally inserted central catheter, weight, length, position

Introduction

A peripherally inserted central catheter (PICC) is a technique for inserting a catheter through peripheral veins so that the catheter tip is placed in the superior vena cava (SVC) or inferior vena cava (IVC) to establish a safe and stable infusion pathway. The PICC has the characteristics of safety, long retention time, and low associated infection rate, providing ideal venous access for newborns, especially for premature infants with a severe nutritional deficiency (1). During the indwelling catheter, ensuring the catheter tip within the vena cava is critical because malposition may induce adverse outcomes such as infectious endocarditis, atrial fibrillation, and pleural effusion (2–4). Therefore, it is necessary to regularly track and locate the PICC tip in premature infants from the first location to prevent displacement (5).

Currently, PICC positioning mainly includes body surface measurement, intracavitary ECG, chest radiography (CR), and ultrasonography (US). The body surface measurement method and intracavitary ECG positioning are only used for the first catheter placement, and cannot continuously track the catheter position (6, 7), while CR has been considered the "gold standard" for confirming the sites of catheter tips, it has several drawbacks such as non-dynamic and retrospective imaging, ionizing radiation, and longer time consumption (8). The traditional operation process did not locate and track the PICC during the indwelling catheter. In the case of suspected complications, the CR would be used for location judgment. However, due to the problem of the clinical use of CR, the implementation of PICC location and tracking was hindered. At this time, the advantages of PICC tip location and tracking under US were also highlighted (9–11). Research shows that US can not only clearly display the position of the PICC tip in the vena cava (12) but it also can timely detect and guide the correction of catheter ectopic (13, 14). US can directly display the superior and inferior vena cava and its right atrium entrance, which provides a basis for accurately determining the position of the catheter tip in the vena cava (15).

The catheter displacement of premature infants is caused by body length and weight growth. Weight and length are the most intuitive indicators to measure growth, and the measurement is simple and accurate (16, 17). Studying the correlation between the change of catheter tip position in different body positions will help to provide the theoretical basis for the tracking of PICC catheter position. However, only a few studies have reported on the application of US in the neonatal intensive care unit (NICU).

Hence, in this study, we enrolled a consecutive series of 210 premature infants, aiming to understand more about the values of US in tracking and locating the position of catheter tip under different body positions.

Methods

Estimation of sample size

We used the "Confidence Intervals for Kappa" in PASS15 software to estimate the sample size of this study. According to clinical experience and pre-experimental results, the kappa coefficient is about 0.806, and its standard deviation is 0.12. If the class I error of the relevant parameters is set as 0.05 ($\alpha = 0.05$) with an allowable error of 0.05 ($\delta = 0.05$), the calculated sample size is 89 children. With the addition of 10% sample loss, at least 98 patients are required.

Participants

Premature infants who were hospitalized in the Department of Neonatology, Children's Hospital Affiliated to Chongqing Medical University from September 2022 to March 2023, and needed PICC catheterization were selected as the study subjects. The inclusion criteria were as follows: ① premature infants requiring PICC catheterization; ② the physical condition of the infant able to withstand US examination; ③ the bleeding and clotting time being normal; ④ no serious contraction or collapse of peripheral blood vessels; ⑤ PICC retention time >1 week; and ⑥ parents are informed and signed informed consent. The exclusion criteria were as follows: ① congenital heart disease or other cardiovascular diseases; ② immunodeficiency disease; ③ severe intestinal inflation, unable to determine the position of catheter tip; ④ the local skin of the ultrasonic observation window being incomplete, with skin lesions or infection; and ⑤ transfer, abandonment of treatment, or death. This study was approved by the hospital ethics committee (2022-369); Clinical trial registration number (ChiCTR220064003).

Placement of PICC

PICC placement was performed by two nurses with PICC operation qualification. Briefly, the neonate was placed in an incubator. Catheterization was performed with a puncturing kit containing 26 GA (1.9 F) single-lumen PICC catheters according to the neonatal PICC catheterization operation specifications.

According to the specifications, it should be avoided placing the catheter tip in the heart of neonates and infants (15). The optimal tip position complied with the recommendation of the 2016 guidelines by the American Infusion Nurses Society (INS), i.e., the safest PICC tip should be located within the lower third of SVC or just below the IVC-and-right-atrial junction (3, 18, 19).

Locating catheter tips by US

US is conducted under a LOGIQ e color Doppler ultrasonic diagnostic system (6S and 8C probes, GE company, USA) by two research members who have at least 5 years of experience in ultrasonic PICC positioning. The ultrasonic probe was set at the midline of the subxiphoid region or at the parasternal line of the right subclavicle region. A hyperechoic "equal sign'-like or sandwich-like structure would be detected within the vena cava, which represents the inserted line. In detail, for clearly viewing the "equal sign" like echoes of the catheter tip

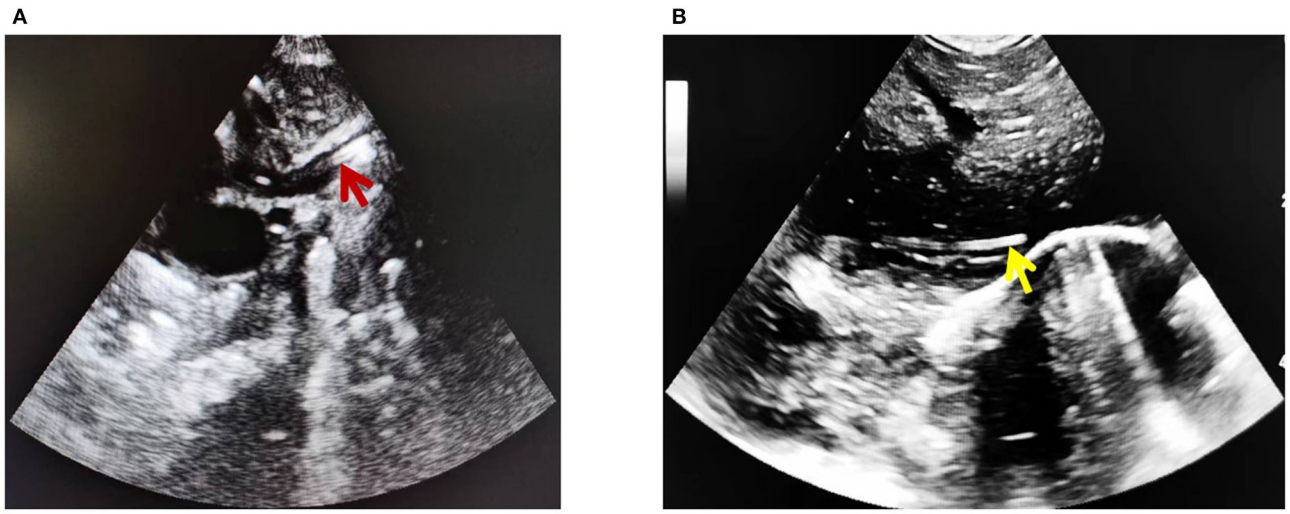

FIGURE 1
PICC ultrasonic imaging of vena cava. **(A)** Superior vena cava (red arrow). **(B)** Inferior vena cava (yellow arrow).

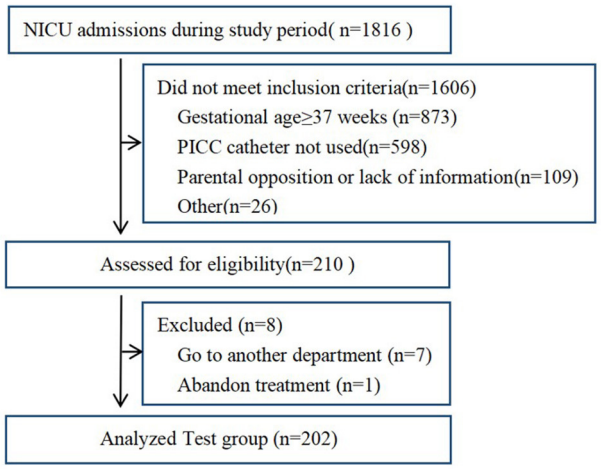

FIGURE 2
Flowchart of the study population.

in SVC, the probe was placed longitudinally at the 2nd−3rd intercostal spaces on the right of the sternum to delineate the long axis of the aortic arch and the short axis of SVC and then rotated clockwise for about 15° and tilted slightly to the right to show the long axis of SVC and the right atrial entrances of SVC and IVC (Figure 1A). Subsequently, the distance between the tip and the right atrial inlet was measured, and improper tip position was US-guided readjusted. For clearly viewing the "equal sign"-like echoes of the catheter tip in IVC, the probe should be placed longitudinally at the midsagittal position of the subxiphoid region and scanned along the inferior rib to delineate the IVC and right atrial inlet (Figure 1B). The tip-to-atrium distance was measured, and improper tip position was readjusted.

Observation and analysis

The puncture site, the distance between the catheter tip and the right atrium inlet, was measured under US on the day of catheterization and every other week after catheterization. Recording the weight and length at the time of the PICC catheter was done every week, and the increase in weight and length after inserting the PICC catheter was calculated. To calculate the correlation between the increase in weight and length of premature infants and the displacement distance of the PICC tip, all data were entered by two PICC specialist nurses, and the results with differences were reviewed and agreed upon by two people. Two people will input all data into the computer, and all electronic data will be checked by a third person.

Statistics

In this study, SPSS 24.0 software was used to statistically process the data. The counting data is expressed in cases and percentage (%). The measurement data conforming to normal distribution are described by mean ± standard deviation, and the measurement data of non-normal distribution are expressed by median and quartile spacing; The correlation between weight gain and length growth and PICC tip shift was analyzed by the Spearman rank correlation analysis, and a P-value of <0.05 was considered to be a statistically significant difference.

Results

Patients

A total of 1,816 newborn infants were screened between September 2022 to March 2023, of which, 1,606 did not meet inclusion criteria, including 873 of gestational age (GA) ≥ 37

TABLE 1 Conditions of catheter retention period.

Item	Min and max	Median and interquartile spacing
Catheter retention time (days)	8–49	15 (11–20.25)
Weight gain (g)	−250 to 1,660	230 (100–370)
length growth (cm)	0–7	1 (1–2)
PICC tip displacement in flexion position (cm)	−1.28 to 4.05	0.33 (−0.2 to 1.03)
PICC tip displacement in straight position (cm)	−2.0 to 3.41	0.09 (−0.41 to 0.70)

weeks; thus, 598 PICC catheters were not used, 109 parents of preterm infants declined to participate, and 26 are excluded for other reasons. Finally, 210 premature infants enrolled, of which eight of them dropped out (seven were transferred to another department and one abandoned treatment). Finally, 202 finished the study before and after self-control trials and were included in the final analysis (Figure 2). The number of involved preterm infants reached the calculated sample size.

Of the included neonate, 121 were boys and 81 were girls. A total of 69 cases received invasive mechanical ventilation, 101 received non-invasive mechanical ventilation, and 32 were not on a ventilator. Upper limb catheterization was performed in 11 cases, including one case of the superficial temporal vein, eight cases of the basilic vein, and two cases of the cephalic vein. Lower limb catheterization was performed in 191 cases, including 128 cases of great saphenous vein and 63 cases of superficial femoral vein. The mean gestational age was (31.75 ± 2.83) weeks, the age at the time of catheterization was (3.09 ± 7.46) days, and the weight on the day of catheterization was (1,758.54 ± 591.58) g.

Catheter indwelling time, weight gain, length growth, and PICC tip displacement distance in flexion and extension positions during catheter indwelling

The results showed that the PICC catheterization time was 15 days, with a weight gain of 230 g and a length growth of 1 cm. The catheter tip displacement was 0.33 and 0.09 cm, as shown in Table 1. From the time of catheterization to the 3rd week, the weight gain was 451 ± 178 g, the length growth was 1.50 (1.00–2.12) cm, and the catheter displacement was 1.27 ± 0.89 cm. By the fifth week, the weight gain was 750 (715–975) g, the length growth was 3.00 (2.00–3.7) cm, and the catheter displacement was 2.23 ± 0.95 cm. The weight and length growth during the catheterization period is shown in Figures 3A, B, respectively. The tip displacement distance in each week in the flexion position was −0.06 ± 0.79, 0.57 ± 0.41, 0.76 ± 0.20, 0.36 ± 0.23, 0.58 ± 0.52, and 0.32 (0.17–0.57) cm; in the straight position, it was −0.31 ± 0.77, 0.51 ± 0.30, 0.62 ± 0.20, 0.36 ± 0.29, 0.43 ± 0.17, and 0.35 ± 0.18 cm, as shown in Figure 3C. The tip displacement in the flexion and straight positions from the beginning of catheterization was −0.06 ± 0.79, 0.51 ± 0.88, 1.27 ± 0.89, 1.64 ± 0.82, 2.23 ± 0.95, 2.64 ± 0.84 cm and 0.31 ± 0.77, 0.20 ± 0.91, 0.82 ± 0.80, 1.18 ± 0.87, −1.62 ± 0.93, 1.98 ± 0.85 cm, respectively, as shown in Figure 3D. In the first week, 134 (66.33%) of the flexion position and 153 (75.74%) of the straight position were displaced to the heart direction, 0.37 (0.26–0.56)/0.66 (0.45–0.87) cm respectively. The fluctuation of the data of catheter tip displacement distance measured in different positions showed that the tip displacement distance was 0.23 (0–0.97) cm in flexion position and 0.25 (0–0.98) cm in the straight position from the second week. The small fluctuation range in the flexion position indicates that the stability of the flexion position is higher. There were five patients with edema. After the edema subsided, the catheter tip was tracked and found to be displaced 1.04 ± 0.24/1.43 ± 0.17 cm in the flexion and straight position of the catheter tip to the heart direction in the first week.

Correlation between weight gain and length growth and PICC catheter tip displacement in flexion and straight positions

Using the Spearman rank correlation analysis, different positions had different correlations between the distance of catheter tip displacement and weight gain. The correlation coefficient in the flexion position was $r_s = 0.681$, with a P-value of < 0.05, and $r_s = 0.661$, with a P-value of <0.05 in the straight position, indicating a significant correlation between the two positions as shown in Figures 4A, B. The correlation between the distance of catheter tip displacement and length growth was also different, with $r_s = 0.629$, a P-value of <0.05 in the flexion position and $r_s = 0.617$, a P-value of <0.05 in the straight position, indicating a significant correlation between the two positions as shown in Figures 4C, D. This suggests that the correlation between the distance of catheter tip displacement and weight gain is higher, especially in the flexion position.

Discussion

Premature infant PICC tip displacement

Due to the catheter displacement being highly likely to occur due to natural growth, and the rate of PICC ectopia can be as high as 35% due to factors such as blood flow dynamics and positional changes (20). We found that 100% of premature infants' catheter tips were affected by positional changes in veins with changes in body position and blood flow. After 1 week of placement, we found that the tips of 134 (66.33%)/153 (75.74%) cases are closer to the heart than at placement. This is consistent with Srinivasan's finding that 32.6% of PICC catheters move toward the heart 24 h after placement (21). With the rapid increase in weight and body length, the catheter tip not only did not move away from the heart but also moved closer to the heart. This may be due to catheter bending or folding during placement, followed by flushing with blood flowing toward the heart, resulting in catheter movement toward the heart. Therefore, even after the initial catheter placement is

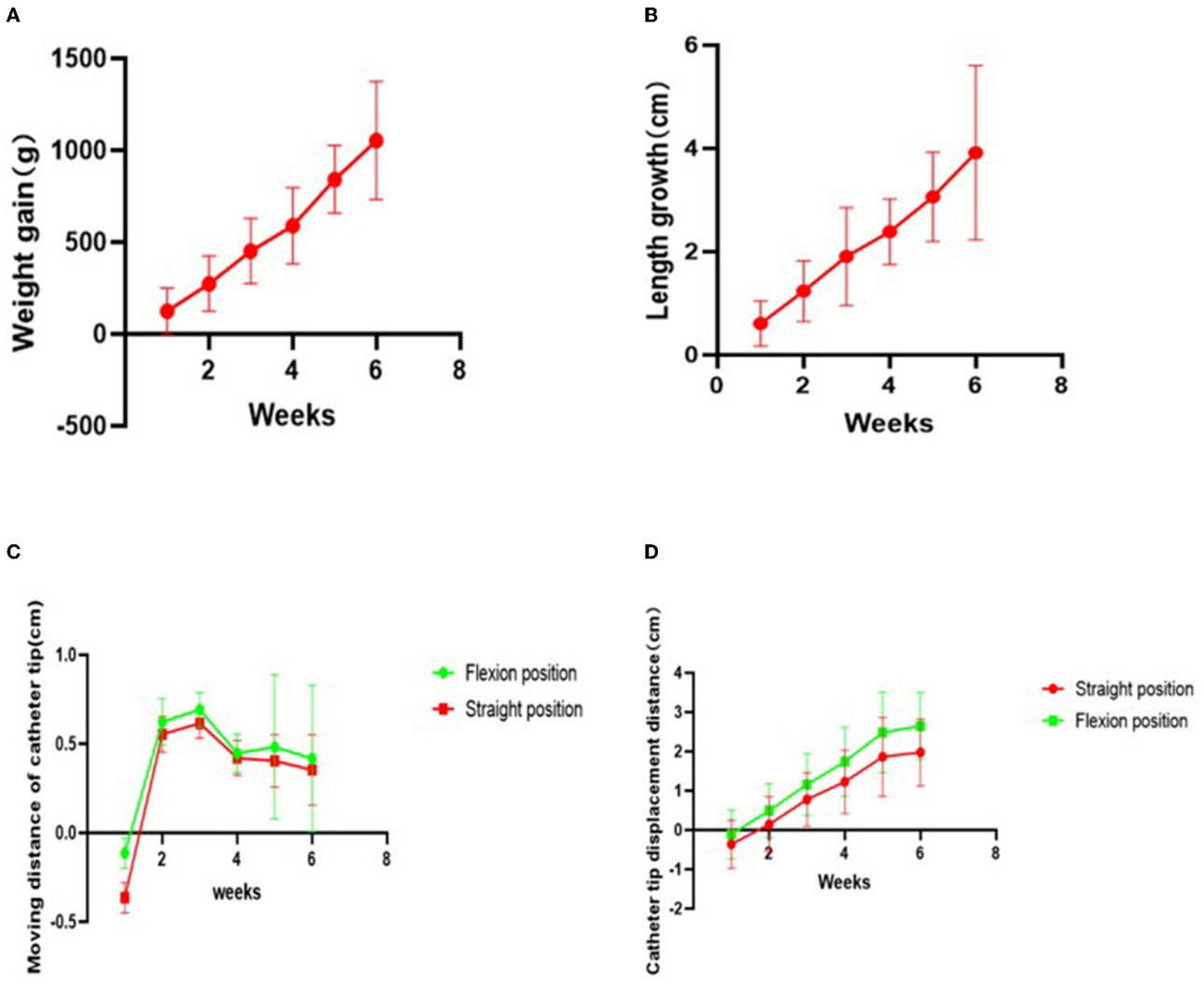

FIGURE 3
(A) Weight gain; **(B)** length growth; **(C)** tip displacement distance of weekly in flexion position and straight position; **(D)** Tip displacement distance in flexion position and straight position.

in the ideal position, there is still a high possibility of catheter tip displacement into the heart cavity. Studies have shown that the incidence of PICC-related arrhythmias is 1%, which can lead to the death of children; most arrhythmias occur within the first 2 weeks after insertion of the catheter (22). Therefore, it is essential to use US tracking to determine whether catheter withdrawal is needed 1 week after placement. In addition, for edematous infants, the catheter tip was tracked after the edema subsided, and it was found that the tips of the catheter moved toward the heart. The appearance and disappearance of edema can lead to catheter tip placement that is too shallow or too deep and may enter the atrium. Therefore, US should be used to locate the catheter in a timely manner after edema subsides to determine whether catheter withdrawal is needed. If the tip of the catheter enters the heart, the position would be adjusted. To do this, US was used to measure the length of the catheter tip that has entered into the heart. Then, adjust the tip to the entrance of the atrium, and make a record of the adjustment.

The relationship between PICC tip displacement and weight gain/length growth in preterm infants

This study showed that the tip of the catheter moved to different degrees with the increase in weight and length and was significantly correlated with weight gain and length growth (r_s = 0.681/r_s = 0.629), with a higher correlation with weight gain. Therefore, assessing weight gain is a more accurate predictor of catheter displacement. The ideal position of PICC is the upper and lower thirds of the vena cava. The length of the SVC in preterm infants is only 2–3 cm, while that of IVC is 4–5 cm (18). Therefore, the maximum limit of the ideal position is 1 and 1.67 cm for the SVC and IVC. The results of this study showed that by the third week, the catheter had moved 1.27 ± 0.89 cm, and the catheter of the SVC had moved out of the ideal position. By the fifth week, the catheter had moved 2.23 ± 0.95 cm, and the catheter of the IVC had moved out of the ideal position. At

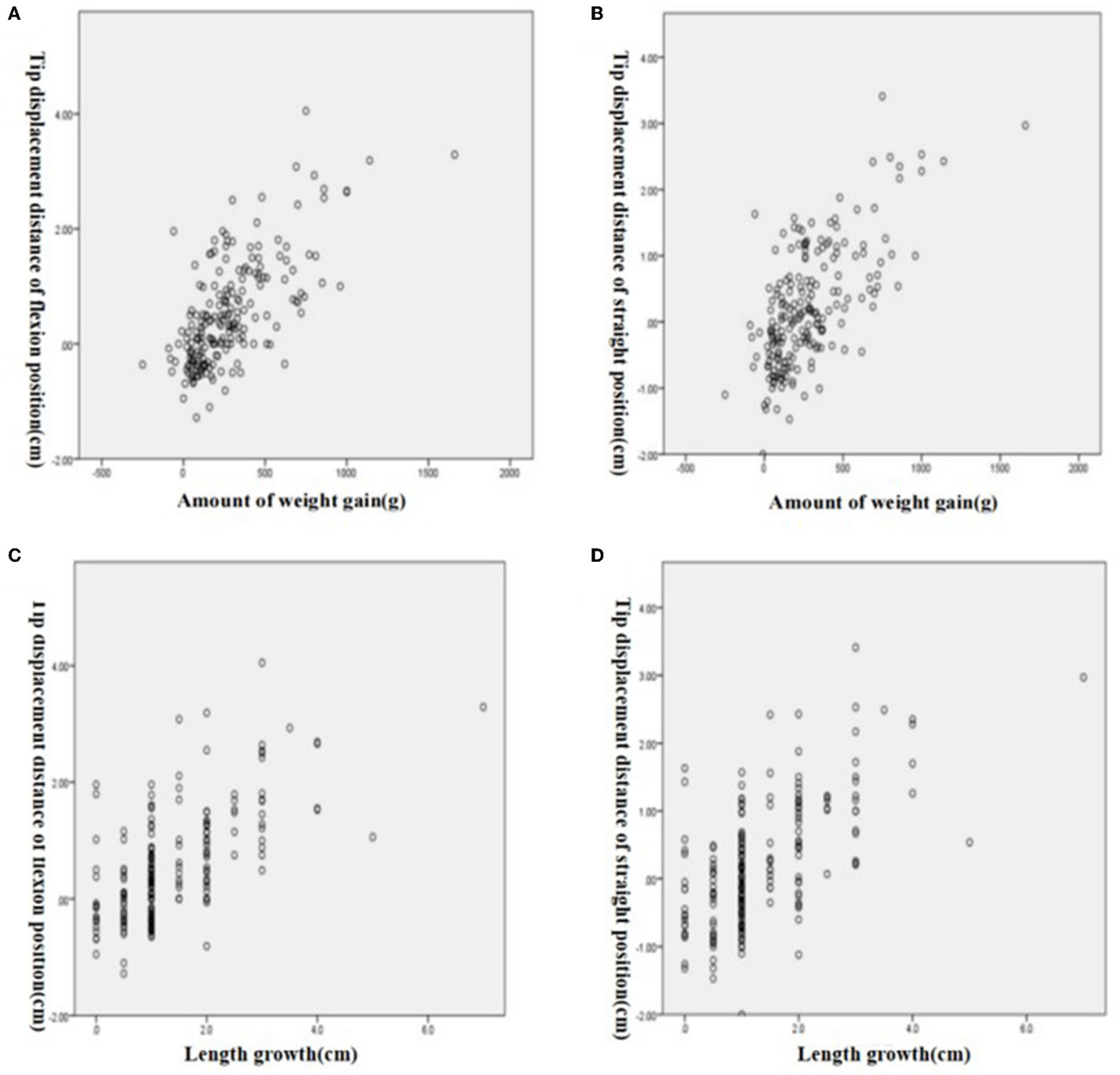

FIGURE 4
Correlation between weight gain and tip displacement distance. **(A)** Flexion position. **(B)** Straight position. Correlation between length grow and tip displacement distance. **(C)** Flexion position. **(D)** Straight position.

this point, the catheter was considered to have reached the stage where it must be repositioned. If the catheter is left in place and fluid is infused, the inadequate blood flow velocity in the non-central vein can result in insufficient drug dilution, and the high osmotic and high concentration liquid can corrode the venous wall, leading to complications (23, 24). Therefore, catheter displacement should be closely monitored starting from the third and fifth weeks after placement. If timely repositioning is not possible, the safety of the catheter can be confirmed by withdrawing blood, flushing the catheter, and reducing the osmotic pressure of the nutrient solution. Tracking the catheter tip position predictively and removing high-risk catheters as early as possible can maximize the prevention of complications (25, 26), which is also consistent with Costa's view that complications of central venous catheters can be prevented (27).

The correlation between PICC tip displacement and weight gain/length growth in flexion/straight positions is different

The correlation between PICC tip displacement in flexion/straight positions and weight gain/length growth differed

in this study. The correlation was higher in the flexion position; therefore, positioning in the flexion position is recommended. Additionally, from the second week onwards, the tip displacement in the flexion position was 0.23 (0–0.97) cm, while in the straight position, it was 0.25 (0–0.98) cm. Thus, the displacement in the flexion position was smaller, consistent with the correlation results, and positioning in the flexion position is also recommended. Tauzin et al. used US to locate the PICC tip and recommended fixing the position to improve accuracy (7). Therefore, the influence of posture should be fully considered, and the positioning posture should be fixed as the flexion position.

Limitations

This study has three limitations that need to be addressed in future research. First, the study is based on a limited sample size of superior vena cava catheters from a single center, with no separate analysis of superior and inferior vena cava catheters. A multi-center study with a larger sample size is needed to overcome this limitation, and separate studies should be conducted on the superior and inferior vena cava catheters. Second, there was no large sample study of edematous patients, future research should focus on a dedicated catheter study for patients with edema. Third, a longitudinal study was not carried out to gain an in-depth understanding of the pros and cons of using US in PICC positioning. Future research should address this by conducting a longitudinal study.

Conclusion

The tip displacement of PICCs in premature infants is significantly correlated with weight gain and length growth. Based on the initial positioning of the catheter, the position should be tracked timely in the first week after placement to determine whether to adjust the catheter position. From the third/fifth week onwards, the frequency of superior/inferior vena cava tracking should be increased. When using US to track the catheter tip, choosing a flexed position is a more reliable method to increase accuracy and consistency.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Children's Hospital of Chongqing Medical University: No. 2022-369. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

XT contributed to the acquisition, analysis, interpretation of the data and acquisition, drafting, and final approval of the manuscript. XZ, JW, and YC provided technical support and conceptual advice. XL conceptualized and designed the study, funding acquisition, project administration and supervision, analysis and interpretation of the data, drafted, and critically reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

Funding

This study was supported by the Chongqing Science and Health Joint Medical Research Project (2023MSXM017).

Conflict of interest

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

The reviewer KM declared a shared parent affiliation with the authors to the handling editor at the time of the review.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 18 July 2023
DOI 10.3389/fmed.2023.1208570

OPEN ACCESS

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RECEIVED 19 April 2023
ACCEPTED 27 June 2023
PUBLISHED 18 July 2023

CITATION
Zhang Z, Deng C-M, Ma J-H, Li S, Lei B and Ding T (2023) Effects of neuraxial labor analgesia on intrapartum maternal fever in full-term pregnancy and its influence on birth outcomes. *Front. Med.* 10:1208570. doi: 10.3389/fmed.2023.1208570

Effects of neuraxial labor analgesia on intrapartum maternal fever in full-term pregnancy and its influence on birth outcomes

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Introduction: This study aimed to explore the relationship between neuraxial labor analgesia and intrapartum fever and to demonstrate the influence of maternal fever on perinatal outcomes within 6 weeks after birth.

Methods: This was a secondary analysis of a multicenter prospective cohort study that enrolled women with single- and full-term cephalic pregnancy in northern China. Intrapartum maternal fever was defined as the highest axillary temperature during labor ≥37.5°C. Data on baseline characteristics, maternal variables, and neonatal outcomes were all collected. The association between neuraxial labor analgesia and intrapartum maternal fever was analyzed with logistic regression models, and the cutoff point was identified by the receiver operating characteristic curve.

Results: Of 577 parturients, 74 (12.8%) developed intrapartum fever. Neuraxial analgesia was associated with an increased risk of maternal intrapartum fever with or without adjusting for confounding factors (adjusted OR = 2.68; 95% CI: 1.32–5.47; $p = 0.007$). Further analysis showed that neuraxial analgesia of <5 h did not increase the risk of intrapartum fever compared with no analgesia (OR = 1.52; 95% CI: 0.63–3.64; $p = 0.35$), and longer neuraxial labor analgesia time (over 5 h) significantly increased the risk of fever (OR = 3.38; 95% CI: 1.63–7.01; $p = 0.001$). Parturients with intrapartum fever suffered more maternal adverse outcomes compared with those without fever ($p < 0.001$). Neonates of women with intrapartum fever had slightly higher rates of composite adverse neonatal outcomes compared with those without fever; however, the difference was not statistically significant ($p = 0.098$).

Conclusion: In women with low-risk pregnancies, a longer time of neuraxial labor analgesia was associated with an increased risk of intrapartum maternal fever. Intrapartum fever was related to adverse maternal outcomes but did not significantly affect neonatal outcomes within 6 weeks after delivery.

KEYWORDS

neuraxial labor analgesia, intrapartum fever, perinatal outcomes, full-term pregnancy, perinatal period

Introduction

Intrapartum maternal fever affects up to one-third of all labors, which might be associated with increased risks of maternal complications, such as intrauterine infection, dystocia, and emergency cesarean delivery (1–3). Moreover, it is also reported to be a potential risk factor for adverse neonatal outcomes, including low Apgar scores, respiratory distress, hypotonia, neonatal brain injury, and even cerebral palsy (4). Multiple obstetric factors, such as intrapartum infection, premature rupture of membranes, Group B streptococcus positive, and prolonged duration of labor, might be involved in the process of maternal fever during labor (5). Moreover, it has been hypothesized that neuraxial analgesia (i.e., epidural-related maternal fever, ERMF) might play a role in intrapartum maternal fever (6, 7).

Neuraxial labor analgesia, including epidural analgesia and combined spinal–epidural analgesia, has been widely used as an effective method to relieve labor pain for decades (8). Many studies have investigated the association between neuraxial labor analgesia and intrapartum maternal fever in the past few years. A randomized clinical trial conducted in Brazil reported that the use of combined spinal and epidural anesthesia was associated with a significant increase in maternal temperature during vaginal delivery (9). The result of a recently published prospective observational study also showed significant associations between epidural labor analgesia and intrapartum maternal fever in all stages of labor (2). However, negative results were also reported (10). Considering the potential adverse effect of intrapartum maternal fever on perinatal outcomes (3), more investigations are still needed to provide further evidence on this issue. The objective of this study was to explore the association between neuraxial labor analgesia and intrapartum maternal fever and to further demonstrate the influence of maternal fever on birth outcomes in low-risk populations of full-term pregnant women.

Materials and methods

Ethics approval

The study protocol was approved by the Clinical Research Ethics Committees in Peking University First Hospital (2014 [714]) and the institutional review boards of other participating centers and was registered with the Chinese Clinical Trial Registry (www.chictr.org.cn; ChiCTR-OCH-14004888) and ClinicalTrials.gov (NCT02823418). Written informed consent was obtained from all participants before enrollment.

Study design and participants

This study was a secondary analysis of multicenter prospective cohort research in northern China, which was conducted from 1 August 2014 to 29 May 2015 in Peking University First Hospital (a tertiary general hospital), Beijing Obstetrics and Gynecology Hospital (a tertiary specialized hospital) and Haidian Maternal and Child Health Hospital (a secondary specialized hospital) in Beijing, China. Detailed inclusion and exclusion criteria of the participants have been described previously (11). In brief, pregnant women were eligible for inclusion if they were nulliparae with full-term single-term cephalic pregnancy (>7 weeks) and prepared for vaginal delivery, who were clinically considered as women with low-risk pregnancies. Patients were excluded if they were younger than 18 years or older than 35 years, had a history of psychiatric disease, had contraindications to neuraxial analgesia, or were admitted to the delivery room outside the daytime working hours (from 5 p.m. to next 8 a.m.).

Procedures

In this study, the decision of whether to receive neuraxial labor analgesia or not was made by the parturients themselves. As a clinical routine, 40 mg methylprednisolone was administered to parturients *via* intravenous infusion or bolus injection before lumber puncture in the participating medical centers to prevent nausea and vomiting. Epidural analgesia or combined spinal–epidural analgesia was performed on women who requested neuraxial analgesia when the cervix was dilated to 1 cm or more. For epidural analgesia, a loading dose of 10 ml mixture (0.1% ropivacaine and 0.5 μg/ml sufentanil) was administered through the epidural catheter. An additional dose of 5 ml mixture was administered 10 min later if the numeric rating scale (NRS, an 11-point scale where 0 = no pain and 10 = the worst pain) pain score remained at least 4. A patient-controlled epidural analgesia (PCEA) pump was connected 30 min later, which was established with a mixture of 0.1% ropivacaine (AstraZeneca AB, Södertälje, Sweden) plus 0.5 μg/ml sufentanil (EuroCept BV, Ankeveen, Netherlands) and programmed to deliver a 6 ml bolus with a 15-min lockout interval. For combined spinal–epidural analgesia, 2 to 3 ml of 0.1% ropivacaine was administered intrathecally. A PCEA pump was connected later, which was established with a mixture of 0.1% ropivacaine and 0.5 μg/ml sufentanil, programmed to deliver a 5 ml bolus with a 15-min lockout interval and a 5 m/h background infusion. Obstetric management during labor, such as oxytocin administration, intramuscular meperidine administration, forceps assistance, and cesarean delivery, were decided by the obstetricians as clinical routine.

Data collection

For all recruited subjects, data on baseline characteristics, maternal variables, and neonatal variables were collected. The detail shows as follows:

(1) Baseline characteristics included sociodemographic information, previous medical history, and obstetrical data of the present pregnancy.

(2) Maternal variables included the use of neuraxial labor analgesia, medications during labor (including oxytocin, meperidine, and antibiotic administration), durations of all stages of labor, body temperature during labor (including baseline temperature, highest temperature, and postpartum temperature), mode of delivery, and estimated blood loss.

(3) Neonatal variables included gender, birthweight, Apgar Scores at 1 and 5 min after delivery, the occurrence of intrauterine fetal distress, assisted ventilation, and admission to the neonatal

ward within 1 day postpartum. We also recorded the mode of infant feeding and other health-related problems through a face-to-face follow-up on the first day after delivery and a telephone interview at 6 weeks postpartum.

The occurrence of intrapartum maternal fever was defined as the highest axillary temperature during labor more than or equal to 37.5°C. Axillary temperature was measured by midwives with mercury thermometers every 2 h or when considered necessary since delivery room admission. Baseline temperature and postpartum temperature were defined as the temperature on admission to the delivery room and 2 h after delivery, respectively.

Statistical analysis

Data were summarized as mean ± standard deviation, number (proportions), or median (interquartile range). The independent *t*-test, Mann–Whitney U-test, and chi-squared ($\chi 2$) test were used to test statistical significance between groups of continuous (normal and non-normal distribution data) and categorical variables, respectively. A logistic regression model was applied to determine the association between neuraxial labor analgesia and intrapartum maternal fever. Variables that showed significant differences between the two groups ($p < 0.05$) as well as variables that might potentially affect intrapartum temperature based on clinical grounds were adjusted in the above model. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated. The receiver operating characteristic (ROC) curve was used to identify the cutoff point of the association between the duration time of neuraxial labor analgesia and intrapartum fever. Exploratory analyses were performed to assess differences in the primary outcome in subgroups. Treatment-by-covariate interactions were assessed separately for each subgroup factor using logistic regression. Two-tailed *p*-values of <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM SPSS Inc., Chicago, IL, USA).

Results

Patient recruitment and baseline characteristics

In total, 1,420 parturients were screened; of these, 793 were eligible, 599 were enrolled and 577 completed the study (Figure 1). There were no significant differences in baseline information between enrolled and not enrolled patients (Supplementary Table S1). All 577 parturients were included in this study with an age range between 22 and 34 years. Of these, 74 (12.8%) developed intrapartum fever (cases), and 503 (87.2%) did not develop a fever (controls). The baseline variables of all parturients are shown in Table 1. There were no significant differences between the two groups with regard to sociodemographic characteristics, medical comorbidity, and obstetrical data. The incidence of fever was higher among people without gynecological diseases ($p = 0.035$).

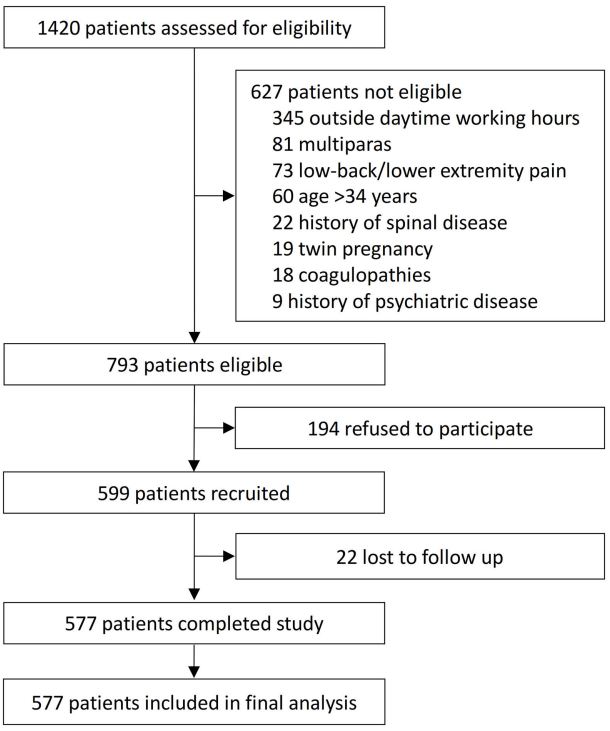

FIGURE 1
Flowchart of the study.

Labor and delivery characteristics

Parturients with intrapartum fever had higher rates of neuraxial labor analgesia ($p = 0.003$) and intrapartum antibiotic administration ($p < 0.001$), had longer durations of the first and second labor stages ($p < 0.001$ and $p = 0.011$, respectively), developed higher postpartum temperature ($p = 0.001$), and underwent more lateral episiotomy ($p = 0.011$). The rates of instrumental and cesarean deliveries were significantly higher in women who suffered from intrapartum fever ($p < 0.001$). Moreover, patients with fever had more blood loss during labor ($p = 0.029$) and longer lengths of postpartum hospital stay ($p = 0.004$) compared with those without fever. Overall, the prevalence of composite adverse maternal outcomes was almost 2-fold in the fever group (59.5% vs. 35.0%, $p < 0.001$). In addition, the length of postpartum hospital stay was significantly longer in parturients with intrapartum fever than those without ($p = 0.004$). All the detailed information on perinatal maternal variables is shown in Table 2.

Association between neuraxial labor analgesia and intrapartum maternal fever

Based on logistic regression models, a univariate analysis was used to demonstrate the association between neuraxial labor analgesia and intrapartum maternal fever; six potential confounders (i.e., gynecological diseases before pregnancy,

TABLE 1 Baseline characteristics of parturients with and without fever.

	All parturients ($n = 577$)	Fever ($n = 74$)	No fever ($n = 503$)	p-value
Maternal age (year)	29.9±2.5	29.9 ± 2.3	30.0 ± 2.6	.764
Body mass index before childbirth (kg/m^2)				.298
<30	484 (83.9%)	59 (79.7%)	425 (84.5%)	
≥30	93 (16.1%)	15 (20.3%)	78 (15.5%)	
Han nationality[a]	545 (94.5%)	67 (90.5%)	478 (95.0%)	.192
Medical comorbidity[c]	42 (7.3%)	4 (5.4%)	38 (7.6%)	.506
Gynecological diseases[d]	54 (9.4%)	2 (2.7%)	52 (10.3%)	.035
Surgery history	83 (14.4%)	8 (10.8%)	75 (14.9%)	.348
Adverse pregnancy history[e]	188 (32.6%)	21 (28.4%)	167 (33.2%)	.409
Dysmenorrhea	317 (54.9%)	38 (51.4%)	279 (55.5%)	.506
Obstetric complications				
Diabetes[f]	130 (22.5%)	14 (18.9%)	116 (23.1%)	.426
Hypertensive disorders[g]	34 (5.9%)	3 (4.1%)	31 (6.2%)	.472
Hypothyroidism	43 (7.5%)	3 (4.1%)	40 (8.0%)	.233
Anemia[h]	60 (10.4%)	7 (9.5%)	53 (10.5%)	.777
Prepartum hemoglobin (g/l)	12.4±1.2	12.4±1.3	12.4±1.1	.682
PROM[i]	108 (18.7%)	18 (24.3%)	90 (17.9%)	.185
Duration of gestation (day)	277±7	278±7	277±7	.509
Labor description				.320
Spontaneous	392 (67.9%)	54 (73.0%)	338 (67.2%)	
Induction	185 (32.1%)	20 (27.0%)	165 (32.8%)	

Data are presented as mean ± SD, number (%).
[a]Other nationalities included Manchu, Mongol, Huis, Koreans and Yi.
[b]Included Buddhism, Islam and Christianity.
[c]Included asthma, arrhythmia, latent glomerulonephritis, abnormal liver function and positive hepatitis B surface antigen.
[d]Included hysteromyoma, ovarian cysts, dysfunctional uterine bleeding, polycystic ovary syndrome and pelvic inflammatory disease.
[e]Included history of miscarriages, induced abortion, and midtrimester induction of labor due to fetal anomalies.
[f]Included both impaired glucose tolerance and gestational diabetes mellitus (GDM) diagnosed by the obstetrics.
[g]Included preeclampsia-eclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia and gestational hypertension according to the American College of Obstetrics and Gynecology (ACOG) guideline.
[h]The concentration of hemoglobin lower than 110 g/l.
[i]Premature rupture of membranes.

obstetric complications, premature rupture of membranes, baseline temperature, intrapartum meperidine administration, and birthweight of newborns) were adjusted in the adjusted logistic regression model. The result showed that intrapartum maternal fever was associated with neuraxial labor analgesia with or without adjustment for potential confounders (adjusted OR = 2.68; 95% CI: 1.32–5.47; $p = 0.007$) (Table 3).

ROC curve was applied to investigate the cutoff points of the association between the duration time of neuraxial labor analgesia and intrapartum fever. The result suggested that 5 h was the cutoff point (Supplementary Figure S1). As the duration of neuraxial labor analgesia increased, the risk of intrapartum maternal fever increased. Compared with those parturients without neuraxial labor analgesia, the risk of intrapartum maternal fever in parturients with shorter neuraxial labor analgesia time (<5 h) and parturients with longer neuraxial labor analgesia time (over 5 h) increased by 52% (OR = 1.52; 95% CI: 0.63–3.64; $p = 0.35$) and 238.0% (OR = 3.38; 95% CI: 1.63–7.01; $p = 0.001$), respectively. All of the above results are shown in Table 3.

Subgroup analyses of factors related to intrapartum maternal fever were performed to evaluate the consistency of the effect of neuraxial labor analgesia on intrapartum maternal fever (Figure 2). The results of the subgroup analysis did not show the heterogeneity of risk of incident intrapartum maternal fever from neuraxial labor analgesia besides the subgroup of parturients whether spontaneous delivery or not.

Neonatal outcomes

For neonatal information, the birthweight of a newborn was significantly heavier in parturients with intrapartum fever ($p = 0.016$) (Table 4). There were no significant differences in rates of fetal distress, low 1 and 5 min Apgar scores, ventilation support,

TABLE 2 Labor and delivery characteristics of parturients with and without fever.

	All parturients ($n = 577$)	Fever ($n = 74$)	No fever ($n = 503$)	p-value
Neuraxial analgesia	417 (72.3%)	64 (86.5%)	353 (70.2%)	.003
Epidural	272 (65.2%)	42 (65.6%)	230 (65.2%)	
Combined spinal-epidural	145 (34.8%)	22 (34.4%)	123 (34.8%)	
Duration of labor				
First stage (min)[a]	550 (360–780)	730 (510–998)	540 (340–750)	**<.001**
Second stage (min)[a]	46 (28–79)	67 (39-103)	45 (27–75)	**.011**
Third stage (min)[a]	7 (5–10)	6 (5–10)	7 (5–10)	.967
Intrapartum oxytocin administration	384 (66.6%)	46 (62.2%)	338 (67.2%)	.391
Intrapartum meperidine administration[b]	14 (2.4%)	1 (1.4%)	13 (2.6%)	.811
Intrapartum antibiotic administration	281 (48.7%)	66 (89.2%)	215 (42.7%)	**<.001**
Artificial rupture of membranes	215 (37.3%)	25 (33.8%)	190 (37.8%)	.507
Baseline temperature[c]	36.7±0.3	36.7±0.3	36.7±0.3	**.216**
Maximum recorded temperature in labor	37.0±0.4	37.7±0.3	37.0±0.3	**<.001**
Postpartum temperature[d]	37.0±0.3	37.1±0.3	37.0±0.3	**.001**
Mode of delivery				**.001**
Spontaneous delivery	382 (66.2%)	35 (47.3%)	347 (69%)	
Cesarean delivery	137 (23.7%)	27 (36.5%)	110 (21.9%)	
instrumental delivery	58 (10.1%)	12 (16.2%)	46 (9.1%)	
Lateral episiotomy[e]	186 (42.3%)	28 (59.6%)	158 (40.2%)	.011
Estimated blood loss (ml)	200 (200–300)	300 (200–400)	200 (150–300)	.029
Postpartum hemorrhage[f]	39 (6.8%)	7 (9.5%)	32 (6.4%)	.322
Exclusive breast-feeding 1-day postpartum	465 (80.6%)	60 (81.1%)	405 (80.5%)	.909
Composite adverse maternal outcome[g]	220 (38.1%)	44 (59.5%)	176 (35.0%)	**<.001**
Length of postpartum hospital stay (days)	2 (2–4)	3 (2–4)	2 (2–4)	**.004**

Data are presented as mean ± SD, number (%) or median (interquartile range).
[a]Excluded 137 patients (27 with intrapartum maternal fever and 110 without) who underwent emergency cesarean delivery during the first stage of labor.
[b]Meperidine 100 mg was administered intramuscularly according to the prescription of obstetricians.
[c]Temperature at the beginning of labor.
[d]Temperature 2 h postpartum.
[e]Results of parturients who gave spontaneous or forceps delivery.
[f]Defined as blood loss of more than 500 mL after vaginal delivery or 1,000 mL after cesarean section within 24 h following delivery.
[g]Defined as any of the followings: instrumental delivery, cesarean delivery or post-partum hemorrhage.
P values in bold indicates those <0.05.

neonatal ward admission, neonatal infection, and readmission to hospital within 6 weeks after birth between the two groups. In total, the proportion of composite adverse neonatal outcomes was slightly higher in infants with febrile mothers, although the difference was not statistically significant (15 [20.3%] vs. 66 [13.1%], $p = 0.098$) (Table 4).

Discussion

Our study demonstrated that, among young nulliparous women with single and full-term cephalic pregnancy, the use of neuraxial analgesia during labor, especially duration of neuraxial analgesia of more than 5 h, was associated with an increased risk of intrapartum fever. Moreover, intrapartum fever was related to maternal adverse outcomes but did not significantly affect the short-term outcomes of neonates.

Maternal intrapartum fever, also called intrapartum hyperthermia, is commonly defined as a temperature more than 37.5°C or 38°C during labor in previous studies (3). The incidence of intrapartum hyperthermia has varied strikingly from 1 to 37% due to different populations and diagnostic criteria (12, 13). Although 38°C was used mostly in previous studies as the definition of maternal fever, we still used 37.5°C as the threshold of clinical fever because the association between low-grade fever (≥37.5°C) and adverse neonatal outcomes has been previously reported (13, 14). It is worth mentioning that the incidence of maternal fever in our study was lower than in other works of literature among Chinese women (15). It is possible that the relatively low concentration of

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TABLE 3 Associations between neuraxial labor analgesia and intrapartum maternal fever.

	Fever/total (n/N)	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI) [a]	*p*-value
Neuraxial labor analgesia					
No	10/160	Reference	Reference	Reference	Reference
Yes	64/417	2.72 (1.36–5.44)	**.005**	2.68 (1.32–5.47)	**.007**
Duration of neuraxial labor analgesia					
No neuraxial analgesia	10/160	Reference	Reference	Reference	Reference
<5 h	13/149	1.43 (0.61–3.38)	.41	1.52 (0.63–3.64)	.35
≥5 h	51/268	3.53 (1.74–7.16)	**<.001**	3.38 (1.63-7.01)	**.001**

OR, odds ratio; CI, confidence interval.

[a]Adjusted for gynecological diseases before pregnancy, obstetric complications, PROM, baseline temperature, intrapartum meperidine administration and birthweight of newborns.

P values in bold indicates those <0.05.

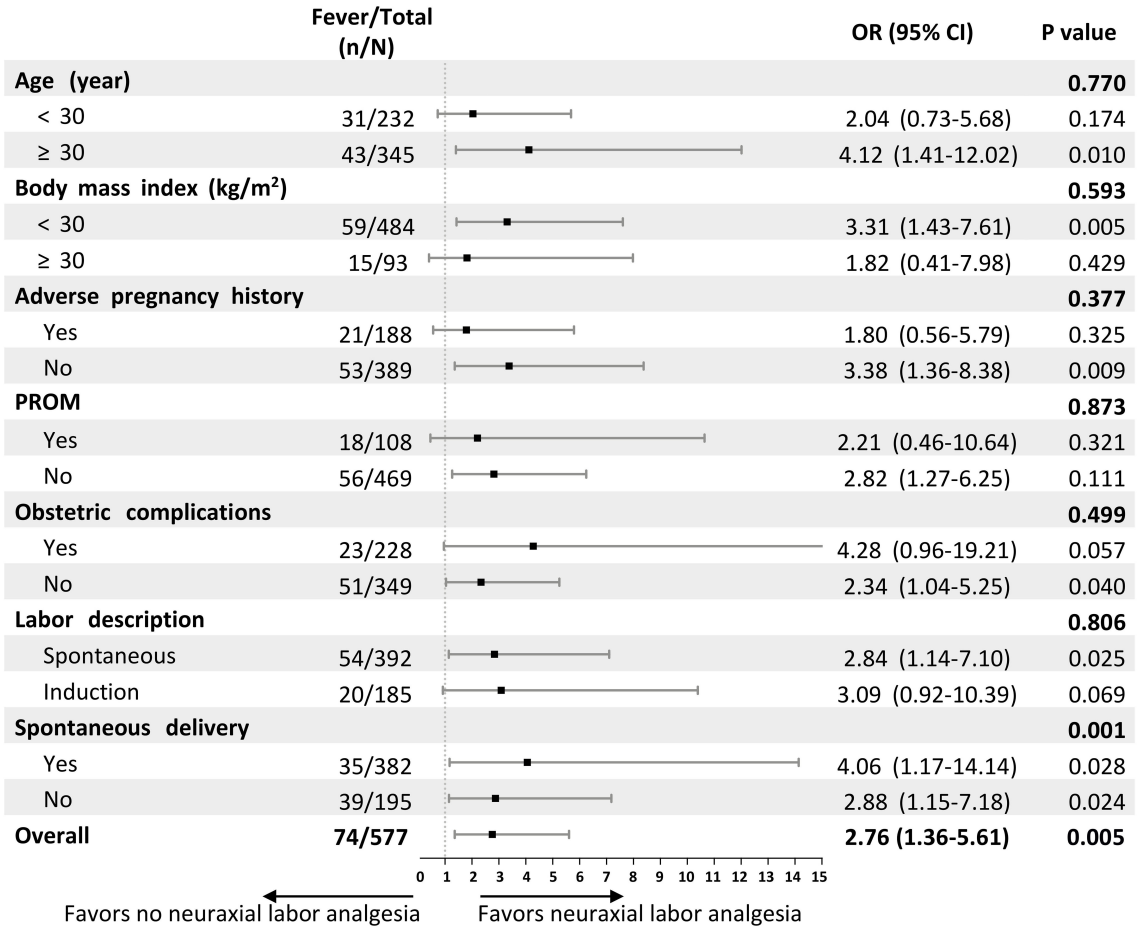

FIGURE 2
Forest plot assessing interactions between subgroups and the associations between neuraxial labor analgesia and intrapartum maternal fever. ORs and interim-adjusted 95% CIs are shown. The estimated overall OR was derived from a logistic regression model adjusted for the confounder variable in this study including gynecological diseases before pregnancy, obstetric complications, PROM, baseline temperature, and intrapartum meperidine administration. For the subgroup analyses, we assessed the treatment-by-covariate interaction on the association between neuraxial labor analgesia and intrapartum maternal fever, adjusting for the same variables. OR, Odds ratio; CI, confidence interval; PROM, premature rupture of membrane.

neuroblockade we used for neuraxial analgesia and also different obstetric practices, such as methylprednisolone, meperidine, and antibiotic administrations, might be involved in the lower incidence of intrapartum fever. Goetzl et al. reported that the administration of high-dose corticosteroids during labor resulted in a 90% reduction of maternal fever in parturients with epidural analgesia, suggesting that steroids might decrease the risk of epidural intrapartum fever (16). Thus, we speculated that intrapartum steroid treatment of parturients in this study might be associated with the reduction of intrapartum fever to some extent, and the underlying relationship needs to be further explored.

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TABLE 4 Neonatal variables of parturients with and without fever.

	All parturients ($n = 577$)	Fever ($n = 74$)	No fever ($n = 503$)	p-value
Male	317 (54.9%)	46 (62.2%)	271 (53.9%)	.181
Birthweight (g)	3419 ± 396	3530 ± 417	3402 ± 391	**.016**
Fetal distress[a]	83 (14.4%)	15 (20.3%)	68 (13.5%)	.122
1-min Apgar score	10 (10)	10 (10)	10 (10)	.407
1-min Apgar score <7	11 (1.9%)	0 (0%)	11 (2.2%)	.199
5-min Apgar score	10 (8–10)	10 (10)	10 (10)	.466
5-min Apgar score <7	4 (0.7%)	0 (0%)	4 (0.8%)	.984
Immediate need for assisted ventilation	47 (8.1%)	8 (10.8%)	39 (7.8%)	.369
Neonatal ward admission within 1-day after birth[b]	56 (9.7%)	10 (13.5%)	46 (9.1%)	.236
Neonatal infection	27 (4.7%)	6 (8.1%)	21 (4.2%)	.135
Hemodynamic instability	0 (0%)	0 (0%)	0 (0%)	.999
Seizures	0 (0%)	0 (0%)	0 (0%)	.999
Composite adverse neonatal outcome[c]	81 (14.0)	15 (20.3%)	66 (13.1%)	.098
6-Week postpartum				
Exclusive breast-feeding	397 (68.8%)	49 (66.2%)	348 (69.2%)	.607
Baby readmitted to hospital	9 (1.6%)	1 (1.4%)	8 (1.6%)	.999

Data are presented as mean ± SD, number (%) or median (interquartile range).
[a]Fetal distress was considered when category III tracing or repeated category II tracing was presented by electronic fetal monitoring during labor.
[b]Newborns were admitted to neonatal ward for further monitoring and/or treatment which were considered necessary by the pediatricians.
[c]Defined as any of followings: assisted ventilation, 1-min Apgar score <7, 5-min Apgar score <7, or neonatal ward admission within 1-day after birth.
P values in bold indicates those <0.05.

Our results showed that in women with low-risk pregnancies, neuraxial analgesia was significantly associated with an increased incidence of mild maternal fever, which was in line with previous studies (2, 15). In fact, the etiology of epidural-related maternal fever remains elusive and the sterile inflammation process was considered to be a possible mechanism (17). A randomized controlled trial with prophylactic antibiotics before epidural analgesia showed no difference in the rate of maternal fever between groups, supporting the non-infectious inflammation hypothesis of epidural fever (18). A study reported that acetaminophen prophylaxis did not prevent maternal hyperthermia or fever secondary to epidural analgesia, also suggesting a non-infectious inflammatory process (19). In addition, local anesthetics used in epidural were also reported to trigger non-infectious inflammation pathways *via* immunomodulation and cell injury (20, 21). Overall, non-infectious inflammation might be involved in the ERMF and the exact mechanisms need to be further clarified.

Our study also found that the risk of intrapartum fever increased significantly in parturients with neuraxial labor analgesia time of more than 5 h. A recently published observational study also reported weak time and dose-dependent correlations between PCEA and intrapartum fever, and an analgesic time over 6.3 h increased the risk of maternal intrapartum fever (22). However, inconsistent results also existed. Wang et al. found that although the duration of analgesia in the early PCEA group was significantly longer than that in the late PCEA group, the average maternal temperature and the incidence of fever were not significantly different, suggesting that the duration of epidural analgesia might not be an important determinant of epidural-related fever (23, 24). Further research is still needed to further clarify the time and dose-dependent correlations.

Numerous studies have demonstrated that intrapartum hyperthermia was associated with a series of adverse obstetric outcomes in mothers. Dior et al. found that maternal fever was significantly associated with adverse maternal outcomes, including postpartum hemorrhage, labor dystocia, and cesarean section (25). The study of Lange et al. also reported that parturients who developed fever were more likely to have prolonged durations of labor and required cesarean delivery (26). Results of this study showed that febrile parturients underwent more cesarean section or instrumental delivery, suffered more postpartum blood loss, and had a longer length of postpartum hospital stay, further demonstrating that intrapartum fever was associated with adverse maternal outcomes. It is possible that the elevation of body temperature is an early indicator of potential obstetric abnormalities, and early attention and interventions should be taken to decrease the potential adverse events followed by intrapartum fever.

In this study, we evaluated neonatal outcomes of term infants and found no significant association between intrapartum maternal fever and adverse neonatal outcomes within 6 weeks after birth. However, the effects of intrapartum fever on newborns remain controversial and conflicting evidence existed in this field (13, 27, 28). A retrospective cohort study reported that

adverse neonatal outcomes including assisted ventilation, Apgar scores <7, and NICU admission increased infants' exposure to maternal hyperthermia (1). A recently published meta-analysis including 41 studies suggested that maternal intrapartum fever of any cause was associated with neonatal brain injury (3). It is possible that the definition of maternal fever in this study was over 37.5°C, less than that of some other studies, resulting in fewer influences on intrauterine fetuses. In addition, the inclusion of low-risk parturients, who were young and with single-term pregnancies in our study, might lead to relatively low-risk infants. Moreover, obstetric and pediatric management in participating medical centers might influence the birth outcomes to some extent. Further studies with larger sample sizes and longer time of follow-ups are still needed to explore the long-term effect of maternal fever on neonatal outcomes.

There are strengths and also some limitations in this analysis. Intrapartum maternal fever is a prevalent occurrence, affecting approximately one-third of all labors, which is associated with an increased risk of maternal complications and has the potential to impact neonatal outcomes. However, the impact of epidural-related maternal fever on maternal and neonatal outcomes within 6 weeks following childbirth remains inconclusive. Our data contribute additional evidence on this issue, particularly focusing on primiparous women with low-risk and term pregnancies in the Asia population. Furthermore, many previous studies investigating perinatal outcomes of epidural analgesia were conducted without an opioid-free control group, which may have introduced interference when comparing results to those involving opioids. In this study, the use of opioids was relatively conservative, aligning with local clinical routine, and the proportion of administration of opioid drugs in the control group was very low. Therefore, our study offers insights into the effects of neuraxial analgesia, to some extent, without the confounding influence of opioids. Meanwhile, the study also has some limitations. First, the maternal temperature during labor was not continuously monitored, which might lead to a potential misdiagnose of intrapartum fever. Second, as an observational study, it is inevitable that unidentified confounding factors might influence the results. Although a multivariate regression model was adopted to adjust for potential confounders of maternal fever, we cannot neglect the possible interference of perinatal factors. Third, as routine screening for inflammatory parameters and placental pathology was not performed during hospitalization, data collection before and/or after the neuraxial procedures was not feasible. Fourth, the neonatal outcomes may not be comprehensive enough. Future studies should consider adding more neonatal parameters, such as fetal acidosis, antibiotic treatment, and admission to the neonatal intensive care unit in the neonatal outcome assessment. Finally, as a secondary analysis of a multicenter research database, the sample size might be not enough to establish a causal relationship.

Despite limitations, we found that in nulliparae with single- and full-term cephalic pregnancy, a longer time of neuraxial labor analgesia was associated with an increased risk of intrapartum maternal fever. Intrapartum fever was related to adverse maternal outcomes but did not significantly affect the neonatal outcomes of low-risk mothers within 6 weeks after delivery.

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 Clinical Research Ethics Committees in Peking University First Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZZ and C-MD contributed to the study design, data collection, and manuscript writing. J-HM contributed to the study design, data analysis, and manuscript writing. SL and BL helped to recruit patients and collected the clinical data. TD contributed to the study design, manuscript writing, and revision. All authors read and approved the final manuscript.

Funding

This study was supported by the Capital Characteristic Clinic Project (Z151100004015160, TD) and National High Level Hospital Clinical Research Funding (Multi-center Clinical Research Project of Peking University First Hospital) (2022CR56, TD). The study sponsors had no role in the study design, collection, analysis, interpretation of data, and writing of the report.

Acknowledgments

The authors thank Drs. Si-Chao Xu and Shu-Ting He (MD, Department of Anesthesiology and Critical Care Medicine, Peking University First Hospital, Beijing, China), Ming-Jun Xu (MD, Department of Anesthesiology, Beijing Obstetrics, and Gynecology Hospital, Capital Medical University, Beijing, China), and Lei Wang (MD, Department of Anesthesiology, Haidian Maternal & Child Health Hospital, Beijing, China) for their help in collecting data.

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.2023.1208570/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Receiver operating characteristic curve of the duration time of neuraxial labor analgesia and intrapartum fever (sensitivity = 0.813, specificity = 0.382, the area under the ROC = 0.577, and 95%CI: 0.504–0.650).

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frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 27 July 2023
DOI 10.3389/fmed.2023.1200314

OPEN ACCESS

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RECEIVED 04 April 2023
ACCEPTED 18 July 2023
PUBLISHED 27 July 2023

CITATION
Huang J, Zheng H, Zhu X, Zhang K and Ping X (2023) The efficacy and safety of haloperidol for the treatment of delirium in critically ill patients: a systematic review and meta-analysis of randomized controlled trials. *Front. Med.* 10:1200314.
doi: 10.3389/fmed.2023.1200314

The efficacy and safety of haloperidol for the treatment of delirium in critically ill patients: a systematic review and meta-analysis of randomized controlled trials

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Purpose: Delirium is common during critical illness and is associated with poor outcomes. Therefore, we conducted this meta-analysis to investigate the efficacy and safety of haloperidol for the treatment of delirium in critically ill patients.

Methods: Randomized controlled trials enrolling critically ill adult patients to compare haloperidol with placebo were searched from inception through to February 20th, 2023. The primary outcome were delirium-free days and overall mortality, secondary outcomes were length of intensive care unit stay, length of hospital stay, and adverse events.

Results: Nine trials were included in our meta-analysis, with a total of 3,916 critically ill patients. Overall, the pooled analyses showed no significant difference between critically ill patients treated with haloperidol and placebo for the delirium-free days (MD −0.01, 95%CI −0.36 to 0.34, $p = 0.95$, $I^2 = 30\%$), overall mortality (OR 0.89, 95%CI 0.76 to 1.04, $p = 0.14$, $I^2 = 0\%$), length of intensive care unit stay (MD −0.06, 95%CI −0.16 to 0.03, $p = 0.19$, $I^2 = 0\%$), length of hospital stay (MD −0.06, 95%CI −0.61 to 0.49, $p = 0.83$, $I^2 = 0\%$), and adverse events (OR 0.90, 95%CI 0.60 to 1.37, $p = 0.63$, $I^2 = 0\%$).

Conclusion: Among critically ill patients, the use of haloperidol as compared to placebo has no significant effect on delirium-free days, overall mortality, length of intensive care unit and/or hospital stay. Moreover, the use of haloperidol did not increase the risk of adverse events.

KEYWORDS

haloperidol, delirium, critically ill adult patients, ICU, meta-analysis

Introduction

Delirium, an acute disturbance in attention and awareness, is a common condition affecting about a third of critically ill patients (1, 2). It is a powerful predictor of prolonged mechanical ventilation, extended length of intensive care unit (ICU) and hospital stay, elevated short-term mortality and worse long-term outcomes (2–5). Notably, critically ill patients treated in ICU have a lot of risk factors associated with ICU therapeutic interventions, including receiving MV, inappropriate sedation and physical restraint (6–8).

The present guidelines advised the multicomponent, non-pharmacological interventions for treatment and prevention of delirium in critically ill patients, including early mobilization, avoidance of oversedation and excess benzodiazepines, family participation, reorientation, cognitive and sensory stimulation (1, 9). Previous studies suggested that these therapy strategies were feasible and safe, had an important role in both treatment and prevention of delirium (10, 11). However, the pharmacologic management of delirium in the ICU remains a subject of debate (12). Current clinical guidelines did not advocate for any particular pharmacotherapeutic intervention in the management of delirium (13, 14). Haloperidol, a highly effective antipsychotic compound, is still the most common treatment for delirium in ICU. An international cohort study investigated 1,260 patients from 13 countries, showed that nearly half of the patients with delirium received haloperidol during the ICU stay (15). Although the clinical benefits of haloperidol for the management of delirium have been proved in non-critically ill patients (14), the use of haloperidol is not supported by existing guidelines because clinical evidence of its effect is limited (1, 16). Furthermore, it has not been approved by the US Food and Drug Administration for the management of delirium as well.

Recently, Andersen-Ranberg and coworkers completed the latest randomized controlled trials (RCTs) to investigate the effect of haloperidol for the treatment of critically ill patients with delirium in ICU (17). The findings suggest that the patients treated with haloperidol did not have a longer survival time at 90 days, as well as the delirium-free and ventilation-free days. To date, both RCTs and meta-analyses have not resolved whether use of haloperidol in critically ill patients had clearly beneficial effects on delirium outcomes. Therefore, we tend to accomplish this updated mate-analysis to further evaluate the effect of haloperidol for the treatment of delirium in critically ill patients.

Methods

This meta-analysis was conducted in strict accordance with the updated PRISMA statement (18) (Supplementary material 1). The study protocol was preregistered on Open Science Framework.[1] To identify relevant RCTs meeting our eligibility criteria, we conducted a comprehensive literature search of PubMed, Embase, Scopus, and Cochrane Library from inception up to February 20th, 2023. The literature search was conducted with keywords containing "haloperidol," "delirium," "critically ill," "ICU," and "randomized." The full search strategies are given in Supplementary material 2.

1 https://osf.io/jwk65

Eligibility criteria

Studies fulfilled the inclusion criteria were included:

1. Type of study: randomized trials;
2. Population: critically ill adult patients (at least 18 years old). If population was unspecified, we deemed the patient population met one of the following criteria to be critically ill patients: the patients enrolled and study concluded in any types of ICU; the patients received therapies which is normally delivered in ICU (e.g., invasive mechanical ventilation); the patients' illness required intensive care; the patients had been transferred into ICU during study period;
3. Intervention: the use of haloperidol through all routes of administration, without dose limits;
4. Comparison: the use of placebo, or no any type of intervention;
5. Outcomes: the primary outcome of interest were delirium-free days (delirium was assessed by researchers or clinicians from included trials) and overall mortality (including hospital, ICU, 28 day mortality or other. If several mortality rates were reported in one study, we used the mortality at hospital charge in our analysis). Secondary outcomes were length of intensive care unit stay, length of hospital stay, and adverse events.

Data extraction and quality assessment

Relevant studies were retrieved and their characteristics (including author, years of publication, study design, sample size, characteristics of population, intervention duration and dose, delirium assessment and incidence rate) were extracted by two authors (JH and HZ) independently.

The methodological quality of including studies was independently conducted by two authors (JH and XZ), utilizing the Cochrane risk of bias tool (19). Any discrepancies in the evaluations were resolved through a consensus-based approach, involving a third adjudicator (XP).

Statistical synthesis and analysis

The odds ratios (OR) with 95% confidence intervals (CI) were calculated using the Mantel–Haenszel method for dichotomous outcomes, and mean difference (MD) with 95% CI were calculated using the inverse variance method for continuous outcomes. The heterogeneity between studies was assessed by the Higgins inconsistency (I^2) statistics (20), substantial heterogeneity was identified when I^2 value > 30%. If no significant heterogeneity existed, we adopted a fixed-effects model to perform the analysis, otherwise a random-effects model was used. In addition, publication bias was evaluated through the use of the funnel plot and Egger's regression test (21).

To identify potential sources of heterogeneity, a predefined subgroup analysis stratified by population (patients with delirium or without delirium). Furthermore, a sensitivity analysis was performed through the consecutive exclusion of each study to investigate the effect of individual studies.

Results

Study identification and characteristics

An initial search of the literature resulted in the identification of 421 articles, of which 247 were deemed duplicates and excluded. Through the screening of abstracts, an additional 136 studies were excluded. Following a thorough evaluation of the full text, 29 additional studies were excluded for various reasons (Supplementary material 3 recorded the list of excluded studies). Ultimately, nine RCTs (17, 22–29) met the inclusion criteria and were included in this study, The literature screening flowchart is shown in Figure 1.

The characteristics of the included studies are presented in Table 1. A total of 3,916 patients were analyzed, with 1980 patients receiving haloperidol and 1936 patients receiving placebo during the respective study periods. Different screening tools were used to evaluate the incidence of delirium, including Confusion Assessment Method for Intensive Care Unit (CAM-ICU) (30), Intensive Care Delirium Screening Checklist (ICDSC) (31), Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. The number of patients in each study ranged from a minimum of 68 up to 1,439. The sample size of six studies (22–27) were relatively small (<400), and the rest of three studies (17, 28, 29) enrolled more than 400 patients. The included studies varied in study population: six trials (17, 22–24, 26, 28) included all critically ill patients, two (25, 29) included patients who were admitted to the surgical ICU postoperatively, and one (27) included elderly patients having emergency admission and high risk for delirium. The incidence of delirium ranged from 16.9 to 100%. In three trials (17, 23, 24), all patients developed delirium during the study period. Van den Boogaard et al. (28) and Wang et al. (29) reported the mortality rate for patients with and without delirium, separately. Different doses, timing and route of administration were also identified: the daily doses of haloperidol ranged from 1.5 to 20 mg, the haloperidol was administered through enteral route in two trials (27, 29) and parenteral route in seven trials (17, 22–26, 28).

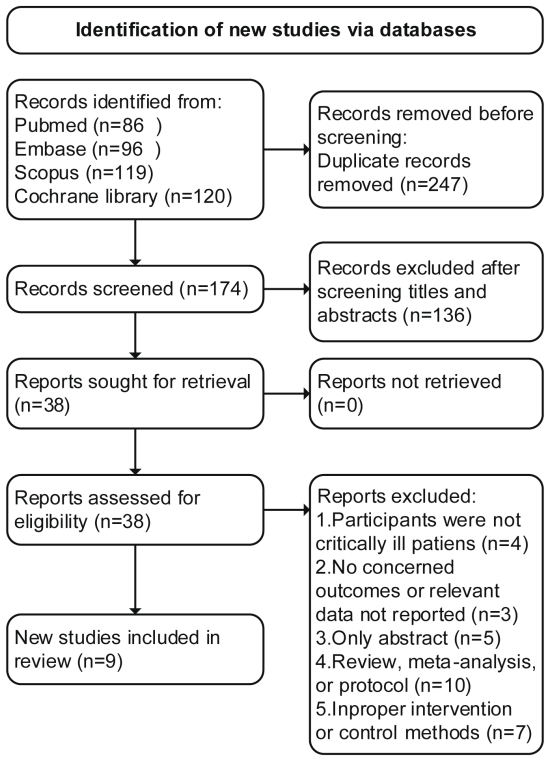

FIGURE 1
PRISMA 2020 flow diagram for the meta-analysis.

Quality assessment

The quality assessment of the included studies was conducted using the Cochrane risk of bias tool, and the results are presented in Figure 2. Three studies did not report the details of allocation concealment. For the blinding method for outcome assessment, one trial had high risk of bias since the statisticians were aware of group assignments and treatment allocation, and three trials had unclear risk of bias, which may result in an underestimation or overestimation of the true effect.

We conducted an assessment of publication bias utilizing the Egger's test and funnel plot, and the results did not indicate a significant risk of publication bias (Egger's test, $p > 0.05$; Supplementary material 4).

Primary outcome

Six trials reported the delirium-free days and nine trials reported the overall mortality. The delirium-free days was similar between haloperidol and control groups (MD −0.01, 95%CI −0.36 to 0.34, $p = 0.95$, $I^2 = 30\%$; Table 2 and Figure 3A). Similarly, there was no significant difference in overall mortality (OR 0.89, 95%CI 0.76 to 1.04, $p = 0.14$, $I^2 = 0\%$; Table 2 and Figure 3B) between patients received haloperidol and placebo.

Prespecified subgroup analysis stratified by population (patients with delirium or without delirium) was performed to investigate the potential source of heterogeneity (Table 2). Compared with placebo, a trend toward reduced overall mortality by haloperidol was observed in patients with delirium (OR 0.85, 95%CI 0.70 to 1.03, $p = 0.09$, $I^2 = 19\%$; Figure 4), although it was not statistically significant. Furthermore, the sensitivity analysis showed no significant difference in the short-term outcomes, indicating the good robustness (Supplementary material 4).

Secondary outcomes

A total of seven trials reported the length of ICU and hospital stay, there was no significant difference between patients received haloperidol and placebo (ICU: MD −0.06, 95%CI −0.16 to 0.03, $p = 0.19$, $I^2 = 0\%$, Figure 5A; hospital: MD −0.06, 95%CI −0.61 to 0.49, $p = 0.83$, $I^2 = 0\%$, Figure 5B). There were eight trials reported the incidence of adverse events, the result indicated that the use of haloperidol did not increase the incidence of adverse events (OR 0.90, 95%CI 0.60 to 1.37, $p = 0.63$, $I^2 = 0\%$, Figure 5C). Upon the results of sensitivity analysis, we found that the results were consistent with

TABLE 1 Characteristics of included studies.

Study and year	Design	Number (haloperidol/placebo)	Population	Characteristics (haloperidol/placebo)	Intervention duration and dose	Delirium assessment and incidence of delirium during study period	Outcomes
Andersen-Ranberg (2022)	Multicenter, double-blinded	501/486	Patients ≥18 years old, admitted to ICU and had received a positive result on a screening test for delirium	Age: 70/71; Male (%): 64.7/66.9; Surgical patients (%): 36.5/31.5; Ventilatory support (%): 63.9/62.8	2.5 mg of intravenous haloperidol three times daily until discharge or death in the ICU, up to a maximum of 90 days	CAM-ICU or ICDSC, 100%	90 day mortality, length of hospital stay, delirium-free days, adverse events
Schrijver (2018)	Multicenter, double-blinded	118/124	Patients ≥70 years old, acutely hospitalized through the emergency department for a medical or surgical specialty and at risk for delirium	Age: 83.5/83.4; Male (%): 48.3/41.1; Surgical patients (%): 25.4/21.0; Ventilatory support (%): 63.9/62.9	1 mg of haloperidol through enteral way every 12 h for 7 days	DSM-IV criteria, 16.9%	90 day mortality, length of hospital stay, adverse events
Girard (2018)	Multicenter, double-blinded	192/184	Patients ≥18 years old admitted to ICU with mechanical ventilation, vasopressors, or intra-aortic balloon pump	Age: 61/59; Male (%): 56.3/58.1; Surgical patients (%): 26.6/28.2; Ventilatory support (%): 92.7/92.4	2.5 mg of intravenous haloperidol twice a day for 14-day study period or ICU discharge	CAM-ICU, 100%	90 day mortality, length of ICU stay, length of hospital stay, delirium-free days
Khan (2018)	Single-center, double-blinded	68/67	Patients ≥18 years old received thoracic surgery and admitted to surgical ICU	Age: 60.0/62.3; Male (%): 67.6/71.6; Surgical patients (%): 100/100; Ventilatory support (%): 100/100	0.5 mg of intravenous haloperidol three times daily for a total of 5.5 mg	CAM-ICU, 25.2%	In-hospital mortality, length of ICU stay, length of hospital stay, adverse events
van den Boogaard (2018)	Multicenter, double-blinded	732/707	Non-neurological ICU patients, aged ≥18 years old, with an expected stay >1 day on the ICU	Age: 66.7/67.0; Male (%): 62.7/61.4; Surgical patients (%): 46.0/46.4; Ventilatory support (%): 68.0/64.6	2 mg of intravenous haloperidol three times daily for 28 day study period or ICU discharge	CAM-ICU, 33.1%	90 day mortality, length of ICU stay, length of hospital stay, delirium-free days, adverse events
Al-Qadheeb (2016)	Multicenter, double-blinded	34/34	Mechanically ventilated patients admitted ICU and expected to have an ICU admission at least 24 h	Age: 61.7/59.3; Male (%): 52.9/58.8; Surgical patients (%): 32.4/26.5; Ventilatory support (%): 100/100	1 mg of intravenous haloperidol four times daily for 10 day study period or delirium occurred, or ICU discharge	SAS or ICDSC, 29.4%	In-hospital mortality, length of ICU stay, adverse events
Page (2013)	Single-center, double-blinded	71/70	Patients ≥18 years old admitted to ICU with mechanical ventilation	Age: 67.9/68.7; Male (%): 52.1/64.3; Surgical patients (%): 40.8/30.0; Ventilatory support (%): 100/100	2.5 mg of intravenous haloperidol three times daily for 14 day study period or ICU discharge	CAM-ICU, 67.4%	28 day mortality, length of ICU stay, length of hospital stay, delirium-free days

(Continued)

TABLE 1 (Continued)

Study and year	Design	Number (haloperidol/placebo)	Population	Characteristics (haloperidol/placebo)	Intervention duration and dose	Delirium assessment and incidence of delirium during study period	Outcomes
Wang (2012)	Multicenter, double-blinded	229/228	Patients ≥65 years old who were admitted to ICU after noncardiac surgery	Age: 74.0/74.4; Male (%): 63.3/62.7; Surgical patients (%): 100/100; Ventilatory support (%): 100/100	0.5 mg of intravenous haloperidol bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 h	CAM-ICU, 19.3%	28 day mortality, length of ICU stay, length of hospital stay, delirium-free days
Girard (2010)	Multicenter, double-blinded	35/36	Patients ≥18 years old received mechanical ventilation in medical or surgical ICU patients who had an abnormal level of consciousness or receiving sedative or analgesic medications	Age: 51/56; Male (%): 57.1/66.7; Surgical patients (%): 22.9/22.2; Ventilatory support (%): 100/100	5 mg of haloperidol through enteral way every 6 h for 14 days	CAM-ICU, 100%	21 day mortality, length of ICU stay, delirium-free days

CAM-ICU, confusion assessment method for the intensive care unit; ICDSC, intensive care delirium screening checklist; DSM-IV, diagnostic and statistical manual of mental disorders, 4th edition; ICU, intensive care unit.

those of the overall analysis, suggesting that our findings are robust (Supplementary material 4).

Discussion

In this updated meta-analysis of RCTs, which involved 3,916 critically ill patients, results showed that haloperidol treatment had no impact on delirium-free days, overall mortality, or length of ICU and hospital stay when compared to placebo. However, it seemed to have a potential beneficial effect on overall mortality among critically ill patients with delirium, whereas it was not statistically significant. In addition, we found that usage of haloperidol did not increase the incidence of adverse events.

Among critically ill patients, delirium is a common occurrence and it is often addressed through the administration of pharmacological interventions, with haloperidol being the most commonly used pharmacologic intervention (15). Prior to our study, several systematic reviews and meta-analyses (32–36) have evaluated the efficacy of haloperidol in preventing and/or treating delirium in adult patients. However, these studies included in different population (surgical patients, patients in ward or ICU), and management (prevention and treatment). Our study distinguishes itself from previous literature by conducting a meta-analysis of high-quality randomized controlled trials (RCTs) that focused on a single management approach (treatment with haloperidol) and a specific population (critically ill adult patients) in the context of hospital-associated delirium. We excluded several trials carried out in the setting of elective surgery because the participants were not critically ill patients, and the effect of haloperidol in hospitalized non-ICU patients has been well assessed (37). Furthermore, in consideration of the potential clinical heterogeneity, we only included trials comparing haloperidol with placebo. The objective of our meta-analysis was to provide an updated and comprehensive analysis of the available RCTs on the safety and effectiveness of haloperidol for the treatment of delirium in adult critically ill patients.

Delirium is a common condition among critically ill patients that is associated with increased morbidity and mortality. Despite numerous hypotheses, the pathogenesis of delirium remains unknown (38, 39). It is believed that alterations in neurotransmitters, specifically an excess of dopamine and cholinergic deficiency, play a central role. Haloperidol, a D2 dopamine receptor antagonist, is a potential pharmacological option for the prevention and treatment of ICU-related delirium due to its ability to disinhibit acetylcholine and reduce the use of psychotropic sedatives/analgesics (40, 41). However, there is currently no clear evidence to support the use of haloperidol for this indication, and guidelines from the Society of Critical Care discourage its use in critically ill patients. Likewise, our findings do not support the notion that haloperidol provides either beneficial or adverse effects, and the level of uncertainty surrounding its clinical utility remains considerable. Although the results of subgroup analysis indicated that the use of haloperidol might have a potential beneficial effect on overall mortality among critically ill patients with delirium, whereas it was not statistically significant.

The lack of evidence concerning the utilization of haloperidol as a therapeutic option for delirium poses a considerable challenge to clinicians responsible for managing critically ill patients. To effectively

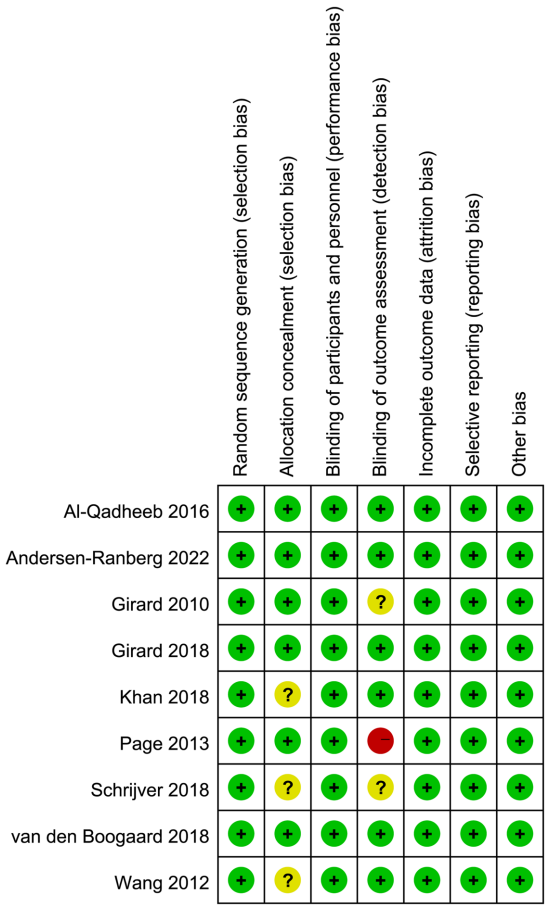

FIGURE 2
Assessment of quality by the Cochrane risk of bias tool.

TABLE 2 Outcomes of this meta-analysis.

Outcome	*N*	Result
Delirium-free days	6	MD −0.01, 95%CI −0.36 to 0.34, $p = 0.95$, $I^2 = 30\%$
Overall mortality	9	OR 0.89, 95%CI 0.76 to 1.04, $p = 0.14$, $I^2 = 0\%$
Delirium	5	OR 0.85, 95%CI 0.70 to 1.03, $p = 0.09$, $I^2 = 19\%$
Non-delirium	2	OR 0.99, 95%CI 0.72 to 1.35, $p = 0.93$, $I^2 = 0\%$
Length of ICU stay	7	MD −0.06, 95%CI −0.16 to 0.03, $p = 0.19$, $I^2 = 0\%$
Length of hospital stay	7	MD −0.06, 95%CI −0.61 to 0.49, $p = 0.83$, $I^2 = 0\%$
Adverse events	8	OR 0.90, 95%CI 0.60 to 1.37, $p = 0.63$, $I^2 = 0\%$

N, number of studies; ICU, intensive care unit; OR, odds ratio; MD, mean difference; CI, confidence interval.

manage delirium in critically ill patients, clinicians are advised to prioritize non-pharmacological interventions and strategies, such as early mobilization and mild sedation (10, 11). Furthermore, clinicians are encouraged to optimize modifiable risk factors and exercise caution when considering the use of antipsychotic medications in the management of delirium (42, 43). Although the low level of certainty surrounding the efficacy of haloperidol, it is essential to implement systematic screening protocols to detect patients exhibiting signs of delirium. Moreover, haloperidol may still be considered as a viable treatment option in instances where preventative measures and non-pharmacological interventions have been exhausted, in line with current recommendations (1).

Strengths and limitations

Our study has some strengths, including a broad and comprehensive strategy for study selection, exhaustive inclusion criteria, and high-quality statistical analysis methodology. Notably, our study stands out from previous research by incorporating the most up-to-date randomized trials, including the AID-ICU trial. This large-scale trial, which involved almost 1,000 patients from various ICUs, features significant improvements in methodology, including strict allocation concealment and blinding methods for the trial drug and better separation between groups for antipsychotic exposure. Our study provides the latest evidence on antipsychotic therapy in intensive care patients and highlights the importance of rigorous methodology in clinical trials. Moreover, considering the clinical heterogeneity in different types of patients could have affected the results, we performed subgroup analyses stratified by population and provided the evidence of potential benefit with haloperidol in patients with delirium. Such findings provide important practical recommendations for clinical management for patients with delirium.

However, the current study had certain limitations as well. First, four of the included trials (22, 24–26) are typically defined as small studies (<100 patients per arm), which may lead to small study effect bias (44). The pooled results of studies with small sample size might underestimate the beneficial effect of haloperidol in reducing mortality (Supplementary material 4). Secondly, the doses, timing and route of administration of haloperidol varied among including trials, as well as the types of patients and severity of illness. Moreover, the studies included in our analysis had varying criteria for intervention discontinuation or resumption, which may have introduced heterogeneity in the results.

Another limitation of our study is the lack of patient-level data, which prevented us from assessing the impact of sedative use on clinical outcomes. Notably, the use of certain sedatives, such as dexmedetomidine and light sedation, may have contributed to delirium prevention, whereas benzodiazepines may have lowered the delirium threshold. It should be noted that several trials included in our analysis utilized open-label antipsychotics and non-pharmacological interventions, which may have confounded our outcomes and should be controlled in future research. Moreover, some studies reported continuous variables using median and interquartile range, which were converted to mean and standard deviation, potentially introducing bias into our results. Finally, since most of the included studies used the CAM-ICU and ICDSC for detecting delirium, which was more sensitive in detecting active or hyperactive delirium (45). The hypoactive delirium has a high potential to be under-recognized and undiagnosed. The results of our meta-analysis are more applicable to the critically ill patients with active or hyperactive delirium, instead of hypoactive delirium.

Conclusion

In conclusion, the use of haloperidol compared to placebo did not significantly increase the delirium-free days, reduce the overall mortality, shorten length of ICU stay and length of hospital stay in

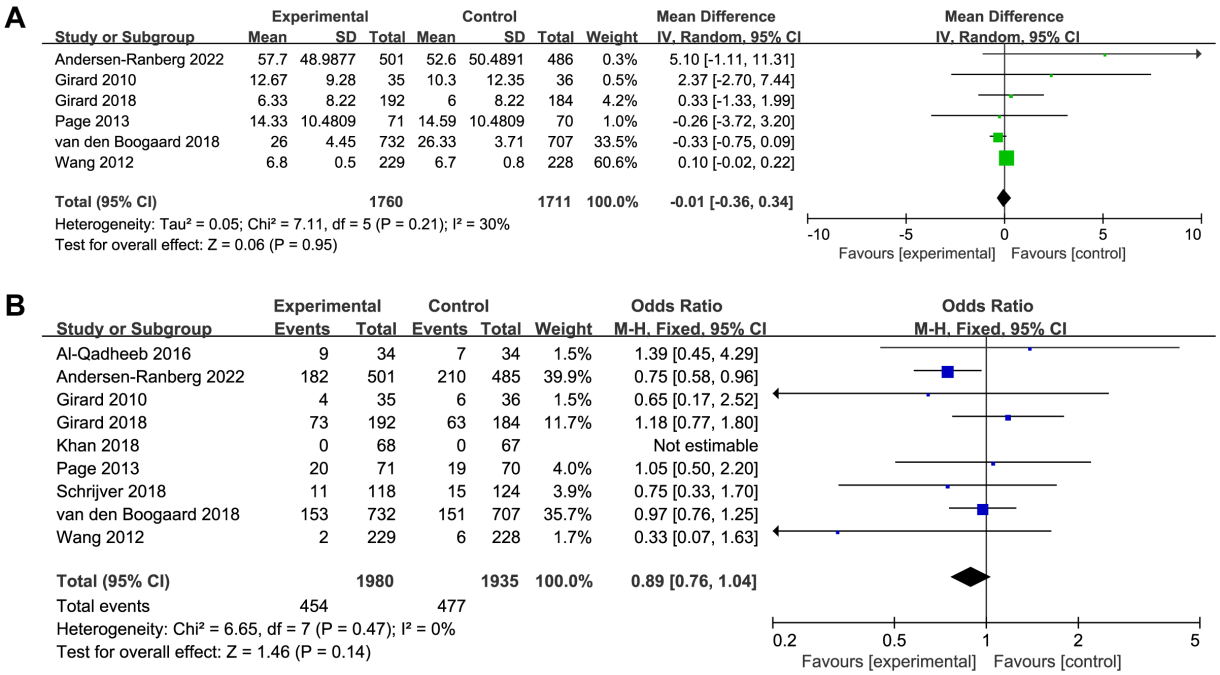

FIGURE 3
Forest plot showing the association between haloperidol and **(A)** delirium-free days and **(B)** overall mortality.

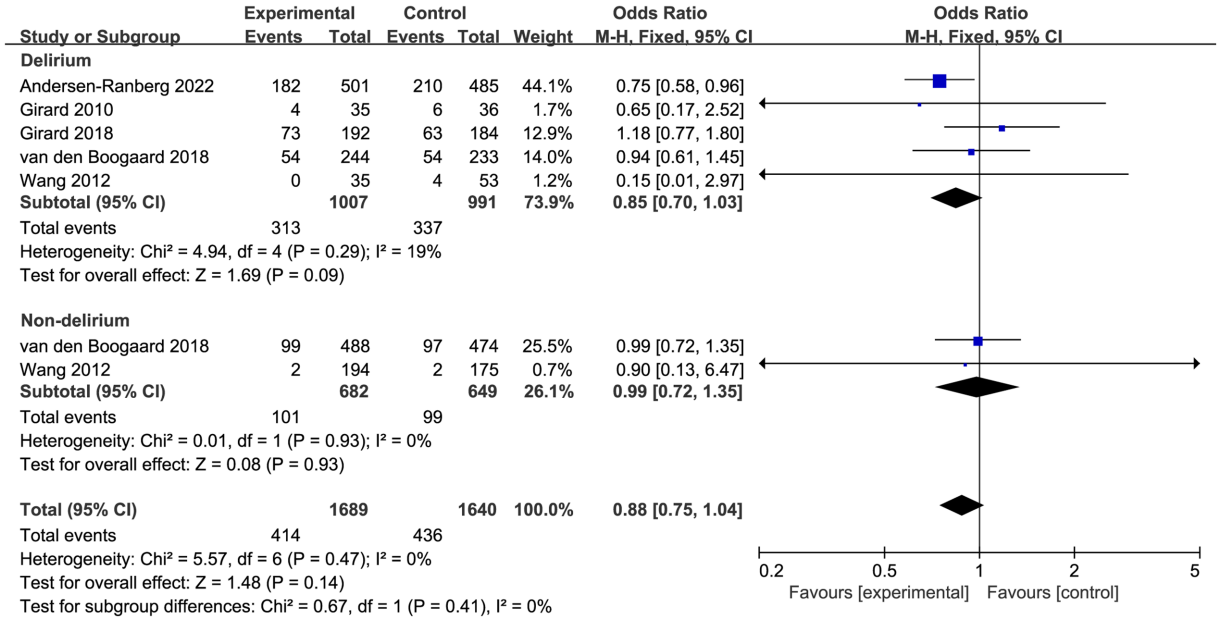

FIGURE 4
Forest plot showing the subgroup analysis of overall mortality, patients with delirium versus patients without delirium.

critically ill patients. Additionally, there was no increased risk of adverse events. Individualized clinical decision-making is critical in the administration of haloperidol for delirium treatment, considering the patient's condition, delirium subtype, and potential adverse effects.

In our opinion, further large-scale, well-designed RCTs are warranted to provide a more comprehensive understanding of the efficacy and safety of haloperidol for the prevention and treatment of different subtype of delirium in critically ill patients.

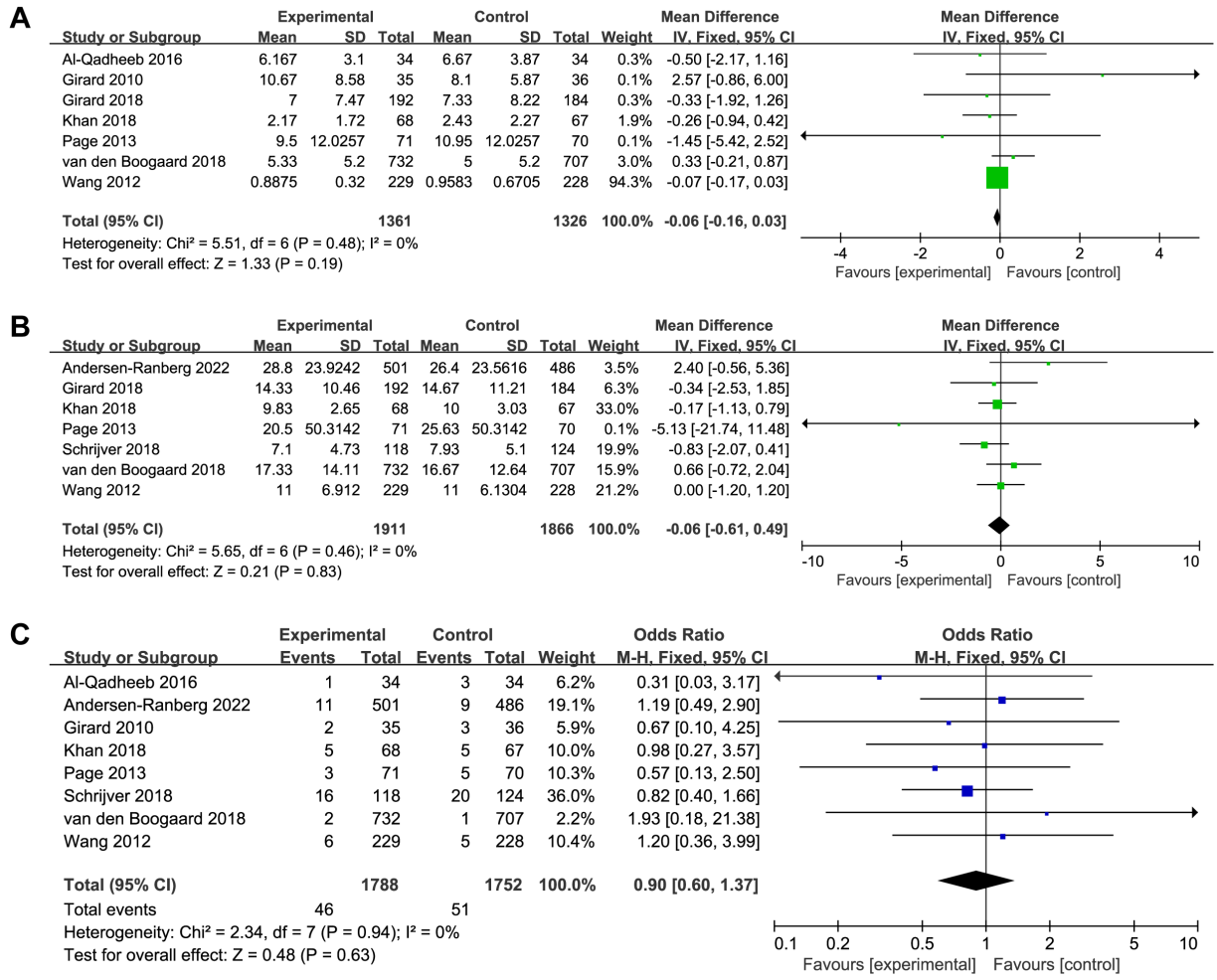

FIGURE 5
Forest plot showing the association between haloperidol and **(A)** length of ICU stay, **(B)** length of hospital stay, and **(C)** adverse events.

Data availability statement

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

Author contributions

JH conceived the idea, performed the analysis, and drafted the initial draft writing of this paper. HZ and XZ contributed to the collection and interpretation of data. KZ provided technical support and helped to draft the work. XP contributed to the revision of this paper and the final approval of the version to be published. All authors contributed to the article and approved the submitted version.

Funding

This work was supported in part by grants from the Hangzhou bio-medicine and health industry development support science and technology project (2022WJC076).

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.2023.1200314/full#supplementary-material

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TYPE Clinical Trial
PUBLISHED 07 September 2023
DOI 10.3389/fmed.2023.1212646

OPEN ACCESS

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RECEIVED 26 April 2023
ACCEPTED 15 August 2023
PUBLISHED 07 September 2023

CITATION
Ding Y, Huang T, Ge Y, Gao J and Zhang Y (2023) Effect of trans-nasal humidified rapid insufflation ventilatory exchange on reflux and microaspiration in patients undergoing laparoscopic cholecystectomy during induction of general anesthesia: a randomized controlled trial.
Front. Med. 10:1212646.
doi: 10.3389/fmed.2023.1212646

Effect of trans-nasal humidified rapid insufflation ventilatory exchange on reflux and microaspiration in patients undergoing laparoscopic cholecystectomy during induction of general anesthesia: a randomized controlled trial

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Background: Reflux aspiration is a rare but serious complication during induction of anesthesia. The primary aim of this study is to compare the incidence of reflux and microaspiration in patients undergoing laparoscopic cholecystectomy during induction of general anesthesia using either a facemask or trans-nasal humidified rapid insufflation ventilatory exchange.

Methods: We conducted a single-center, randomized, controlled trial. Thirty patients were allocated to either a facemask or a trans-nasal humidified rapid insufflation ventilatory exchange (THRIVE) group. Pre-oxygenation for 5 min with a facemask or THRIVE, positive pressure ventilation for 2 min or THRIVE for 2 min after anesthesia induction was followed. Before endotracheal intubation, the secretion above and below the glottis was collected to measure pepsin content and analyze blood gas. The ELISA assay for supra- and subglottic human pepsin content was used to detect the presence of reflux and microaspiration. The primary outcome was the incidence of reflux and microaspiration. Secondary outcomes were apnea time, PaO_2 before tracheal intubation, and the end-expiratory carbon dioxide partial pressure.

Results: Patients in the THRIVE group had a significantly longer apnea time (379.55 ± 94.12 s) compared to patients in the facemask group (172.96 ± 58.87 s; $p < 0.001$). There were no differences observed in PaO_2 between the groups. A significant difference in gastric insufflation, reflux, and microaspiration was observed between the groups. Gastric insufflation was 6.9% in the THRIVE group vs. 28.57% kPa in the facemask group ($p = 0.041$); reflux was 10.34% in the THRIVE group vs. 32.14% kPa in the facemask group ($p = 0.044$); and microaspiration was 0% in the THRIVE group vs. 17.86% kPa in the facemask group ($p = 0.023$).

Conclusion: The application of THRIVE during induction of general anesthesia reduced the incidence of reflux and microaspiration while ensuring oxygenation and prolonged apnea time in laparoscopic cholecystectomy patients. THRIVE may be an optimal way to administer oxygen during the induction of general anesthesia in laparoscopic cholecystectomy patients.

Clinical trial registration: Chinese Clinical Trial Registry, No: ChiCTR2100054086, https://www.chictr.org.cn/indexEN.html.

KEYWORDS

trans-nasal humidified rapid insufflation ventilatory exchange, laparoscopic cholecystectomy, reflux, microaspiration, general anesthesia

Introduction

Trans-nasal humidified rapid insufflation ventilatory exchange (THRIVE), known as high-flow nasal cannula (HFNC) oxygen therapy, refers to a new type of oxygen therapy that directly delivers a specific concentration of high-flow air-oxygen mixed gas to the patient through heating and humidification without the need for a closed nasal catheter (1). THRIVE provides warmed and humidified gas at a maximum flow rate of 70 L/min, giving patients stable FiO_2 while reducing anatomical dead space in the upper airway and increasing the patient's intratracheal oxygen concentration (2). Studies have shown that continuous THRIVE can reduce the patient's respiratory work while producing a degree of constant positive end-expiratory pressure (PEEP) effect (3–7). The positive pressure effect increases with increasing flow (8). For every 10 L/min increase in flow rate, the patient can obtain 1 cm H_2O PEEP with a closed mouth and 0.5 cm H_2O PEEP with an open mouth (9). The positive pressure effect produced by THRIVE opens the patient's upper airway and reduces intrapulmonary shunts (10, 11), which further increases the patient's oxygen reserve. The application of THRIVE during the induction of general anesthesia has been shown to prolong apnea time (10, 12–18). Pre-oxygenation with THRIVE can effectively reduce adverse events related to emergency endotracheal intubation in critically ill patients (16), and can ensure sufficient oxygenation induced by rapid anesthesia in emergency surgery patients (14).

Laparoscopic cholecystectomy (LC) is one of the most common elective abdominal operations (19). Patients with symptomatic gallbladder diseases have been reported to exhibit delayed gastric emptying despite following fasting guidelines. Gastric ultrasound assessment has revealed that 13% of patients scheduled for elective cholecystectomy had a full stomach because of symptomatic gallbladder disease (20). During the induction of anesthesia in general anesthesia patients, positive pressure-assisted ventilation is often accompanied by gastric insufflation, with an incidence of up to 50% (21). The increased intragastric pressure caused by a large amount of gastric insufflation, combined with the decreased tension of the lower esophageal sphincter and the suppression of the protective reflex of the upper airway under anesthesia, may further increase the risk of reflux aspiration in patients (13, 22). Anesthesiologists, therefore, remain vigilant against the high risk of reflux aspiration in patients during the induction period of general anesthesia.

Reflux aspiration is a phenomenon in which gastric acid, bile, and other gastric contents are abnormally regurgitated into the oropharynx and accidentally inhaled into the lungs. Reflux microaspiration is a rare but serious complication that occurs during the induction of anesthesia. How to effectively avoid reflux microaspiration caused by induction of general anesthesia has been a concern for anesthesiologists. Currently, the detection of pepsin can be considered a non-invasive method for effectively diagnosing reflux and microaspiration (23, 24). Still, there are no universally accepted standards for defining values of pepsin concentration for diagnosing reflux and microaspiration. For instance, Weitzendorfer et al. (25) showed a specificity of 86.2% and sensitivity of 41.5% for the diagnosis of reflux using a 216 ng/mL concentration of salivary pepsin as the threshold value. Similarly, Jaillette et al. (26) used a patient's intratracheal pepsin concentration of 200 ng/mL as the diagnostic threshold for microaspiration.

Pre-oxygenation with THRIVE can ensure the patient's full oxygenation without the need for a closed mask for positive pressure-assisted ventilation. This has potential value for anesthesia induction in people with a high risk of full stomach or reflux aspiration. However, it is unclear whether patients would benefit from the use of THRIVE during induction of anesthesia. We hypothesized that THRIVE could be beneficial to patients undergoing induction of general anesthesia for laparoscopic cholecystectomy. Therefore, we designed a randomized controlled study to observe the effect of THRIVE on reflux and microaspiration in laparoscopic cholecystectomy patients during induction of general anesthesia.

Methods

Study design

The study received approval from the Ethics Committee of Northern Jiangsu People's Hospital (2021ky288), was registered in the China Clinical Trial Registration Center (ChiCTR2100054086), and was performed between 10 December 2021 and 31 March 2022. After obtaining written informed consent, adult patients (18–60 years old) who were scheduled to undergo elective laparoscopic cholecystectomy were recruited for the present study. Exclusion criteria were as follows: difficult airway; abnormal gastric anatomy; previous esophageal or gastric surgery; history of chronic obstructive pulmonary disease; history of gastroesophageal reflux; and history of nasal surgery. Patients were randomly allocated to either a trans-nasal humidified rapid insufflation ventilatory exchange or a standard facemask for pre-oxygenation. Allocation was completed using sealed envelopes assigned in a 1:1 ratio. The envelopes were numbered sequentially and were opened by the investigator after patient consent was obtained.

Perioperative management

All patients routinely fasted before the operation (a minimum of 2 h for clear fluid and 8 h for solid intake). Standard peri-operative monitoring, including an electrocardiogram (ECG), non-invasive blood pressure (NIBP), and a pulse oximeter, was undertaken. An intravenous line was placed, and Ringer's lactate solution was given peri-operatively. Ultrasonic images of the gastric antrum were collected in the supine position.

Study protocol

Patients assigned to the facemask group were provided 100% oxygen for 5 min via a standard facemask, using a circle system with an oxygen rate of 6 L/min. The pressure mask was used to artificially assist positive pressure ventilation after the induction of anesthesia, the adjustable pressure-limiting (APL) valve was adjusted to 15 cmH_2O, and then endotracheal intubation was performed at 2 min.

Patients in the THRIVE group were pre-oxygenated for 5 min using an Opti Flow-™ nasal high-flow cannula. The oxygen flow rate began at 30 L/min and increased to 50 L/min during anesthesia induction. The flow rate was immediately increased to 70 L/min after the patient's consciousness completely disappeared. This flow was maintained until the tracheal tube was placed. The patient's mouth was kept closed during the process, and endotracheal intubation was performed after 2 min. Chin lift and/or jaw thrust were used during apnea to maintain an open airway.

General anesthesia was induced using a titrated dose of 0.05 mg/kg midazolam, 0.4 μg/kg sufentanil, 2.0 mg/kg propofol, and was followed by 0.6 mg/kg rocuronium. Apnea time was defined as the period from the end of rocuronium injection until blood oxygen saturation (SpO_2) decreased to 94%. Following the decrease of SpO_2 to 94%, the ventilator was immediately connected for mechanical ventilation, and the end-expiratory carbon dioxide partial pressure ($P_{ET}CO_2$) during the first mechanical ventilation was recorded after intubation. Then, manual lung recruitment was performed until SpO_2 returned to the level of entry. Heart rate and NIBP were maintained to fluctuate within the normal range during the operation, and vasoactive drugs were given when necessary.

Gastric antrum ultrasonography was performed in both groups before endotracheal intubation. The cross-sectional area (CSA) of the gastric antrum was measured, and the gastric insufflation was monitored. Before endotracheal intubation, the secretion above and below the glottis was collected to measure the content of pepsin to evaluate the occurrence of reflux and microaspiration. Blood gas analysis was performed before endotracheal intubation. The safe apnea time from the end of intravenous muscle relaxation to 94% reduction to SpO_2 was recorded. Furthermore, $P_{ET}CO_2$ was recorded during the first mechanical ventilation after intubation.

The primary outcome was the incidence of reflux and microaspiration. Secondary outcomes were PaO_2 before tracheal intubation, apnea time, and $P_{ET}CO_2$.

Ultrasonic examination of gastric antrum: A gastric ultrasound examination was performed using an ultrasound system with a 2–5 MHz convex array probe. The probe was placed along the sagittal plane of the epigastric area, and the gastric antrum was visualized in the parasagittal plane, just right of the midline, surrounded by the anterior left lobe of the liver and by the posterior pancreas. The CSA was measured by using a free tracing tool (27). During ultrasonic detection, gastric insufflation was determined by the significantly increased area in the sound shadow within the gastric antrum area or the typical "comet tail sign" (Figure 1) (28).

The enzyme-linked immunosorbent assay (ELISA) for supra- and subglottic human pepsin content in two groups of patients: After induction of anesthesia, the patient's vocal canal was exposed using a visual laryngoscope. Under visual conditions, a single-use sampler was placed, the supra- and subglottic secretions were scraped, and the head of the sampler was broken off and collected into sterile EP tubes. The supra- and subglottic secretion specimens were lyophilized at −20°C for testing, and an ELISA kit (Shanghai Hepai Biotechnology Co., Ltd.) was used for the assay. The supra- and subglottic secretion was collected in a tube containing citric acid by centrifugation at 3,000 r/min for 10 min, and the supernatant was taken for the assay. The pepsin concentration of the sample was calculated according to the equation of the curve after the standard linear regression curve was drawn according to the concentration of the standard. A threshold value of 216 ng/mL of pepsin was defined for supraglottic secretion (25); a value of <216 ng/mL was defined as negative for reflux, and >216 ng/mL was defined as positive for reflux. A threshold value of 200 ng/mL was defined for subglottic secretions (26); a value of <200 ng/mL was defined as negative for microaspiration and >200 ng/mL was defined as microaspiration positive.

Statistical analysis

The measurement data that was normally distributed was expressed as mean ± standard deviation ($\bar{x}\pm s$). The measurement data that was not normally distributed was expressed by median (M) and interquartile interval (IQR). Numerical variables were analyzed using an independent samples *t*-test or the Mann–Whitney U test. Categorical data were analyzed using a chi-square test. A value of $p < 0.05$ was considered statistically significant. All tests were performed using SPSS Statistics26.

Sample size estimation

No previous study has investigated the use of pepsin to define reflux microaspiration. To determine sample size, we randomly selected 20 patients according to the inclusion criteria in the study protocol for a preliminary trial, and these patients were not included in the formal study. Before anesthesia induction, 10 patients each received regular facemask oxygen inhalation and THRIVE pre-oxygenation, and the CSA of the gastric antrum was measured before intubation. The pre-tracheal intubation CSA areas of patients in the facemask and THRIVE groups were $3.58 \pm 1.02\ cm^2$ and $3.06 \pm 0.98\ cm^2$, respectively.

Using a type-1 error of 5% and type-2 error of 20% (power 80%), a sample size of 25 patients in each group was calculated. However, to account for attrition and study dropouts due to equipment errors (i.e., the replacement of the analysis package of the blood gas analyzer), we included 60 total patients, and the sample size was increased to 30 per group.

Results

Patient characteristics

Seventy patients were assessed for eligibility. Ten patients were excluded (Figure 2), and 60 patients were included. In one patient, the ultrasonographic examination of gastric antrum CSA was not successful due to interference of intestinal flatulence; one patient failed to complete the blood gas analysis on time due to the replacement of the blood gas analyzer; and one patient failed to keep their mouth closed per requirement. Participant characteristics are summarized in Table 1.

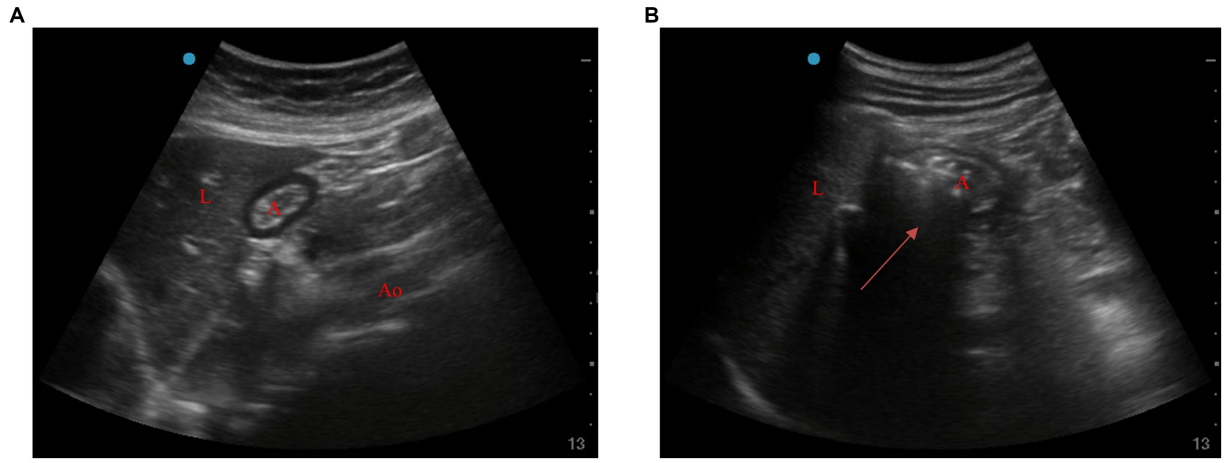

FIGURE 1
Ultrasonic images of gastric antrum before and after ventilation. **(A)** Before ventilation, **(B)** after ventilation (arrow). A, antrum; L, liver; Ao, aorta.

TABLE 1 Characteristics of 57 patients pre-oxygenated with THRIVE or facemask for induction of anesthesia.

	Facemask ($n = 28$)	THRIVE ($n = 29$)	p-value
Age: years	53 (12)	52 (16)	0.637
Gender: male/female	13/15	12/17	0.701
Height: m	1.7 ± 0.1	1.6 ± 0.1	0.352
Weight: kg	69 ± 12	62 ± 10	0.089
ASA physical status: I/II	13/15	15/14	0.689
BMI: kg/m^2	24 ± 2	23 ± 2	0.084
Hypertension	6 (21.4%)	5 (17.2%)	0.689
Diabetes	2 (7.1%)	2 (6.9%)	1.000
Baseline HR: beats/min	81 ± 14	78 ± 12	0.357
Baseline MAP: mmHg	104 ± 13	96 ± 12	0.053
Baseline SpO_2: %	98 (1)	99 (2)	0.535
Preoperative diagnosis			
Gallstone	25 (89.3%)	26 (89.7%)	
Adenomyosis of gallbladder	2 (7.1%)	1 (3.4%)	
Gallbladder polyps	1 (3.6%)	2 (6.9%)	
Anesthesia time: min	55 (34)	50 (23)	0.268
Operation time: min	40 (30)	35 (18)	0.094
Fluid infusion: mL	1,000 (0)	1,000 (0)	0.531
Hemorrhage: mL	5 (5.0)	5 (2.5)	0.716

Values are mean (SD), median (IQR), or number (proportion).
ASA, American Society of Anesthesiologists; BMI, body mass index; HR, heart rate; MAP, mean arterial pressure; SpO_2, blood oxygen saturation.

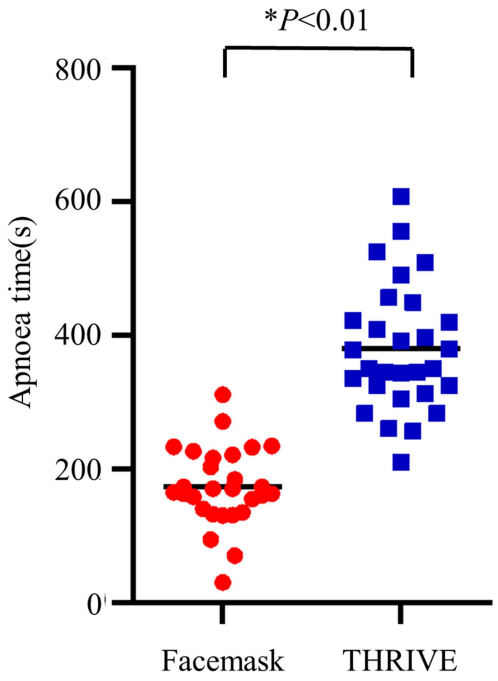

FIGURE 2
Apnea time. THRIVE pre-oxygenation (blue squares); facemask pre-oxygenation (red dots).

Apnea time, arterial blood gas, and the first breath after intubation

We observed a longer apnea time in the THRIVE group compared to the facemask group (173 ± 59 s vs. 380 ± 94 s, $p < 0.001$) (Table 2). Increased levels of $P_{ET}CO_2$ in and a higher level of PaO_2 before intubation were seen in the THRIVE group (Table 2). Other conditions were similar between the facemask and THRIVE groups (Table 2; Figures 2, 3).

CSA, gastric insufflation, reflux, and microaspiration

The baseline CSA and CSA before intubation did not differ between the facemask and THRIVE groups, but statistically significant reductions in gastric insufflation, reflux, and microaspiration were observed in the THRIVE group (Table 3). Five

TABLE 2 $P_{ET}CO_2$ in first breath after intubation, blood gas analysis, and apnea time.

	Facemask ($n = 28$)	THRIVE ($n = 29$)	p-value
PaO_2: mmHg	192 ± 119	347 ± 131	0.000
$PaCO_2$: mmHg	54 ± 6	54 ± 8	0.129
pH	7.3 ± 0.4	7.3 ± 0.4	0.719
Lac: mmol/L	0.6 (0.3)	0.6 (0.3)	0.570
Hct: %	37 ± 5	37 ± 5	0.915
HCO_3^-: mmol/L	27.1 ± 1.9	28.4 ± 2.9	0.054
Hb: g/dL	11.4 ± 2.5	11.5 ± 1.7	0.848
Apnea time: s	173 ± 59	380 ± 94	0.000
$P_{ET}CO_2$ in first breath after intubation; mmHg	46 ± 5	52 ± 6	0.000

Values are mean (SD) or median (IQR).

TABLE 3 CSA, gastric insufflation, reflux, and microaspiration.

	Facemask ($n = 28$)	THRIVE ($n = 29$)	p-value
Baseline CSA; cm^2	3.1 ± 1.1	3.0 ± 0.9	0.780
CSA>3.4 cm^2	9 (32.1%)	6 (20.7%)	0.326
CSA before intubation; cm^2	3.7 ± 1.0	3.2 ± 1.0	0.046
CSA>3.4 cm^2	19 (67.9%)	9 (31.0%)	0.005
Gastric insufflation	8 (28.6%)	2 (6.9%)	0.041
Reflux	9 (32.1%)	3 (10.3%)	0.044
Micro aspiration	5 (17.9%)	0 (0%)	0.023

Reflux was defined as supraglottic pepsin concentration > 216 ng/mL, and microaspiration was defined as subglottic pepsin concentration > 200 ng/mL.

patients (17.86%) in the group that was pre-oxygenated with a facemask had microaspiration. No microaspiration was seen in the THRIVE group ($p = 0.023$; Table 3).

Discussion

Our main result was that the use of THRIVE during induction of anesthesia reduced the incidence of regurgitation and microaspiration in patients. This may be because the THRIVE oxygen delivery method can effectively circumvent gastric inlet caused by artificial positive pressure-assisted ventilation. Routine mask-assisted positive pressure ventilation during induction of anesthesia is frequently complicated by gastric insufflation (21). This can cause gastric dilatation, leading to increased intragastric pressure, which can increase the risk of regurgitant aspiration in patients (13, 22). In the present study, the incidence of gastric insufflation significantly decreased in patients in the THRIVE group compared to the group on conventional mask ventilation. A previous study demonstrated that a maximum inspiratory airway pressure of <15 cm H_2O allowed adequate pulmonary ventilation with reduced gastric inlet (29), whereas THRIVE produced a stable and continuous positive intra-airway pressure effect without mask positive pressure ventilation (9).

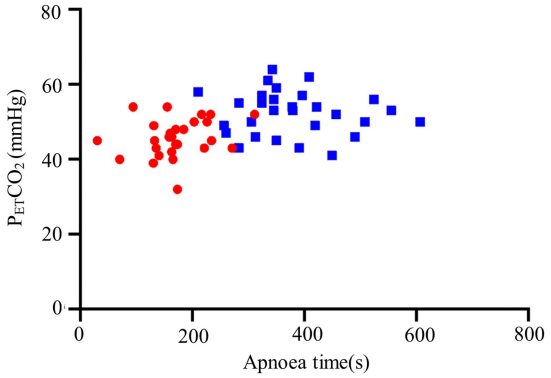

FIGURE 3
$P_{ET}CO_2$ during the first breath after intubation and apnea time. THRIVE (blue squares); facemask (red dots).

For every 10 L/min increase in flow rate, the patient can obtain 1 cm H_2O PEEP with a closed mouth and 0.5 cm H_2O PEEP with an open mouth (9), which results in a PEEP of less than 10 cm H_2O even at oxygen flows up to 70 L/min (8, 30). In our study, pepsin concentrations were used to define reflux and microaspiration. However, a previous study by Sjöblom et al. (14) reported that the person intubating was responsible for checking the pharynx for signs of reflux, and thus, this measurement may be more informative compared to assessing pepsin concentrations.

Ultrasound measurement of the patient's CSA was used in the present study to further assess the effect of THRIVE on the patient's gastric contents. A total of 91% sensitivity and 71% specificity for the diagnosis of a full stomach was obtained at a threshold value of 3.4 cm^2 of CSA (31). These results showed that THRIVE reduced the patient's pre-tracheal intubation CSA and decreased the proportion of patients with CSA >3.4 cm^2. Moreover, THRIVE intervention did not affect the basal value of the patient's gastric contents. Rather, it reduced the occurrence of gastric inlet and failed to cause an increase in gastric contents compared to traditional induction of anesthesia with positive pressure-assisted ventilation by mask. THRIVE can reduce the occurrence of regurgitation and microaspiration during induction of anesthesia in LC patients. McLellan et al. (21) performed an ultrasound assessment of 1:1 gastric contents before and after HFNC intervention in 60 healthy adult volunteers who fasted for at least 8 h. The results showed no signs of gastric distension or increase in gastric secretions when using HFNC during spontaneous ventilation in healthy adult volunteers.

In the present study, $PaCO_2$ in arterial blood before tracheal intubation was not significantly different between the facemask and THRICE patients, which may be related to the fact that during apnea, THRIVE promotes the clearance of CO_2 from the anatomical dead space and reduces the repetitive inhalation of CO_2, achieving partial clearance of CO_2 (10, 17, 32). The results of our study showed that the use of THRIVE during induction of anesthesia at the same time as oxygen administration significantly prolonged the time to apnea. In addition, we demonstrated higher $P_{ET}O_2$ levels in the THRIVE patient group at the first breath after intubation. These results are inconsistent with previous studies (14, 17). Apneic oxygenation using THRIVE has been shown to generate a slower increase in arterial CO_2 over time (10). This finding may be related to the longer safe apnea

time, with slow transient CO_2 accumulation inevitably occurring as the patient's apnea time prolongs. Similar studies have shown that oxygen administration with THRIVE significantly prolongs the time to 95% SpO_2 in obese patients compared to regular mask oxygen administration (18). However, prolonged (30 min) apneic oxygenation with THRIVE can be limited by hypercapnia and severe acidosis (33), suggesting that hypercapnia may be a limitation of the application of THRIVE during apnea.

There are a number of limitations to our study. First, the study could not be blinded due to the nature of the intervention. Second, the study population consisted of mostly young and healthy patients. The value of THRIVE in the induction period of general anesthesia for additional populations, such as patients with poor preoperative pulmonary function and older adult and obese patients, needs further investigation. Finally, the use of THRIVE with differing oxygen flow rates and the duration of oxygen inhalation during the induction of anesthesia should be explored.

In conclusion, the application of THRIVE during the induction of general anesthesia can ensure patient oxygenation, prolong apnea time, and reduce the occurrence of reflux and microaspiration in laparoscopic cholecystectomy patients. Thus, THRIVE could improve oxygen administration during the induction of general anesthesia in laparoscopic cholecystectomy patients.

Data availability statement

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

Ethics statement

The studies involving humans were approved by Ethics Committee of Northern Jiangsu People's Hospital (2021ky288), was registered in China Clinical Trial Registration Center (ChiCTR2100054086). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

YD: writing original draft. TH and YZ: data analysis. YG and YZ: writing review and editing. JG: supervision and conceptualization. All authors contributed to the article and approved the submitted version.

Funding

This research was supported by The National Natural Science Fund, China (82172190, 82101299).

Acknowledgments

We thank the staff and the hepatobiliary and pancreatic surgeons of Northern Jiangsu People's Hospital for their great support in the implementation of this study.

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.2023.1212646/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 15 November 2023
DOI 10.3389/fmed.2023.1288243

OPEN ACCESS

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RECEIVED 04 September 2023
ACCEPTED 31 October 2023
PUBLISHED 15 November 2023

CITATION
Lee S, Kim M, Kang HY, Choi J-H, Kim MK and You AH (2023) Comparison of oxygen reserve index according to the remimazolam or dexmedetomidine for intraoperative sedation under regional anesthesia—A single-blind randomized controlled trial.
Front. Med. 10:1288243.
doi: 10.3389/fmed.2023.1288243

Comparison of oxygen reserve index according to the remimazolam or dexmedetomidine for intraoperative sedation under regional anesthesia—A single-blind randomized controlled trial

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Introduction: We aimed to evaluate the difference in intraoperative oxygen reserve index (ORi) between the sedatives remimazolam (RMMZ) and dexmedetomidine (DEX).

Methods: Seventy-eight adult patients scheduled for sedation under regional anesthesia were randomly assigned to either the DEX (n = 39) or RMMZ (n = 39) group. The primary outcome was the difference in perioperative ORi between the groups. The secondary outcomes included respiratory depression, hypo- or hypertension, heart rate (HR), blood pressure, respiratory rate and postoperative outcomes. Additionally, the number of patients who experienced a decrease in intraoperative ORi to < 50% and the associated factors were analyzed.

Results: The ORi was significantly higher in the RMMZ group at 15 min after sedation maintenance. There were no significant differences in respiratory depression between the two groups. The intraoperative HR was significantly higher in the RMMZ group after the induction of sedation, 15 min after sedation maintenance, and at the end of surgery. No other results were significantly different between the two groups. The incidence of a decrease in intraoperative ORi to < 50% was significantly higher in the DEX group. Factors associated with a decrease in the intraoperative ORi to < 50% were diabetes mellitus, low baseline peripheral oxygen saturation (SpO_2), and DEX use. In the receiver operating characteristic curve analysis for a decrease in the intraoperative ORi to < 50%, the cutoff baseline SpO_2 was 97%.

Conclusion: RMMZ is recommended as a sedative for patients with a low baseline SpO_2 and intraoperative bradycardia. Further studies should be conducted to establish the criteria for a significant ORi reduction.

KEYWORDS

dexmedetomidine, heart rate, oxygen reserve index, peripheral oxygen saturation, randomized controlled trial, regional anesthesia, remimazolam, sedation

1. Introduction

Regional anesthesia is preferred over general anesthesia because of its various advantages such as less cognitive dysfunction, faster recovery, and reduced respiratory complications (1). When surgery is performed under regional anesthesia, a sedative is administered to reduce patient anxiety and discomfort (2). Traditionally, small doses of midazolam and propofol are administered for sedation (3). However, since these drugs may induce severe respiratory depression or drops in blood pressure (BP), careful patient monitoring is required (4, 5).

Dexmedetomidine (DEX) is a relatively safe drug with weak respiratory depression effects and is currently widely used in clinical practice (6, 7). As an alpha-2 agonist, it induces a sleep pattern similar to physiological sleep (8). However, loading-dose infusion may induce hemodynamic deterioration or delay emergence from sedation because of its long lasting action (9, 10).

Remimazolam (RMMZ), is a recently developed very short-acting, intravenous infusion-based benzodiazepine (11, 12). Similar to midazolam, RMMZ acts on gamma-aminobutyric acid A receptors to induce sedation or anesthesia (13). Additionally, the duration of action is short and predictable owing to its fast on- and offset. Similar to other benzodiazepines, sedation can be reversed using flumazenil (14, 15), and research on its hemodynamic stability is being actively reported (16). However, high doses of RMMZ also cause respiratory depression (17).

Respiratory monitoring is essential during sedation because of the possibility of respiratory depression caused by sedative agents. The risk factors for respiratory depression are advanced age, female sex, obstructive sleep apnea, chronic obstructive pulmonary disease, cardiac disease, diabetes mellitus (DM), hypertension, neurologic disease, renal disease, and obesity (18, 19). Generally, peripheral oxygen saturation (SpO_2) and end-tidal carbon dioxide are monitored to detect respiratory depression (20). However, the oxygen reserve index (ORi), a recently developed non-invasive continuous parameter, can provide a better oxygenation profile since it reflects an increase in blood oxygen partial pressure within a range that does not reflect SpO_2 (21, 22). Rather, ORi represents a blood oxygen partial pressure range of 100–200 mmHg assigned a numerical value of 0–1 (23). Previous studies have used ORi to adjust the perioperative fraction of oxygen supply (24, 25). Research related to the early warning of desaturation using ORi has also been actively conducted (21–23, 26, 27). ORi provides an early warning of the occurrence of desaturation, approximately 30–90 s earlier than SpO_2. When monitoring patients in the operating room, the ORi can be used to predict and prepare for desaturation in advance. If these early warning features of ORi are used for sedation, anesthesia can be administered safely by maintaining the patient oxygenation and preparing for desaturation (28, 29).

However, studies comparing the ORi between DEX and RMMZ during sedation have not yet been conducted. Therefore, the authors of this study hypothesized that there would be a difference in intraoperative ORi according to the use of DEX or RMMZ during sedation and attempted to evaluate this difference using a randomized controlled trial. In addition, we assessed whether postoperative outcomes differed depending on the drug used.

2. Materials and methods

2.1. Study design and ethical approval

This study was designed as a single-blind randomized controlled trial to compare the ORi between two groups during sedation with DEX or RMMZ. Ethical approval was obtained from the Institutional Review Board of Kyung Hee University Hospital (KHUH 2023-02-036) on March 17, 2023. The study complied with the principles of the Declaration of Helsinki and followed the Consolidated Standards of Reporting Trials checklist. Before enrollment, the study was registered with the Clinical Research Information Service (No.: KCT0008339; registration date: April 07, 2023; principal investigator: Ann Hee You). The study protocols are available from the Clinical Research Information Service. Written informed consent was obtained from all participants.

2.2. Participants

This study included adult patients aged between 18 and 100 years who were scheduled for elective surgery under regional anesthesia and sedation at a single tertiary hospital. The exclusion criteria were pregnancy, allergy to the study drugs, preoperative oxygen supply, inability to communicate, non-supine surgical posture, severe obesity with a body mass index > 35 kg/m^2, and American Society of Anesthesiologists physical status class $\geq$ IV. Participant recruitment began in April 2023 and ended in July 2023.

Abbreviations: ORi, oxygen reserve index; RMMZ, remimazolam; DEX, dexmedetomidine; MOAA/S, modified observer's assessment of alertness/sedation; PACU, post-anesthesia care unit; PONV, postoperative nausea and vomiting; AKI, acute kidney injury.

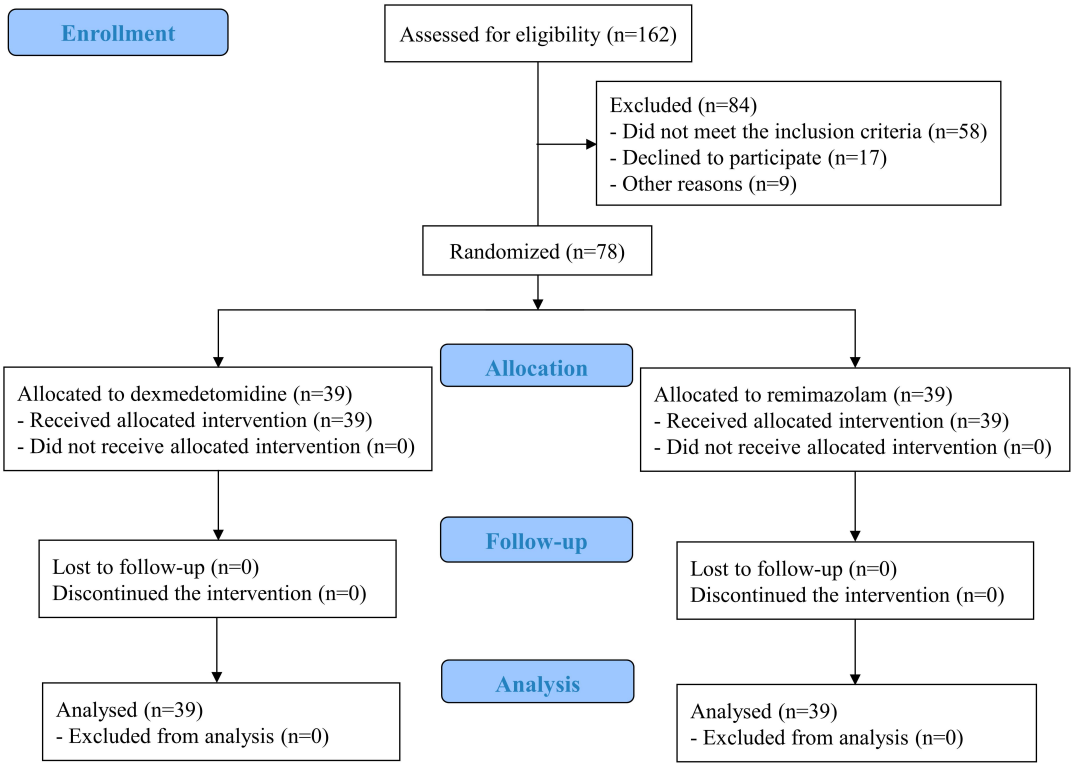

FIGURE 1
Flow chart of patient selection.

2.3. Randomization and blindness

Participants were randomized into the DEX or RMMZ groups on the morning of surgery using sealed envelopes. A random allocation sequence was generated with 1:1 allocation and random block size using Excel 2019 (Microsoft). Owing to the difference in the drug administration method, we were unable to fully double-blind this study; rather, the study was single-blinded since only patients were unaware of group assignment. However, postoperative outcomes were evaluated by a single researcher (MK) who was blinded to the group assignment.

2.4. Study protocol

After patients entered the operating room, a Masimo Radical 7 pulse oximeter probe (Masimo Radical 7; Masimo Corp., Irvine, CA, USA) was attached to the patient's finger to measure the ORi. Heart rate (HR) and rhythm were monitored using a 3-lead electrocardiogram, and BP was measured every 5 min non-invasively using an arm cuff. Brachial plexus block and spinal anesthesia were performed for upper and lower extremity surgeries, respectively. After regional anesthesia, oxygen was supplied at 6 L/min via a non-rebreathing facial mask during the entire sedation. Before study drug administration, preoxygenation was performed to measure the ORi plateau value as a baseline. The modified observer's assessment of alertness/sedation (MOAA/S) scale was used to evaluate the depth of sedation (30, 31). During the induction and maintenance of sedation, the sedative dose was adjusted to a target MOAA/S scale 3. In the RMMZ group, 2.5 mg was administered intravenously over 1 min to induce sedation; when a MOAA/S scale score of 3 was not reached, an additional 2.5 mg was administered. During maintenance of sedation, RMMZ was continuously administered intravenously at a rate of 0.1–1 mg/kg/h. In the DEX group, 1 μg/kg was intravenously administered for 10 min to induce sedation, and continuous intravenous infusion was administered within the range of 0.2–0.7 μg/kg/h to maintain sedation. The TERUFUSION® INFUSION PUMP TE-171 (Terumo®, Tokyo, Japan) infusion device was used in both groups. Sedatives were discontinued during the surgical wound dressing stage.

2.5. Outcomes

The primary outcomes were defined as the difference in ORi between the two groups during sedation. ORi was measured as the baseline value at the plateau level in the preoxygenation stage, after the induction of sedation, 15 min after sedation maintenance, and at the end of surgery. Most ORi values in room air were 0, and the ORi plateau level in the preoxygenation stage before the administration of sedative drugs was set as the baseline.

Cases of respiratory depression during sedation were evaluated as the secondary outcomes. Respiratory depression was defined as a decrease in SpO_2 due to the cessation of spontaneous breathing. HR, BP, and respiratory rate (RR) were measured at the aforementioned time points and in the post-anesthesia care unit (PACU). A change of > 20% compared with the baseline systolic

TABLE 1 Demographic and intraoperative data of the study cohort.

	DEX (n = 39)	RMMZ (n = 39)	p-value
Age (year)	58 [47–67]	60 [52–71]	0.565
Male, n (%)	21 (53.9%)	21 (53.9%)	1.000
Body mass index (kg/m^2)	23.9 [21.5–26.5]	23.6 [21.4–24.8]	0.366
ASA-PS class I/II/III, n (%)	10 (25.6%)/ 16 (41.0%)/ 13 (33.3%)	9 (23.1%)/ 20 (51.3%)/ 10 (25.6%)	0.641
Smoking, non/ex/current, n (%)	32 (82.1%)/ 0 (0.0%)/ 7 (17.9%)	31 (79.5%)/ 3 (7.7%)/ 5 (12.8%)	0.187
Diabetes, n (%)	12 (30.77%)	12 (30.77%)	1.000
Hypertension, n (%)	17 (43.59%)	17 (43.59%)	1.000
Asthma or COPD, n (%)	4 (10.3%)	5 (12.8%)	1.000
Obstructive sleep apnea, n (%)	6 (15.4%)	7 (17.9%)	1.000
Hematocrit (%)	39.2 [36.3–43.0]	38.9 [35.4–43.2]	0.791
Platelet ($\times 10^3/\mu$L)	207 [184–260]	215 [181–251]	0.803
Creatinine (mg/dL)	0.89 [0.66–2.32]	0.79 [0.62–1.04]	0.389
Baseline SpO_2 (%)	98 [97–99]	98 [98–99]	0.652
Type of regional anesthesia			0.735
Brachial plexus block, n (%)	35 (89.7%)	33 (84.6%)	
Spinal anesthesia, n (%)	4 (10.3%)	6 (15.4%)	
Sedative dose			
Induction dose of DEX (μg)	60 [50–70]	0	
Total dose of DEX (μg)	85 [67–107]	0	
Induction dose of RMMZ (mg)	0	2.5 [2.4–4.0]	
Total dose of RMMZ (mg)	0	13.5 [9.3–21.2]	
Fluid administration (ml)	100 [50–175]	100 [50–225]	0.192
Surgery time (min)	55 [35–80]	60 [30–88]	0.538

Continuous data are presented as medians [interquartile ranges], and categorical data are presented as n (%). DEX, dexmedetomidine; RMMZ, remimazolam; ASA-PS, American Society of Anesthesiologists physical status; COPD, chronic obstructive pulmonary disease; SpO_2, peripheral oxygen saturation.

BP was defined as intraoperative hypo- or hypertension, and the incidence of both was evaluated. The RR was measured through end-tidal carbon dioxide monitoring. Regarding postoperative outcomes, the PACU length of stay (LOS), postoperative nausea and vomiting (PONV), delirium, acute kidney injury (AKI) until postoperative day 2, and postoperative hospital LOS were evaluated based on medical records. AKI was defined as an alteration of postoperative serum creatinine $\geq$ 0.3 mg/dL compared to the preoperative level, according to the kidney disease: improving global outcomes criteria (32). Additionally, the number of patients who experienced a decrease in intraoperative ORi to $<$ 50% compared to the plateau level during the preoxygenation stage and associated factors were evaluated.

2.6. Sample size calculation

Chen et al. (33) reported a minimum value of SpO_2 of 88.22 $\pm$ 2.16 and 89.90 $\pm$ 2.03 when RMMZ and DEX were administered as sedatives, respectively, during bronchoscopy. Based on these results, 35 patients were included in each group as a G-power analysis (t-tests, means: difference between two independent means [two groups], *a priori*: compute required sample size–given α, power, and effect size, two tails, effect size d 0.802, α err 0.1, power 0.95, allocation ratio N2/N1 1). Considering a predicted dropout rate of 10%, the total target number of patients in the current study was 78, with 39 patients in each group.

2.7. Statistical analysis

Data are presented as medians [interquartile ranges] or numbers (%), as appropriate. The normality of continuous variables was evaluated using the Shapiro–Wilk test. Independent variable t-tests or Wilcoxon rank–sum tests were used to analyze continuous variables. The chi square or Fisher's exact test was used for categorical variables. Univariate logistic regression analysis was used to identify the factors causing a decrease in the intraoperative ORi to $<$ 50% compared with the plateau value during preoxygenation; all variables with $p < 0.2$ and previously described

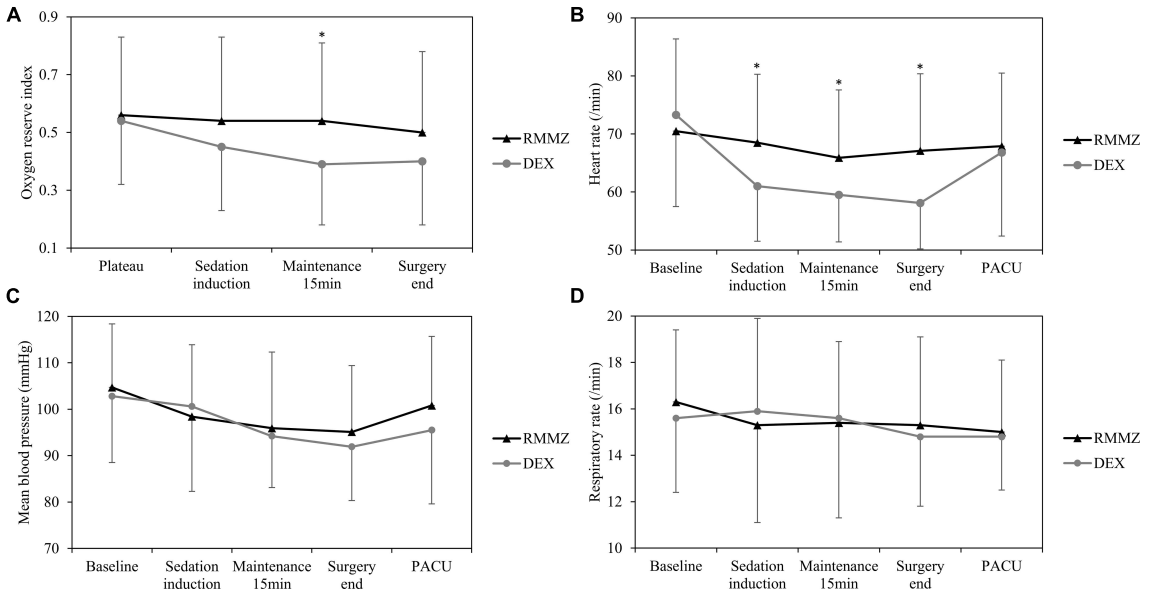

FIGURE 2
Perioperative **(A)** oxygen reserve index (ORi), **(B)** heart rate, **(C)** mean blood pressure, and **(D)** respiratory rate. Plateau means the maximum value of ORi in the preoxygenation stage. Sedation induction means after induction of sedation. Maintenance 15 min means 15 min after maintenance of sedation. *Significant differences. RMMZ, remimazolam; DEX, dexmedetomidine; PACU, post-anesthesia care unit.

clinically important factors were included in the multivariate analysis. Receiver operating characteristic (ROC) curve analysis was performed to identify factors predicting a decrease in the intraoperative ORi to < 50%, and the cutoff value was obtained using the maximum Youden index (sensitivity + specificity−100). For all data, statistical significance was set at $p < 0.05$. Statistical analyses were performed using the commercial statistical software SPSS (version 22.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study population and demographic data

Of 162 patients, 84 were excluded, and 78 were randomly assigned to either group while ensuring both groups were the same size. The analysis was performed on 39 patients in each group without any loss to follow-up (Figure 1). There were no significant differences between the two groups in demographic data, medical history, preoperative laboratory test results, surgical site, amount of fluid administered during surgery, operative time, or intraoperative sedation level based on the MOAA/S scale (Table 1; Supplementary Tables 1, 2). No serious complications related to anesthesia or surgery occurred during the study period.

3.2. Primary outcome

The ORi was significantly higher in the RMMZ group at 15 min after sedation maintenance. After the induction of sedation and at the end of surgery, the ORi tended to be higher in the RMMZ group; however, the difference was not statistically significant (Figure 2A; Supplementary Table 3).

TABLE 2 Perioperative outcomes of the study cohort.

	DEX (n = 39)	RMMZ (n = 39)	p-value
Respiratory depression, n (%)	6 (15.4%)	5 (12.8%)	1.000
Decreased ORi of > 50%, n (%)	17 (43.6%)	7 (17.9%)	0.027*
Intraoperative hypotension, n (%)	10 (25.6%)	10 (25.6%)	1.000
Intraoperative hypertension, n (%)	2 (5.1%)	4 (10.3%)	0.671
PACU LOS (min)	32 [31–45]	33 [31–37]	0.886
PONV, n (%)	4 (10.3%)	7 (17.9%)	0.515
Delirium, n (%)	1 (2.6%)	0 (0.0%)	1.000
Acute kidney injury, n (%)	1 (2.6%)	0 (0.0%)	1.000
Postoperative hospital LOS (day)	1 [1–1]	1 [1–2]	0.120

Continuous data are presented as medians [interquartile ranges], and categorical data are presented as n (%). *Statistically significant ($p < 0.05$). DEX, dexmedetomidine; RMMZ, remimazolam; ORi, oxygen reserve index; PACU, post-anesthesia care unit; LOS, length of stay; PONV, postoperative nausea and vomiting.

3.3. Secondary outcome

No significant difference was observed between the two groups in respiratory depression during sedation (Table 2). Intraoperative HR was significantly higher in the RMMZ group after induction of sedation, 15 min after sedation maintenance, and at the end

TABLE 3 Univariate and multivariate logistic regression analyses of factors associated with a decrease in the intraoperative ORi to < 50%.

	Univariable		Multivariable	
	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Female	0.98 [0.37–2.58]	0.970		
Age	1.00 [0.97–1.03]	0.787	0.98 [0.94–1.01]	0.225
ASA-PS				
I	Reference			
II	0.72 [0.21–2.55]	0.603		
III	1.39 [0.39–5.20]	0.612		
Smoking status				
None	Reference		Reference	
Ex-smoker	1.00 [0.04–11.02]	1.000	1.04 [0.03–17.70]	0.979
Current smoker	0.40 [0.06–1.69]	0.263	0.17 [0.02–1.23]	0.106
Body mass index	0.99 [0.86–1.15]	0.936		
Diabetes mellitus	2.67 [0.96–7.48]	0.058	5.59 [1.45–25.78]	0.017*
Asthma or COPD	1.14 [0.22–4.78]	0.859	0.93 [0.11–7.27]	0.941
Obstructive sleep apnea	1.51 [0.41–5.15]	0.512	1.34 [0.23–7.33]	0.734
Hematocrit	0.99 [0.95–1.01]	0.631		
Baseline SpO_2	0.59 [0.38–0.87]	0.011*	0.58 [0.35–0.90]	0.022*
Plateau ORi	1.94 [0.27–14.53]	0.509		
DEX group	3.53 [1.30–10.48]	0.017*	4.58 [1.36–18.15]	0.019*
Regional anesthesia				
Spinal anesthesia	Reference		Reference	
Brachial plexus block	1.91 [0.43–13.38]	0.436	3.00 [0.40–45.05]	0.346

*Statistically significant ($p < 0.05$). ORi, oxygen reserve index; OR, odds ratio; CI, confidence interval; ASA-PS, American Society of Anesthesiologists physical status; COPD, chronic obstructive pulmonary disease; SpO_2, peripheral oxygen saturation; DEX, dexmedetomidine; OS, orthopedic surgery; GS, general surgery.

of surgery. However, HR was not significantly different in the PACU (Figure 2B). There was no significant difference in mean BP and RR between the two groups (Figures 2C, D; Supplementary Table 3). The incidences of intraoperative hypo- or hypertension were comparable between the groups. There were no significant differences between the groups in the PACU LOS, incidence of PONV, delirium, AKI, and postoperative hospital LOS (Table 2).

The number of patients with a decrease in the intraoperative ORi to < 50% was significantly higher in the DEX group (Table 2). Univariate logistic regression revealed that low baseline SpO_2 and DEX were associated with a decrease in the intraoperative ORi to < 50%. In the multivariate logistic regression, DM, low baseline SpO_2, and DEX were associated with a decrease in the intraoperative ORi to < 50% (Table 3). In the ROC curve analysis of intraoperative ORi to < 50%, the optimal cutoff value of the initial SpO_2 was 97, with an area under the curve of 0.65 [0.51–0.79], sensitivity of 0.45, specificity of 0.82, positive predictive value of 0.52, and negative predictive value of 0.77.

4. Discussion

In many previous randomized controlled trials, RMMZ was reported to cause less respiratory depression than propofol (34–40). Tang et al. (41) reported that respiratory depression and hypoxia occurred less frequently with RMMZ than those with traditional sedative drugs. When administered as a sedative, DEX is also known to have insignificant depressive effects on respiration (42, 43). Kim et al. (44) reported that in spinal anesthesia, respiratory depression was more frequent in RMMZ than in DEX during intraoperative sedation (21.2 vs. 2.0%; $p = 0.002$); this result differs from the results of the current study. However, few studies have compared the respiratory effects of administering RMMZ and DEX as sedatives, and further studies are required to elucidate these effects in the future. The current study will be a valuable reference for further research. In this study, we confirmed respiratory depression using a relatively safe method of using the decrease in ORi; moreover, the ORi tended to be higher in the RMMZ group. However, the incidence of respiratory depression during sedation was comparable between the two groups. ORi is a relatively recently developed index, and further research is needed to determine whether a reduction in ORi is associated with respiratory depression and specifically to determine what percentage of reduction is clinically significant. Severe respiratory depression did not occur in either group in the current study, and both drugs were safely used for sedation.

Chae et al. (17) reported the optimal dose of RMMZ decreased with age based on the 95% effective doses during the induction of general anesthesia. In the present study, the dose of RMMZ

administered until the induction of sedation reached an MOAA/S scale score of 3 also tended to decrease with age. Therefore, dose reduction should be considered when administering RMMZ to induce sedation in patients of advanced age.

In present study, DM was among the factors associated with a decrease in ORi to < 50%. Patients with DM may have an impaired response to hypoxia, which can be accompanied by foot ulcers, nephropathy, and retinopathy (45). When the participants in the present study were analyzed according to DM (non-DM: n = 54; DM: n = 24), there were no significant differences in baseline SpO_2 (non-DM: 98 [98–99]; DM: 98 [97–99]; p = 0.448), plateau ORi in the preoxygenation phase (non-DM: 0.55 [0.40–0.78]; DM: 0.48 [0.33–0.65]; p = 0.291), and respiratory depression (non-DM: 9 (16.7%); DM: 2 (8.3%); p = 0.533) during sedation. Therefore, further research is required to determine whether DM is associated with ORi reduction owing to an impaired response to hypoxia, deteriorating oxygenation, or measurement issues due to peripheral blood flow impairment caused by DM.

Several studies have reported DEX-induced bradycardia (46, 47). Studies have also reported that there is less reduction in HR when RMMZ is administered than that with the administration of other anesthetic drugs (48, 49). Similar results were obtained in the present study. Therefore, RMMZ can be considered as a sedative for patients with concerns of bradycardia during surgery. Additionally, when using DEX, a 10 min loading procedure is required, and this time should be measured using a drug infusion device or alarm clock (50). Bradycardia is common during this procedure, and the anesthesiologist must closely observe patients' vital signs (46, 47). RMMZ does not require a loading procedure; therefore, it can be administered more easily in clinical settings than DEX. For price comparison, based on this study, an average of 85 μg of DEX was administered during a 1 h surgery under sedation, and the cost for one vial of DEX is approximately $34.4 (United States dollars [USD]) in our institution. When using RMMZ, an average of 13.5 mg is administered, which costs approximately $17.6 USD per 20 mg vial. Costs may vary depending on the surgical and anesthetic situation and institution. Based on this study, RMMZ can reduce costs by approximately half compared with DEX. However, DEX is known to have an analgesic effect, whereas RMMZ is known to have a minimal analgesic effect (51). Based on these characteristics, further research should be conducted to evaluate the overall satisfaction with each drug for surgeons and patients.

5. Limitations

This study had several limitations. First, the authors arbitrarily set the 50% ORi reduction criterion. The decrease in ORi according to the degree of respiratory depression has not yet been reported, and it does not necessarily mean respiratory depression. For patients with a higher ORi, the information from this study can be used to reduce oxygen supplementation to decrease the degree of hyperoxia. Further studies are required to determine the extent to which the ORi is clinically significant. Second, double blinding could not be achieved because of the significant differences in drug infusion methods between DEX and RMMZ. To compensate for this limitation, the postoperative outcome assessor was blinded to the group assignment. Third, the types of surgery were not uniform. However, there was no significant difference in surgical site or type between the two groups. Several types of surgeries were included to generalize the study results to patients undergoing sedation. Fourth, as this study was a single center study with a relatively small sample size, our results cannot be generalized to other institutes and did not show significant differences in postoperative outcomes. We plan to perform a further large-scale multicenter study, and we expect to show significant differences in postoperative outcomes and intraoperative ORi at more time points. Finally, the degree of sedation could not be quantified objectively using the depth of anesthesia monitoring equipment, such as the bispectral index, since equipment that incurred additional costs was difficult to access. To compensate for this limitation, the degree of sedation was maintained at the same level in both groups, using the MOAA/S scale.

6. Conclusion

When RMMZ was used as a sedative, the ORi was higher at 15 min after sedation maintenance than when DEX was used. Factors associated with a decrease in the intraoperative ORi to < 50% were the use of DEX, low baseline SpO_2, and DM. A baseline SpO_2 of < 97% can predict a decrease in intraoperative ORi to < 50%. Intraoperative HR was higher with RMMZ than with DEX. RMMZ is recommended as a sedative for patients with low baseline SpO_2 and concerns of possible bradycardia. Further large-scale multicenter randomized controlled trials should be conducted to evaluate the differences in respiratory aspects in sedation management between classical sedatives and RMMZ. Additionally, future studies on the degree of clinically significant reduction in ORi should be conducted.

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 humans were approved by the Institutional Review Board of Kyung Hee University Hospital (KHUH 2023-02-036) on 17 March 2023. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SL: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Visualization, Writing –

original draft. MSK: Conceptualization, Methodology, Writing – original draft. HK: Data curation, Software, Writing – original draft. J-HC: Conceptualization, Supervision, Writing – review and editing. MKK: Investigation, Supervision, Writing – review and editing. AY: Conceptualization, Data curation, Investigation, Project administration, Resources, Supervision, Writing – review and editing.

Funding

The authors declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We thank Jae-Hong Ryoo, M.D., Ph.D. (Kyung Hee University College of Medicine) as a statistical expert for the data analysis and interpretation.

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.2023.1288243/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Clinical Trial
PUBLISHED 14 December 2023
DOI 10.3389/fmed.2023.1225384

OPEN ACCESS

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RECEIVED 19 May 2023
ACCEPTED 20 November 2023
PUBLISHED 14 December 2023

CITATION
Konkayev A and Bekniyazova A (2023) Vibroacoustic therapy in the treatment of patients with COVID-19 complicated by respiratory failure: a pilot randomized controlled trial.
Front. Med. 10:1225384.
doi: 10.3389/fmed.2023.1225384

Vibroacoustic therapy in the treatment of patients with COVID-19 complicated by respiratory failure: a pilot randomized controlled trial

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Introduction: Coronavirus infection is a dangerous airborne disease that can lead to serious lung damage. Data on the effectiveness of low-frequency chest vibrations in the treatment of lung diseases are available; however, not so many of them exist. Vibroacoustic pulmonary therapy is a component of physiotherapy that improves lung perfusion and drainage without requiring active patient participation. This study aimed to increase statistical efficiency through maximizing the relevant information obtained from the clinical data. Calculating the sample size to determine the power of subsequent studies was also necessary.

Research methods: A pilot randomized parallel trial involving 60 patients was conducted. The patients were divided into two equal groups, where they received sessions of vibroacoustic pulmonary therapy using the "VibroLung" device in two modes "acute respiratory distress syndrome (ARDS)" and "Pneumonia," with identical treatment. The patients were > 18 years old with detected COVID-19 by PCR and grade 2 and 3 lung lesions detected by computer tomography (CT). Blood sampling was performed in the morning at the same time before and after the hardware massage to determine PaO_2, $PaCO_2$, and P/F.

Results: As a result of the test, the following data were obtained: on the first day in the group using the "ARDS" mode, PaO_2 indicators averaged 65, CI 95% [58.6–73.2] and on average 77.5, CI 95% [69.8–85.2], "before" and "after," respectively, which indicates improved oxygenation after the procedure. However, in the second group with the "Pneumonia" mode after its use, $PaCO_2$ was higher after the session, on average 48.7, CI 95% [40.8–56.6], whereas before that, the following indicators had, on average 43.6, CI 95% [37.2–50].

Conclusion: Thus, the data obtained yielded ambiguous results, which are the basis for further study in future randomized controlled trials. As the treatment of coronavirus infection has no etiological treatment, even small shifts in the therapy of this category of patients can be significant.

Clinical trial registration: ClinicalTrials.gov, identifier NCT05143372.

KEYWORDS

COVID-19, vibroacoustic therapy, respiratory insufficiency, physiotherapy, pilot randomized trial

Introduction

COVID-19 is a highly contagious infectious disease that has had a significant impact worldwide since 2019. COVID-19 continues to affect the human body without requiring any special treatment (1, 2). In addition to the general symptoms of intoxication, the disease course varies from mild-to-severe damage to the lungs and other body systems. The treatment of patients with coronavirus pneumonia requires an adequate comprehensive approach, including physiotherapy (3, 4). The symptoms of this pathology include cough, shortness of breath, and sputum discharge (5). Vibroacoustic lung therapy can be a rational component of physiotherapy in the treatment of respiratory diseases, which, instead of manual massage, saves the time and effort of medical personnel who already have a heavy load (6). This improves perfusion and drainage functions, ultimately improving respiratory activity. Vibroacoustic therapy is of interest in many areas of medicine, there are many questions about the effective parameters of the technique (frequency, amplitude, etc.). The range of applications of vibroacoustic therapy (VAT) is wide, including the treatment of pain, fibromyalgia, neurological pathologies. A preliminary review of the treatment of pain with the use of VAT has shown a positive effect, but more reliable studies and results in this area are needed (7).

A review of 7 studies of patients with cerebral palsy showed a positive effect on motor function when using VAT (8).

In addition, there are studies in favor of low-frequency vibration (0.5–120 Hz) in patients with acute stroke with thrombolysis, dissolution of blood clots, which is important for patients with coronavirus infection (9–11).

The "VibroLung" device was used as a component of physiotherapy during the pilot trial in patients with respiratory diseases and is actively used in hospitals in the Commonwealth of Independent States (CIS) countries (6).

The purpose of this pilot test was to determine the acceptability of vibroacoustic massage.

Information on the topic was unavailable when searching the MEDLINE and Cochrane databases. In the past, when treating a patient with a coronavirus infection and concomitant background, an integrated approach using a vibroacoustic device has shown effectiveness and interest in continuing trials (12).

Materials and methods

The study is a simple, blind, randomized parallel trial. Data were collected from the intensive care unit of the City Infectious Diseases Hospital of Astana, Republic of Kazakhstan, from December 2021 to July 2022.

Inclusion criteria:

- Age > 18 years,
- Confirmed COVID-19 using PCR test,
- The degree of lung damage according to computed tomography: CT-2 (25–50% of lung parenchyma is affected); CT-3 (50–75% of lung parenchyma is affected).

Exclusion criteria:

- Age < 18 years,
- Acute stroke,
- Acute coronary syndrome,
- Traumatic chest injury,
- Infectious processes in the chest area.

Consent to participate in this project was obtained from the participants or their guardians before the intervention. The trial included 60 patients (**Supplementary material**) diagnosed with pneumonia caused by coronavirus infection, confirmed using computed tomography and PCR tests for the presence of the virus. All the described patients were on a mechanically ventilator. They were divided into two equal groups. In one group, patients underwent vibroacoustic pulmonary therapy using the "VibroLung" device in a mode called "acute respiratory distress syndrome (ARDS)" (main group n = 30), in the other—in the "Pneumonia" mode (comparison group n = 30). In the "ARDS" mode, the physical emphasis is evenly distributed on slow and fast modulations with a frequency of 20 to 300 Hz, which provides both endobronchial resonance and parenchymal effects, but, as is typical for nosology and hyperhydration of the lungs in ARDS, such effects are most effective. In the "Pneumonia" mode, the effect of fast and slow modulations is applied evenly over all frequencies, aimed at draining a multi-caliber tracheobronchial tree–within 120–300 Hz (13).

Both groups had an identical algorithm of action: sessions were conducted six times a day for 5 min for 3 days in combination with treatment in accordance with the protocol for the treatment of patients with coronavirus infection of the Ministry of Health of the Republic of Kazakhstan (14). The effectiveness of the effect increases with an increase in the multiplicity, but not with an increase in the duration of the procedure (session). Effective duration of the procedure: 3–5 min (15).

The emitters of the device were applied to the most affected areas of the patient's lungs, corresponding to the CT or radiography data, and one or the other mode of the device was turned on. Because the device has long cords for emitters and is portable, the patient's position does not matter and does not require active participation, which is important for patients undergoing artificial lung ventilation. Immediately before the procedure, arterial blood was collected once in the morning to determine PaO_2, $PaCO_2$, and P/F blood, as well as 10 min after the session.

The initial patient data will be shown below (**Table 1**).

All data were entered into the MC Excel database as patients were registered by the researcher. At the end of the set period, the data were statistically processed.

The sample size was not calculated owing to the uneven admission of patients with coronavirus infection at different times from 2021 to 2022 because of the variability of the peak incidence.

Participants were randomly assigned to either the treatment or comparison group at a 1:1 ratio using a random number generator on the site www.randomizer.org. The researcher handed the medical workers a preprepared opaque envelope with randomly assigned numbers. Owing to the need to select a mode on the device display screen, all medical personnel knew regarding the selected mode when it was hidden from the patient.

Abbreviations: VALT, vibroacoustic lung therapy; VAT, vibroacoustic therapy.

Medical workers trained in the procedure and use of the device conducted a session of vibroacoustic therapy, as well as performed blood sampling.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 20.

The Kolmogorov–Smirnov criterion was used to determine the normality of data. Student's *t*-tests were used only for normally distributed data. In cases with an abnormal distribution, intragroup analysis was performed using the Wilcoxon test in each group before and after VALT.

Ethical approval

The study was approved by the Ethics Committee of the Research Institute of Orthopedics and Traumatology in Astana on 19.11.21 and registered on ClinicalTrials.gov., ID: NCT05143372.

Results

Regarding the initial data of patients in both groups, age and sex did not show large differences, as did scores on the APACHE II, qSOFA, and PADUA scales. Based on laboratory data, patients showed a difference in the mean values (SD) of CRP, IL-6, and ECR (Table 1).

When analyzing the results, the following information was obtained: in the group using the "ARDS" mode, on the first day, the average value of PaO_2 increased by 12.5 mmHg. After the procedure, the median increased by 7.8 mmHg, 95% confidence interval: it became [69.8–85.2], and the standard deviation after that was 20.6 mmHg (Table 2).

As for the group using the "Pneumonia" mode, the results on the change in the $PaCO_2$ level on the third day were shown and were "Before" average 43.6, m 37.6, CI 95% [37.2–50], SD 17 and "After" mean 48.7, m 39.6, CI 95% [40.8–56.6] SD 21.1. Vibroacoustic pulmonological apparatus was used in this mode (Table 3).

TABLE 1 Initial demographic data of patients.

Characteristic	Main group ("ARDS" *n* = 30)	Control group ("Pneumonia" *n* = 30)
Age, years, median [IQR]	69 [5.75]	66.5 [21]
Gender, male, *n* (%)	8 (27%)	11 (37%)
Gender, female *n* (%)	22 (73%)	19 (63%)
APACHE II, median [IQR]	10.5 [5.25]	10 [5]
PADUA, median [IQR]	7 [1.25]	6 [1]
qSOFA, median [IQR]	2 [1]	1.5 [1]
CRP, m [SD]	129.9 [82.5]	111 [71.6]
IL-6, m [SD]	177 [257.5]	392 [1077]
ESR, m [SD]	26 [14.8]	30.8 [17.1]

IQR, interquartile range; m, median; n, number; SD, standard deviation.

Discussion

The purpose of this study was to determine the acceptability of vibroacoustic pulmonary massage. Taking into account the results obtained, it is necessary to note a certain positive effect of vibroacoustic lung therapy in the treatment of pneumonia in both modes of operation of the device. It should also be noted that in the "ARDS" mode, an improvement in the oxygen content in arterial blood was observed on the first day, whereas in the "Pneumonia" mode, a decrease in carbon dioxide was observed on the third day of receiving VALT sessions. These results are encouraging, but for greater reliability of the results, further study of the field of physiotherapy methods using a larger sample in a randomized controlled trial is necessary. It depends on the power, frequency or other mechanisms of action of the shaft, which have yet to be studied in more depth.

Coronavirus infection differs from other diseases with an extremely high mortality rate worldwide, including in our region, which limits the long-term results of this study.

Another disadvantage is the need to conduct the study in a single clinic. Thus, establishing a causal relationship between the observed changes is difficult.

For a more specific and accurate generalization of the results of the effects of vibroacoustic lung therapy, continuing the study with long-term follow-up is necessary, as the use of vaccines against the virus has reduced the severity of the disease and reduced the mortality of patients (16). Therefore, a multicenter study with a larger sample size is required. COVID-19 has caused enormous harm to the health of the population worldwide, and today, although not in such quantities, cases of the disease remain being registered. Therefore, owing to the lack of etiological treatment, a rational integrated approach is advisable for this category of patients (17, 18). A number of studies have focused on the positive impact and safety of using low-frequency vibrations and vibrations separately on respiratory function and on the body as a whole; however, no combination of them in one device that we attempted to study, including vibration in coronavirus disease exists (19, 20).

Vibroacoustic waves in the form of triangular-shaped modulations with a relatively "slow" period (1.1–10 s) are used for exposure in order to improve ventilation-perfusion ratios, recruitment and drainage of large-caliber bronchi. Vibroacoustic waves of "faster" modulation (0.2–1.0 s) are used to further improve the drainage function of small-caliber bronchi and sawtooth-shaped alveolar sacs with decreasing and increasing frequency. Due to the acoustic properties of the chest, the rapidly decreasing frequency of vibroacoustic waves causes an effect resembling a light tapping on the chest, the rapidly increasing frequency of vibroacoustic waves resembles the effect of soft pressure on the chest, which contributes to the discharge of sputum. According to clinical observations, the frequency range from 20 to 60 Hz most effectively affects the chest. At the same time, the frequency range of vibroacoustic waves of 37–42 Hz for most patients is the most effective in terms of creating maximum pressure fluctuations in the lumen of the large airways (21). To enhance the effect in this frequency segment, a temporary emphasis is placed in all programs. Exposure at higher frequencies is less prolonged and has less time emphasis, because when exposed at higher frequencies, the penetrating power of the

TABLE 2 Statistical data on the application of the "ARDS" of the VALT mode before and after.

Arterial blood gases	1 day	2 day	3 day
PaO_2 before	*Mean 65, m 66.7, CI 95% [58.6–73.2], SD 19.5*	Mean 73.2, m 73.7, CI 95% [67.3–79.2], SD 16	Mean 70.9, m 73.6, CI 95% [64.1–77.7], SD 18.2
PaO_2 after	*Mean 77.5, m 74.5, CI 95% [69.8–85.2], SD 20.6*	Mean 74.4, m 76.3, CI 95% [67.8–80.9], SD 17.6	Mean 75.4, m 75.7, CI 95% [65.8–85], SD 25.7
$PaCO_2$ before	Mean 42.7, m 36.8, CI 95% [36.4–48.9], SD 16.8	Mean 46, m 40.8, CI 95% [40.2–51.9], SD 15.7	Mean 43.6, m 37.7, CI 95% [37.2–50], SD 17
$PaCO_2$ after	Mean 40.4, m 37.7, CI 95% [35.8–45], SD 12.3	Mean 48.8, m 40.4, CI 95% [40.6–57], SD 22	Mean 48.7, m 39.6, CI 95% [40.8–56.6], SD 21.1
P/F before	Mean 88.8, m 79.5, CI 95% [74.8–107.5], SD 43.8	Mean 90.6, m 83, CI 95% [80–101.4], SD 29.1	Mean 92, m 84.5, CI 95% [78–106], SD 37.6
P/F after	Mean 98.8, m 88.3, CI 95% [84.7–112.9], SD 37.8	Mean 90.6, m 87.3, CI 95% [80–101.2], SD 28.4	Mean 93.5, m 87, CI 95% [80–106.8], SD 35.7

The average value, median, 95% confidence interval, standard deviation are indicated. Statistically significant data are highlighted in italics. IQR, interquartile range; m, median; n, number; SD, standard deviation.

TABLE 3 Statistical data when applying "Pneumonia" of the VALT mode before and after.

Arterial blood gases	1 day	2 day	3 day
PaO_2 before	Mean 67.6, m 66.7, CI 95% [61.3–74], SD 17	Mean 71, m 64, CI 95% [58.2–83.9], SD 34.4	Mean 72, m 65, CI 95% [62.7–81.2], SD 25
PaO_2 after	Mean 72, m 61.9, CI 95% [59.3–84.9], SD 34.4	Mean 72, m 59.3, CI 95% [61–83], SD 29.5	Mean 72.3, m 62, CI 95% [62.3–82.2], SD 26.6
$PaCO_2$ before	Mean 43, m 39, CI 95% [37–48.2],SD 14.1	Mean 46, m 40.8, CI 95% [40.2–51.9], SD 15.7	*Mean 43.6, m 37.6, CI 95% [37.2–50], SD 17*
$PaCO_2$ after	Mean 47.5, m 39.4, CI 95% [40.6–54.5], SD 18.6	Mean 48.8 m 40.4, CI 95% [40.6–57], SD 22	*Mean 48.7, m 39.6, CI 95% [40.8–56.6] SD 21.1*
P/F before	Mean 88.8, m 97, CI 95% [76.2–101.3], SD 33.5	Mean 89.7, m 83.7, CI 95% [75.2–104.2], SD 38.7	Mean 90, m 90, CI 95% [73.8–107.7], SD 45.4
P/F after	Mean 95.2, m 85.2, CI 95% [76.1–114.2], SD 33.5	Mean 89.9, m 74.4, CI 95% [73.7–106], SD 43.3	Mean 92, m 83.2, CI 95% [75.7–108.5], SD 43.9

The average value, median, 95% confidence interval, standard deviation are indicated. Statistically significant data are highlighted in italics. IQR, interquartile range; m, median; n, number; SD, standard deviation.

sound wave is less. Thus, for effective exposure, the best effect is achieved when exposed to a relatively wide frequency range, regardless of the nature of the pathology. Low-frequency pressure fluctuations of 20–60 Hz (22) in the lumen of the respiratory tract contribute to both a better intake of air into the lungs and drainage function. Low-frequency sound waves probably have an effect on the parietal parenchyma, and the rapidly changing frequency of the signal contributes to a better drainage effect of the small bronchi. The more intense the inflammatory process, the more edematous the pulmonary parenchyma is, respectively, it is more accessible to the penetration of higher frequency sound waves (above 100 Hz). For the most optimal effect in various lung pathologies, executive programs can be more divided into 3 groups, depending on the percentage of elements of fast (with a period of 0.2–1 s) and deep slow (1.1–10 s) frequency modulation, which mainly determines the drainage effect. In pathology, where the drainage effect is not a priority (restrictive pathology), the content of such elements is less. In executive programs that pursue the main goal of improving drainage, the content of such elements is greater. The above information is according to the manufacturer's manual.

It is worth noting the undesirable effect observed by a medical professional that when using the "ARDS" mode, vibration has greater power and possibly less comfort than when using the "Pneumonia" mode. The device "Vibrolung" was developed by a domestic manufacturer to improve the course and outcomes of respiratory diseases of various etiologies. According to the developer's instructions, the principle of the shaft effect is based on the generation of an audio signal from a bifocal position by two emitters in the range of 20–300 Hz. The "floating effect" of the sound wave causes a resonant effect, which has a safe and highly effective effect on any kind of lesion of both the lung parenchyma itself and bronchial tree, alveoli, and vessels. The "floating" frequency of the signal allows you to achieve better results with less intensity and exposure time. The resulting vibroacoustic wave causes fluctuations, first of all, of the inhomogeneous parenchyma of the lung and intrapulmonary compartment (edema, mucus, infiltration, hypostatic transudate), which improves drainage, ventilation, and aeration and reduces penetration and spread. With mechanical breathing (ventilator), regular vibroacoustic action reduces the zone of lung collapse and atelectasis due to external pressure, which increases the positive end expiratory pressure (PEEP) without an additional increase in ventilation parameters.

The "ARDS" and "Pneumonia" modes in accordance with the manufacturer's instructions, differ in indications for use. In this regard, distinctive properties of these schemes when used in patients with coronavirus infection, which has not been done before, have been of interest.

Researchers from CIS countries actively use this component of physiotherapy and publish data on successful results in patients with respiratory pathologies; however, no data on COVID-19 exist (7). Other researchers have reflected on the safety of using oscillator devices in human patients with COVID-19 on artificial lung ventilation (23).

According to the instructions for the device, low-frequency waves and vibrations propagating together cause vibrations of the structural units of the pulmonary parenchyma, thereby improving the perfusion and drainage function of the lungs. The formation of secretions in patients with coronavirus infection occurs in one-third of the cases (24).

As the device is relatively new and not sufficiently widespread, the data do not depend on the effectiveness of its use. Evidence for the positive effect of early physiotherapy on outcomes in patients with respiratory diseases is sufficient, but not in those with coronavirus infection (24–26). Vibration provides rapid evacuation of bronchial secretions, accelerates the gravitational redistribution of intra-pulmonary fluid, and improves ventilation–perfusion ratios (4).

Today, in the period after coronavirus infection, its impact on the respiratory system, rehabilitation, and in this case, vibroacoustic pulmonary therapy is of great importance. New lung physiotherapy devices and infections raise an immeasurable number of questions that require to be addressed.

Conclusion

Thus, the use of vibroacoustic massage in the complex therapy of respiratory diseases may restore bronchial conduction disorders, improve lung ventilation and gas exchange, and improve blood circulation (27–30). Consequently, this can have an impact on faster clinical recovery, reducing the duration of inpatient treatment. Therefore, further multicenter randomized controlled trials are required to confirm the effectiveness of vibroacoustic therapy in this new group of critically ill patients. Moreover, to prove its effectiveness in further studies, introducing this component of physiotherapy for coronavirus infection complicated by respiratory insufficiency into clinical practice for future research in the field of rehabilitation of respiratory disorders after COVID-19 is advisable.

Author's note

The authors have read the CONSORT 2010 statement: extension to randomized pilot and feasibility trials, and the manuscript was prepared and revised according to the CONSORT 2010 statement: extension to randomized pilot and feasibility trials.

Data availability statement

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

Ethics statement

The study was approved by the Ethics Committee the National Scientific Center of Traumatology and Orthopedics Named After Batpenov in Astana on 19.11.2021. Written informed consent from patients (guardians) was received.

Authors contributions

AK: conceptualization. AB: review and editing of manuscript. Both authors issued final approval for the version to be submitted.

Acknowledgments

We thank to members of the intensive care unit for the opportunity to conduct research.

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.2023.1225384/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 21 December 2023
DOI 10.3389/fmed.2023.1328636

OPEN ACCESS

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RECEIVED 27 October 2023
ACCEPTED 06 December 2023
PUBLISHED 21 December 2023

CITATION
Mao H, Yu Y, Wang Q and Li H (2023) Association between pre-ICU statin use and ARDS mortality in the MIMIC-IV database: a cohort study.
Front. Med. 10:1328636.
doi: 10.3389/fmed.2023.1328636

Association between pre-ICU statin use and ARDS mortality in the MIMIC-IV database: a cohort study

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Background: Acute respiratory distress syndrome (ARDS) is a severe condition associated with high morbidity, mortality, and healthcare costs. Despite extensive research, treatment options for ARDS are suboptimal.

Methods: This study encompassed patients diagnosed with ARDS from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database. Pre-intensive care unit (ICU) statin use was assessed as the exposure variable. Kaplan–Meier survival analysis was conducted to evaluate mortality at 30 and 90 days. Adjusted multivariable Cox models were utilized to estimate hazard ratios. Subgroup analyses and propensity score-matching (PSM) were undertaken for further validation.

Results: Our study comprised 10,042 participants diagnosed with ARDS, with an average age of 61.8 ± 15.3 years. Kaplan–Meier survival analysis demonstrated a significantly lower prevalence of mortality at 30 and 90 days in individuals who used statins before ICU admission. Adjusted multivariable Cox models consistently showed a significant decrease in mortality prevalence associated with pre-ICU statin use. After accounting for confounding factors, patients who used statins before ICU admission experienced a 39% reduction in 30-day mortality and 38% reduction in 90-day mortality. We found a significant decrease in ICU stay (0.84 days) for those who used statins before ICU admission. These results were supported by subgroup analyses and PSM.

Conclusion: This large cohort study provides evidence supporting the association between pre-ICU statin use, reduced risk of death, and shorter ICU stay in patients with ARDS, thereby suggesting the potential benefits of statin use in critically ill patients.

KEYWORDS

ICU, Medical Information Mart for Intensive Care-IV, statins, cohort study, mortality

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by severe hypoxemic respiratory failure, with bilateral infiltrates evident on chest imaging, which is not fully explained by heart failure or fluid overload. ARDS is defined by the Berlin criteria (1). Despite significant advancements in the understanding of ARDS since its initial description over 50 years ago (2), treatments primarily offer supportive care rather than a definitive cure, which has led to a prevalence of mortality of up to 45% (3). Furthermore, survivors of ARDS often experience long-term physical, neuropsychiatric, and neurocognitive impairments that affect their quality of life significantly (4). Consequently, there is an immediate and pressing need to identify innovative and efficacious therapies to improve clinical outcomes and address the wide-ranging health consequences associated with ARDS.

Inhibitors of hydroxymethylglutaryl-coenzyme A reductase (statins) are often recommended for primary and secondary prevention of cardiovascular diseases because of their lipid-lowering properties. Recent research has highlighted the crucial anti-inflammatory, immunomodulatory, and antioxidant properties of statins (5, 6). The diverse impacts of statins have attracted growing interest across various medical disciplines, including their potential role in ARDS management. These effects occur primarily at the transcriptional level, which leads to a decrease in the synthesis of cytokines, chemokines, and C-reactive protein (7, 8). A clinical trial comparing rosuvastatin to a placebo found no significant differences in the prevalence of mortality or ventilator-free days (VFDs) (9). Another study evaluating the effects of simvastatin on VFDs and mortality did not show improved clinical outcomes. Nevertheless, the use of statin therapy in ARDS patients appears to be safe with minimal adverse effects, though the exact clinical benefits in this specific population remain uncertain (10, 11). The application of statins in ARDS treatment is controversial (12–14).

We wished to investigate the potential therapeutic benefits of pre-intensive care unit (ICU) statin use in relation to the prognosis of patients with ARDS. A retrospective analysis was conducted on a cohort of 10,042 critically ill patients using data from the MIMIC-IV dataset spanning the period from 2001 to 2019. We aimed to test the hypothesis that pre-ICU statin use in patients suffering from ARDS would be associated with a reduced prevalence of mortality and shorter stay in the ICU.

Methods

All study data were obtained exclusively from the MIMIC-IV database (version 2.2).[1] The MIMIC database contains information from the electronic medical records of the Beth Israel Deaconess Medical Center (Boston, MA, USA): basic demographics, laboratory results, treatment prescriptions, and records on ICU monitoring (15). The extraction process employed the Structured Query Language Server to ensure systematic retrieval of relevant data. Before accessing the database, Yi Yu secured official permission (certificate ID: 6477678) for utilization. The preparation of this report adhered strictly to the Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (16).

Study population and data extraction

Patients included in the present study met the diagnostic criteria for ARDS according to the latest internationally recognized definition (17), the fulfillment of the criteria depends on the indicators present on the day of admission to the ICU. Only adult individuals aged ≥18 years were eligible for inclusion. If patients had multiple admissions to the ICU, only data from their initial ICU admission were considered. Patients with incomplete records of respiratory-support parameters, blood-gas analyses, and vital signs were excluded from the study. Comprehensive data collection encompassed patient demographics, vital signs, comorbidities, laboratory results, scores for clinical severity, treatments (including ventilation, administration of vasoactive drugs, and dialysis), as well as other relevant admission data.

Use of statins

To identify the pre-ICU use of statins, prescriptions for statins before ICU admission were identified by analyzing the medication records in the MIMIC-IV database.

Outcomes and covariates

The primary endpoints assessed were mortality at 30 and 90 days. The secondary outcomes of interest were the duration of ICU stay. The variables considered in the analysis encompassed demographic factors such as sex, age, ethnicity, marital status, and insurance status. In addition, physiological measures were included: body mass index (BMI), ARDS severity, utilization of mechanical ventilation, administration of vasoactive medications, continuous renal replacement therapy (CRRT), results of blood-gas analysis, respiratory rate, oxygen saturation in blood, mean arterial blood pressure, heart rate, white blood cell count, platelet count, as well as levels of hemoglobin, creatinine, and glucose. We collected data on disease-severity scores (Charlson, Sequential Organ Failure Assessment (SOFA), Simplified Acute Physiology Score (SAPS) II) as well as information on comorbidities.

Statistical analyses

Appropriate statistical methods were employed to analyze data and establish a comparison of variables. Quantitative variables were summarized using interquartile ranges (IQRs) and median values, with categorical variables presented as percentages and counts. The Kruskal–Wallis test was used to determine a significant variation in continuous variables between groups given statin therapy. The chi-square test was employed to compare categorical variables. Missing data were handled by replacement with the median value. This approach was selected due to the low percentage of lack of information (0.3–4%) for height and weight variables. To ensure data completeness and increase the accuracy of results, multiple imputation

1 https://mimic.mit.edu/

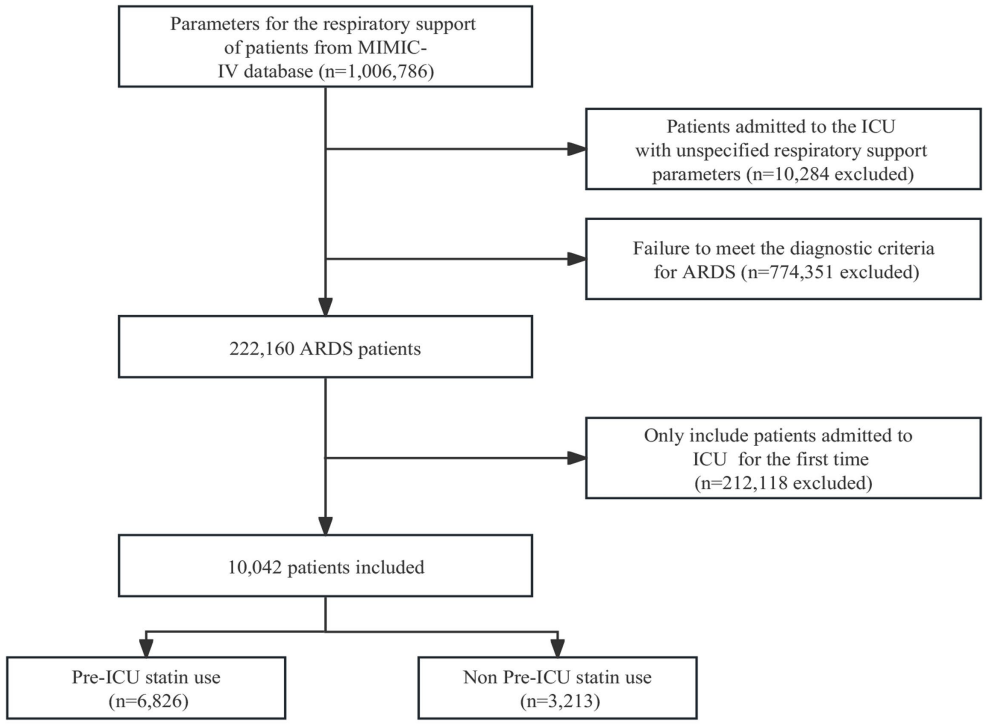

FIGURE 1
Flowchart of this study.

methods were used to handle missing values (5–10%) in the Cox regression analysis and model building. We conducted multiple imputation by employing the R MI procedure using a chained equation approach method and 5 replications to address the missing data.

To investigate the potential impact of previous statin use on the prevalence of mortality within 30-day and 90-day timeframes, we conducted univariate and multivariate Cox regression analyses while adjusting for the aforementioned covariates. To visualize survival trends, Kaplan–Meier curves were generated and compared using the log-rank test. Furthermore, subgroup analyses were undertaken to examine the consistency of our findings across different subgroups, including age (<60 and ≥ 60 years), BMI (<25 and ≥ 25 kg/m^2), sex (male and female), ARDS severity (mild, moderate, severe), ethnicity (white, others), SOFA score (<6 and ≥ 6), and lactate level (<4 and ≥ 4 mmol/L), with interaction effects being assessed. Propensity-score matching (PSM) was employed to enhance the robustness of our results using a 1:1 nearest neighbor-matching algorithm with a caliper width of 0.01. The hazard ratio (HR) for 30-day and 90-day mortality was estimated using a multivariable Cox proportional hazards regression model with a robust variance estimator. $P < 0.05$ (two-sided) was considered significant.

Statistical analyses were conducted using STATA 17.0 (College Station, TX, USA). This program provided the necessary tools and functions for the manipulation and modeling of data. In addition, we utilized packages from R (R Institute for Statistical Computing, Vienna, Austria) and Free Statistics 1.8 to augment analyses by leveraging the specific functionalities and statistical methods contained in these programs.

Results

Participants

The flowchart illustrated in Figure 1 is a comprehensive representation of the sequential selection process employed to identify suitable study participants. Initially, all 222,160 patients underwent screening based on the predefined diagnostic criteria for ARDS. Patients with repeated admissions to the ICU were subsequently excluded from the study cohort. The final analysis was conducted on a refined cohort comprising 10,042 patients. The flowchart captures visually the systematic approach implemented to identify and select this definitive group of participants for further investigation.

Baseline characteristics

The study cohort comprised 10,042 patients with a mean age of 61.8 ± 15.3 years, and 34.9% of the cohort were women. Table 1 provides an in-depth overview of the baseline characteristics observed within this patient population. A meticulous comparison between the two sets of data revealed conspicuous distinctions: the group who did not use statins before ICU admission tended to be younger and women. They exhibited lower levels of partial pressure of oxygen in the arterial blood/fraction of inspired oxygen (PaO_2/FiO_2), increased lactate level, increased use of invasive ventilator and CRRT, higher disease scores, higher prevalence of comorbid sepsis, and noticeably increased prevalence of 30-day and 90-day mortality. In contrast, the group who used statins before ICU

TABLE 1 Characteristics of participants at baseline.

Variable	Total (*n* = 10,042)	Non pre-ICU statin use (*n* = 6,829)	Pre-ICU statin use (*n* = 3,213)	*p*
Age, years	61.8 ± 15.3	59.2 ± 16.4	67.3 ± 11.0	<0.001
Sex, female, n (%)	3,507 (34.9)	2,577 (37.7)	930 (28.9)	<0.001
BMI, kg/m^2	29.6 ± 6.9	29.5 ± 7.2	29.7 ± 6.1	0.3
Ethnicity, n (%)				<0.001
White	6,257 (62.3)	4,047 (59.3)	2,210 (68.8)	
Other	3,785 (37.7)	2,782 (40.7)	1,003 (31.2)	
Insurance type, n (%)				<0.001
Medicaid	802 (8.0)	652 (9.5)	150 (4.7)	
Medicare	3,770 (37.5)	2,311 (33.8)	1,459 (45.4)	
Other	5,470 (54.5)	3,866 (56.6)	1,604 (49.9)	
Heart rate (bpm)	87.0 ± 15.2	88.4 ± 16.3	84.1 ± 12.2	<0.001
MAP (mmHg)	76.7 ± 9.0	77.4 ± 9.7	75.2 ± 7.3	<0.001
Respiration rate (bpm)	19.4 ± 4.0	19.8 ± 4.2	18.5 ± 3.3	<0.001
Temperature (°C)	36.9 ± 0.7	36.9 ± 0.8	36.8 ± 0.5	<0.001
SpO_2 (%)	97.1 ± 2.8	97.0 ± 3.0	97.4 ± 2.0	<0.001
Glucose (mmol/L)	142.4 ± 45.2	144.2 ± 49.3	138.7 ± 34.9	<0.001
pH	7.4 ± 0.1	7.3 ± 0.1	7.4 ± 0.1	<0.001
PO_2 (mmHg)	187.6 ± 75.3	173.8 ± 75.1	216.9 ± 67.1	<0.001
PCO_2 (mmHg)	42.8 ± 9.1	43.1 ± 9.7	42.0 ± 7.5	<0.001
PaO_2/FiO_2	245.8 ± 95.8	241.5 ± 97.2	255.1 ± 92.0	<0.001
Lactate (mmol/L)	2.0 (1.5, 2.8)	2.0 (1.5, 3.0)	1.9 (1.5, 2.5)	<0.001
WBC count (×10^9)	13.8 ± 9.9	13.9 ± 10.2	13.5 ± 9.4	0.045
Hb (g/L)	10.8 ± 1.9	10.9 ± 2.1	10.4 ± 1.6	<0.001
Platelets (×10^9)	190.0 ± 100.6	193.3 ± 105.4	183.0 ± 89.3	<0.001
BUN (mg/dL)	22.3 ± 17.6	23.2 ± 18.8	20.5 ± 14.6	<0.001
Scr (mg/dL)	0.9 (0.7, 1.3)	0.9 (0.7, 1.3)	0.9 (0.8, 1.2)	0.005
Sodium (mmol/L)	138.7 ± 4.4	138.9 ± 4.8	138.2 ± 3.4	<0.001
Potassium (mmol/L)	4.3 ± 0.6	4.3 ± 0.6	4.4 ± 0.5	<0.001
Vasoactive drugs, n (%)	6,672 (66.4)	4,318 (63.2)	2,354 (73.3)	<0.001
CRRT, n (%)	634 (6.3)	533 (7.8)	101 (3.1)	<0.001
Ventilation, n (%)	8,648 (86.1)	6,115 (89.5)	2,533 (78.8)	<0.001
MI, n (%)	1,649 (16.4)	668 (9.8)	981 (30.5)	<0.001
CHF, n (%)	217 (2.2)	139 (2)	78 (2.4)	0.207
CBVD, n (%)	1,456 (14.5)	940 (13.8)	516 (16.1)	0.002
CPD, n (%)	2,360 (23.5)	1,594 (23.3)	766 (23.8)	0.582
Rheumatic disease, n (%)	275 (2.7)	184 (2.7)	91 (2.8)	0.693
Diabetes without complication, n (%)	2,223 (22.1)	1,264 (18.5)	959 (29.8)	<0.001
Diabetes with complication, n (%)	747 (7.4)	353 (5.2)	394 (12.3)	<0.001
Renal disease, n (%)	1,402 (14.0)	797 (11.7)	605 (18.8)	<0.001
Malignant cancer, n (%)	1,275 (12.7)	935 (13.7)	340 (10.6)	<0.001
Severe liver disease, n (%)	744 (7.4)	679 (9.9)	65 (2)	<0.001
Charlson comorbidity index	5.1 ± 2.8	4.8 ± 2.8	5.8 ± 2.5	<0.001
SOFA score	6.8 ± 3.4	7.1 ± 3.7	6.2 ± 2.7	<0.001
SAPS II score	41.0 ± 15.2	41.6 ± 15.8	39.6 ± 13.5	<0.001

(Continued)

TABLE 1 (Continued)

Variable	Total (n = 10,042)	Non pre-ICU statin use (n = 6,829)	Pre-ICU statin use (n = 3,213)	p
Sepsis, n (%)	6,994 (69.6)	5,075 (74.3)	1919 (59.7)	<0.001
30-day mortality, n (%)	1,729 (17.2)	1,442 (21.1)	287 (8.9)	<0.001
90-day mortality, n (%)	1,833 (18.3)	1,527 (22.4)	306 (9.5)	<0.001
ICU stay, days	2.6 (1.3, 5.8)	3.5 (1.7, 7.9)	2.2 (1.3, 4.2)	<0.001

For each variable, mean ± standard deviation, median (interquartile range), or number (percent) was reported (as appropriate).
BMI, body mass index; MAP, mean arterial pressure; SpO_2, pulse oxygen saturation; PH, potential of hydrogen; PO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; PaO_2/FiO_2, arterial oxygen tension/inspired oxygen fraction; WBC, white blood cell; Hb, hemoglobin; BUN, blood urea nitrogen; Scr, serum creatinine; CRRT, continuous renal replacement therapy; MI, myocardial infarct; CHF, congestive heart failure; CBVD, cerebrovascular disease; CPD, chronic pulmonary disease; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit.

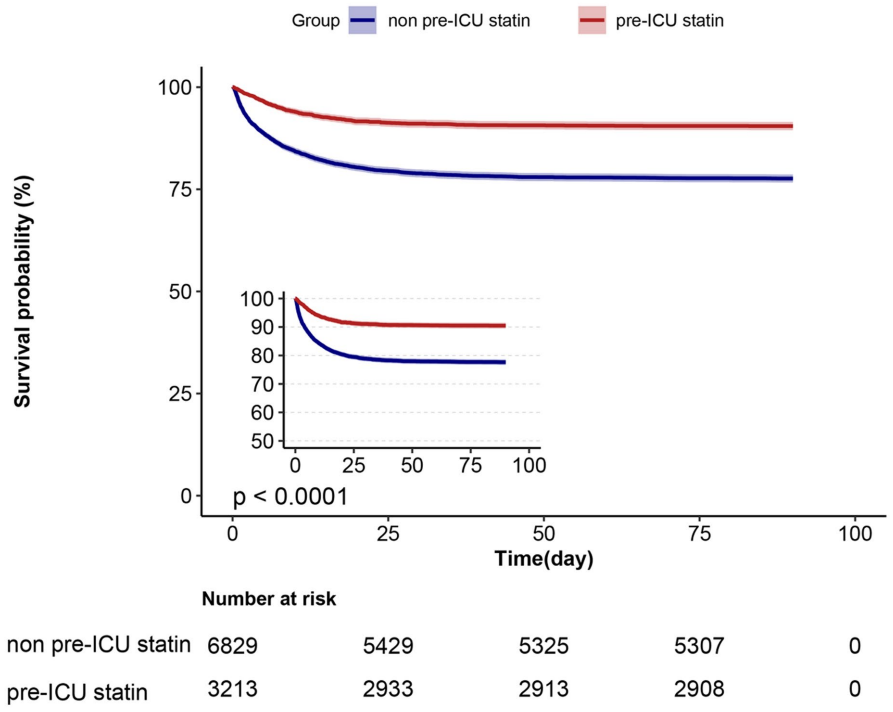

FIGURE 2
Kaplan–Meier survival curves for ICU patients at day 90 and categorized on pre-ICU statin use.

admission statin demonstrated a lower prevalence of vasoactive-drug administration and fewer comorbidities. Supplementary Table S1 presents a comparison of baseline data between the two groups following Propensity-score matching (PSM).

Relationship between pre-ICU statin use and mortality at 30 and 90 days

Survival analyses using the Kaplan–Meier method revealed a significant decrease in the prevalence of mortality at 30 and 90 days among patients who had pre-ICU statin use compared with those who had not (log-rank test: $p < 0.0001$) (Figure 2). In the assessment of 30-day mortality risk, pre-ICU statin use was associated with a significant reduction in death compared with non pre-ICU statin use (HR = 0.39, 95%CI = 0.34–0.44, $p < 0.001$). Consistent results were observed when analyzing data over the course of 90 days, which highlighted comparable outcomes between non pre-ICU statin use and pre-ICU statin use. A notable association between pre-ICU statin use and a lower HR was observed (HR = 0.39, 95%CI = 0.35–0.44, $p < 0.001$) (Table 2).

In extended multivariable Cox models (Table 2), the HRs for pre-ICU statin use remained consistently significant across all models (ranging from 0.36 to 0.61, $p < 0.001$ for all). After adjustment for the covariates listed in Table 2, we found a 39% lower risk of 30-day mortality in patients who received statins before ICU admission (HR = 0.61, 95%CI = 0.53–0.70, $p < 0.001$, model 6) (Table 2). Similarly, there was a 38% lower risk of 90-day mortality in patients who received statins before ICU admission (HR = 0.62, 95%CI = 0.54–0.71, $p < 0.001$, model 6) (Supplementary Table S2). These results indicated the robustness of the findings obtained from our models.

Relationship between pre-ICU use of statins, duration of ICU

In the univariate analysis, the group who used statins before ICU admission had a significantly shorter ICU stay compared with those who did not use used statins before ICU admission. The reduction in ICU stay was 2.14 days ($p < 0.001$, $\beta = -2.14$, 95%CI = −2.43 to −1.86). This finding was consistent with the results obtained from the linear multivariate regression model. It showed a shorter ICU stay for the group who used statins before ICU admission than those who did not use statins before ICU admission. The reduction in ICU stay was 0.84 days ($p < 0.001$, $\beta = -0.84$, 95%CI = −1.13 to −0.55) (Table 3). The results remained significant even after using PSM to control for potential confounding variables ($p < 0.001$, $\beta = -0.69$, 95%CI = −1 to −0.39) (Supplementary Table S3). These results strongly suggested pre-ICU statin administration to be associated with a shorter duration of ICU stay.

Subgroup analyses and sensitivity analyses

Subgroup analyses showed that the relationship between pre-ICU statin use and ICU outcome remained robust and reliable. Specifically, the protective impact of pre-ICU statin use was more pronounced in patients under the age of 60 years and those of non-white ethnicity. No other significant interactions were observed in the subgroups ($p_{interaction} > 0.05$) (Figure 3).

After PSM, the study included 2,547 well-matched pairs in the group with pre-ICU statin use and the non pre-ICU statin use group. There were no significant differences between the two matched groups. Among these matched pairs in the propensity score-matched pool, patients who received statins before ICU admission had a significantly lower prevalence of mortality at 30 and 90 days ($p < 0.001$) (Supplementary Table S1).

The robustness of these findings was confirmed through Cox regression models. The univariable Cox proportional hazards regression model showed a HR of 0.74 (95%CI = 0.63–0.86, $p < 0.0001$) for 30-day mortality and a HR of 0.76 (95%CI = 0.65–0.88, $p < 0.0001$) for 90-day mortality (Table 2). These results indicated a significant reduction in the prevalence of mortality among patients who received statins before ICU admission, which suggested the beneficial effects of pre-ICU statin use on the outcome.

TABLE 2 Values of HR and 95%CI of pre-ICU statin use for 30-day mortality.

	HR	95%CI	*p*
Model 1	0.39	(0.34–0.44)	<0.001
Model 2	0.36	(0.32–0.41)	<0.001
Model 3	0.37	(0.32–0.42)	<0.001
Model 4	0.59	(0.52–0.68)	<0.001
Model 5	0.59	(0.51–0.67)	<0.001
Model 6	0.61	(0.53–0.7)	<0.001
PSM	0.74	(0.63–0.86)	<0.001

Discussion

Main findings

Our study represents the most comprehensive cohort investigation examining the impact of pre-ICU statin use on mortality in patients suffering from ARDS. We found a significant association between pre-ICU statin use and a reduction in ICU stay. Moreover, our results suggest that patients with ARDS given statins before ICU admission had a lower risk-adjusted prevalence of mortality at 30 and 90 days compared with those who did not use statins before ICU admission. Importantly, these findings remained consistent even after accounting for potential confounding factors through PSM. Our study provides strong evidence supporting the potential benefits of pre-ICU statin use in improving the outcome in patients with ARDS.

Effects of pre-ICU statin use on mortality and ICU stay for patients suffering from ARDS

Statin administration has been associated with a reduced prevalence of mortality in individuals diagnosed with ARDS (18, 19). However, those studies used an outdated definition of ARDS. Therefore, the findings from those studies may not be entirely consistent with the current understanding of ARDS. Hence, we aimed to expand on those previous findings by specifically examining the relationship between pre-ICU statin use and death for patients diagnosed according to the latest definition of ARDS.

A retrospective study conducted in multiple medical centers explored the use of statins in patients with coronavirus disease 2019 and found a potential reduction in the risk of developing ARDS (odds ratio = 0.78, 95%CI = 0.69–0.89, $p < 0.001$) (20). A double-blind, randomized controlled trial conducted in the UK and Ireland by Agus and colleagues enrolled 540 intubated and mechanically ventilated patients with ARDS. They demonstrated that simvastatin was a cost-effective treatment for ARDS, resulting in significant gains in quality-adjusted life years and cost savings (21). Similarly, Mansur et al. conducted a prospective observational cohort study in Germany involving 404 patients with sepsis-associated ARDS. Their findings indicated that statin therapy improved 28-day survival exclusively in patients with severe ARDS compared with those not taking statins (88.5% vs. 62.5%, $p = 0.0193$) (19).

TABLE 3 Pre-ICU statin use and ICU stay.

		Model 1		Model 2	
Variable	n. total	β (95%CI)	*p*	β (95%CI)	*p*
Non pre-ICU statin use	6,829	0 (Ref)		0 (Ref)	
Pre-ICU statin use	3,213	−2.14 (−2.43 to −1.86)	<0.001	−0.84 (−1.13 to −0.55)	<0.001

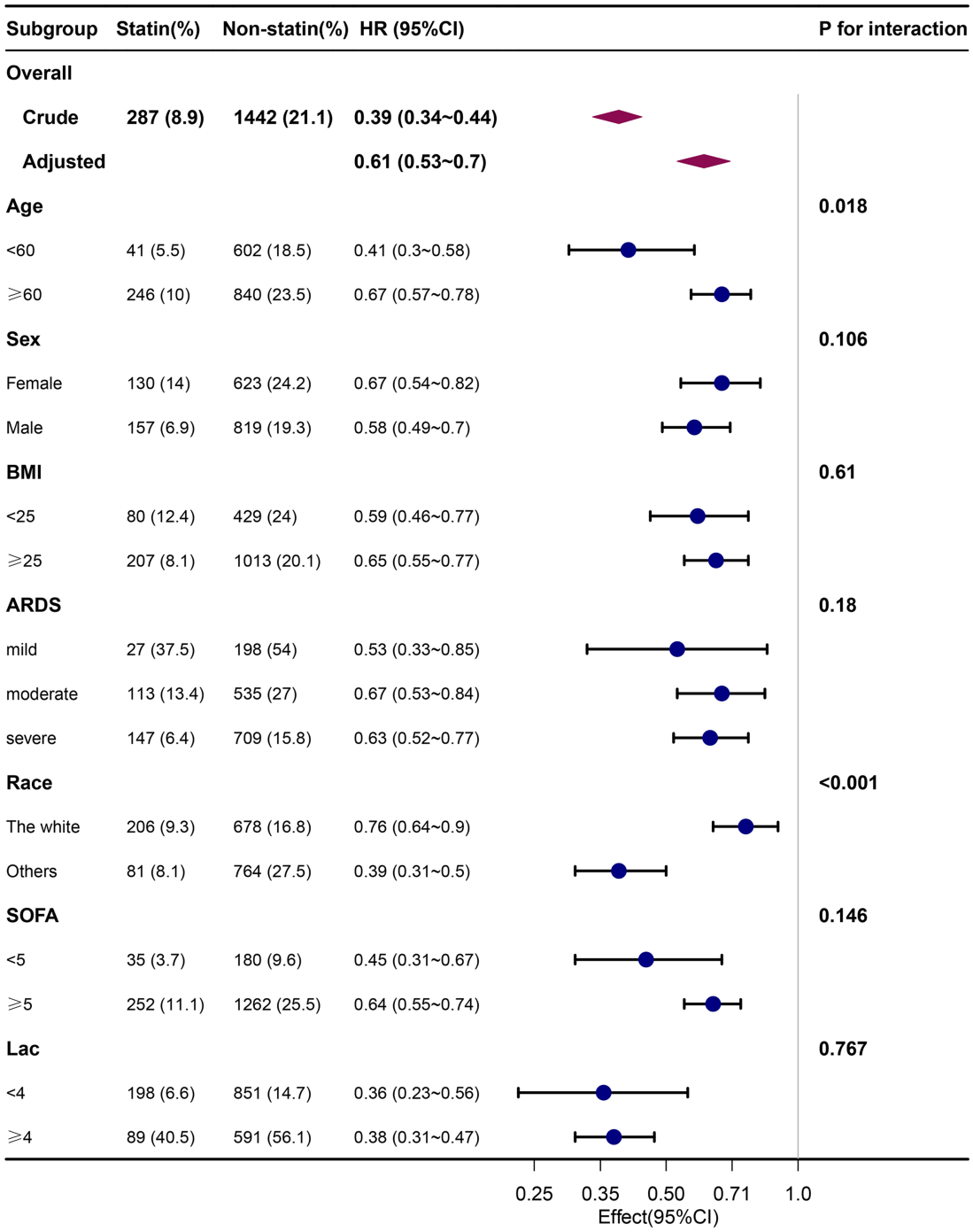

FIGURE 3
Association between pre-ICU statin use and 30-day mortality according to baseline characteristics. Each stratification adjusted for all the factors (age, sex, BMI, ethnicity, insurance, temperature, heart rate, MAP, respiration rate, SPO2, glucose, PH, PO2, PCO2, PO2/FiO2, lactate, sodium, potassium, WBC, HB, PLT, Scr, Bun, ventilation, vasoactive drugs, CRRT, SAPS II, SOFA, charlson comorbidity index, myocardial infarct, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, diabetes without complication, diabetes with complication, renal disease, malignant cancer, severe liver disease, sepsis) except the stratification factor itself. BMI, body mass index; ARDS, Acute Respiratory Distress Syndrome; SOFA, Sequential Organ Failure Assessment.

We observed that pre-ICU statin use was associated with a significant reduction in the prevalence of mortality at 30 days and 90 days in patients with ARDS (HRs were 0.61 (95%CI = 0.53–0.70, $p < 0.001$) and 0.62 (95%CI = 0.54–0.71, $p < 0.001$), respectively). Moreover, pre-ICU statin use was linked to a reduction of ~0.84 days in ICU stay ($\beta = -0.84$, 95%CI = −1.13 to −0.55, $p < 0.001$).

There is conflicting evidence regarding the efficacy of statin use in reducing the risk of ARDS-related death and improving the prognosis, so additional studies are needed to establish a clearer understanding.

A meta-analysis conducted by Nagendran et al. did not demonstrate a clinical benefit from initiating statin therapy in adult patients diagnosed with ARDS. However, that meta-analysis had limitations, including a small number of studies and populations, and only a subset of the included studies utilized established ARDS criteria for patient selection (22). In a cohort study by Oh and coworkers involving a Korean population, pre-ICU statin use did not lead to a significant reduction in 30-day mortality ($p = 0.215$) (23). However, that study had important limitations, including a lack of information on BMI, PaO_2/FiO_2, SAPS-II score, vasoactive-medication usage, CRRT, and the presence/absence of comorbid sepsis. These factors influence the prognosis of patients suffering from ARDS (1, 24).

The precise mechanisms through which statins reduce the risk of death in patients with ARDS are not known. The efficacy of statin therapy in mitigating cardiovascular risk is widely acknowledged, particularly because of deeper understanding of atherosclerosis as an inflammatory condition (25, 26). Experts have identified multiple mechanisms by which statins alleviate inflammation (27, 28) and endothelial dysfunction (29, 30). One study demonstrated a notable reduction in systemic and pulmonary inflammation, as well as indicators of damage to alveolar type-1 epithelial cells and the systemic vascular endothelium, in patients who received statins before treatment. Hence, the anti-inflammatory properties of statins may account for the beneficial prognosis observed with their employment in ARDS (31). Evidence suggests that simvastatin diminishes the pulmonary inflammatory response to endotoxins in healthy individuals (32). Furthermore, statins exhibit antithrombotic advantages (33, 34), as validated by a well-designed, sizable, randomized controlled trial (35, 36).

Strengths of our study

Our study possessed four main strengths. First, we utilized a comprehensive and publicly available database, thereby ensuring the reliability and comprehensiveness of our data. The diagnostic criteria used for ARDS were current and well-defined, which enhanced the accuracy and validity of our study. Second, no study has specifically examined the impact of pre-ICU statin use on the risk of death in patients suffering from ARDS. Our findings provide clear and conclusive evidence that pre-ICU statin use reduces ICU stay significantly and lowers the prevalence of 30-day and 90-day mortality among individuals with ARDS. Third, we employed multiple regression analysis and conducted PSM to establish the robustness and reliability of our study findings. This rigorous analytical approach further strengthens the credibility and internal validity of our results. Fourth, considering the widespread use of statins for primary and secondary prevention of cardiovascular diseases, our findings hold implications and generalizability beyond the ARDS population specifically.

Limitations of our study

Our study had five main limitations. First, ARDS is not a specific disease but instead a syndrome diagnosed based on various clinical and physiological criteria. Patients with ARDS may have different underlying risk factors, complex premorbidities and comorbidities, and potentially diverse pathophysiology (37, 38). However, this shortcoming was offset by the large number of patients enrolled in our study. Second, caution should be exercised when generalizing the findings of our study because it was conducted using data from a single ICU in the USA. The sample size was substantial and fairly representative, but conducting a multicenter prospective study in the future would be valuable to confirm the generalizability of our results. Third, the generalizability of our findings to other causes of ARDS, such as trauma, aspiration, and transfusion, is limited because >69% of patients in our cohort had sepsis-induced ARDS. Nevertheless, further analysis of this specific subset is crucial because sepsis remains the most common cause of ARDS. Fourth, this study was observational, and therefore, did not apply the optimal methodology for evaluating the effects of a drug. A future randomized controlled trial would be more appropriate. Nonetheless, our study provides a foundation for further examination of pre-ICU statin use in ARDS. Nonetheless, the limitations of our study can be mitigated partially by the considerable number of participants involved and adoption of PSM methodology. Fifth, our primary objective was to assess the influence of different types and doses of statins on the prognosis of patients with ARDS. However, the limited sample size in each group resulted in insufficient statistical power, which affected statistical outcomes significantly.

Conclusion

Application of statins before ICU admission in patients with ARDS showed potential clinical advantages. Pre-ICU statin use significantly reduced the prevalence of mortality at 30 and 90 days in patients with ARDS, and led to a shortened ICU stay. These findings suggest the efficacy of statins in the treatment of ARDS. Statin therapy may be a feasible therapeutic choice for ARDS patients and merits further research.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: the MIMIC-IV database (version 2.2; https://mimic.mit.edu/).

Ethics statement

The studies involving humans were approved by the research, which incorporated human participants, underwent comprehensive scrutiny and obtained ethical approval from both the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

HM: Writing – review & editing. YY: Writing – original draft. QW: Writing – review & editing. HL: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was funded by the Guangdong Bureau of Traditional Chinese Medicine (20222065 and 20232049) and the National Natural Science Foundation of China (82104989).

Acknowledgments

We would like to express our sincere appreciation to the Free Statistics team for their invaluable technical support and provision of essential tools for data analysis and visualization.

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.2023.1328636/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 08 January 2024
DOI 10.3389/fmed.2023.1324369

OPEN ACCESS

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RECEIVED 19 October 2023
ACCEPTED 21 December 2023
PUBLISHED 08 January 2024

CITATION
Han Y, Duan J, Chen M, Huang S, Zhang B, Wang Y, Liu J, Li X and Yu W (2024) Relationship between serum sodium level and sepsis-induced coagulopathy.
Front. Med. 10:1324369.
doi: 10.3389/fmed.2023.1324369

Relationship between serum sodium level and sepsis-induced coagulopathy

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Purpose: A discussion about the correlation between the level of serum sodium and sepsis-induced coagulopathy (SIC).

Materials and methods: A retrospective analysis was conducted on sepsis patients who were admitted to the Intensive Care Unit (ICU) of Nanjing Drum Tower Hospital from January 2021 to December 2022. Based on the presence of coagulation disorders, the patients were divided into two groups: sepsis-induced coagulopathy (SIC) and non-sepsis-induced coagulopathy (non-SIC) groups. We recorded demographic characteristics and laboratory indicators at the time of ICU admission, and analyzed relationship between serum sodium level and SIC.

Results: One hundred and twenty-five patients with sepsis were enrolled, among which, the SIC and the non-SIC groups included 62 and 63 patients, respectively. Compared to patients in the non-SIC group, the level of serum sodium of those in the SIC was significantly higher ($p < 0.001$). Multi-factor logistic regression showed serum sodium level was independently associated with SIC (or = 1.127, $p = 0.001$). Pearson's correlation analysis indicated that the higher the serum sodium level, the significantly higher the SIC score was ($r = 0.373$, $p < 0.001$). Additionally, the mortality rate of patients with sepsis in the ICU were significantly correlated with increased serum sodium levels ($p = 0.014$).

Conclusion: An increase in serum sodium level was independently associated with an increased occurrence of SIC and also associated with the poor prognosis for patients with sepsis.

KEYWORDS

sodium, sepsis, coagulation disorders, ICU, hypernatremia

1 Introduction

Sepsis-induced coagulopathy (SIC) is a significant component of sepsis-related multiple organ dysfunction syndrome (MODS) and is strongly linked to the woresning of microcirculatory issues and tissue organ damage in patients (1–3). The prevalence of SIC in adults ranges from 50 to 70% (4), and it occurs more frequently in sepsis patients compared to those with sepsis-induced acute kidney injury (SAKI) (26–50%) (5–7) and sepsis-induced acute liver injury (SALI) (30%) (8). The development of SIC is primarily associated with the activation

of the coagulation pathway, impairment of the anticoagulant system, suppression of fibrinolysis, and platelet aggregation in sepsis patients (9–11). When the organism was infected, inflammatory mediators of pathogen-associated molecular patterns (PAMPs) and pro-inflammatory substances of damage-associated molecular patterns (DAMPs) are synthesized and released into the blood, which puts the organism in a hypercoagulable state (12–14). At this stage, the anticoagulant mechanism is significantly inhibited, which may cause massive microthrombosis and vascular endothelial damage. In the terminal stage, patients may progress to disseminated intravascular coagulation (DIC), which is closely related to the increased mortality rate of patients with sepsis (15, 16). It has been reported that the mortality rate of patients with sepsis combined with DIC is two times greater than that of patients without DIC (17). Any delayed intervention in sepsis-induced coagulation dysfunction may be harmful (18). The International Society on Thrombosis and Hemostasis currently recommends early to identify of coagulation disorders (19).

Sodium ions (Na^+) are the main cations in extracellular fluids and are important for maintaining extracellular fluid volume, regulating acid–base balance, and maintaining normal osmolality and cellular physiological functions. And it is the most effective of all monovalent cations that activate thrombin (20). Nonetheless, as a result of substantial fluid replacement and increased aldosterone secretion, hypernatremia is also more prevalent among sepsis patients. In a study, the occurrence of hypernatremia in ICU-admitted patients varied from 2 to 6%, while the incidence of ICU-acquired hypernatremia reached as high as 26% (21–23). Moreover, Lindner et al. (22) had shown hypernatremia acquired during the ICU was an independent risk factor for patients death. Hypernatremia is also closely associated with sepsis severity, increased rates of organ failure, and increased in-hospital mortality (24, 25).

Na^+, a critical thrombin activator, can bind to a specific thrombin site, leading to thrombin activation and stimulation of osmosis (20). These processes regulate the increased expressions of a transcription factor, the nuclear factor of activated T cells 5 (NFAT5), and its binding to the von Willebrand Factor (vWF) promoter, resulting in platelet aggregation (26). Activated thrombin converts fibrinogen into fibrous protein, forming blood clots (27). Additionally, prior research has indicated a connection between serum sodium concentration and damage to vascular endothelial and glycocalyx barriers (17, 28). Excessive sodium concentration leaded to a reduction in the thickness of the endothelial glycocalyx (eGC), a villous layer covering the vascular endothelium (29, 30). However, the integrity of the glycocalyx is important for maintaining normal coagulation function in the body (31).

Presently, there are no clinic studies that have assessed the correlation of serum sodium level with SIC at home and abroad. Thus, this study aimed to retrospectively analyze the relationship between the serum sodium level and SIC in intensive care unit (ICU) patients with sepsis.

2 Materials and methods

2.1 Clinical information

The clinical data about patients with sepsis who were admitted to the ICU of Nanjing Drum Tower Hospital from January 2021 to December 2022 were retrospectively analyzed. The inclusion criteria were: (1) patients aged ≥18 years; (2) ICU stay ≥24 h; (3) patients conforming to the diagnostic criteria 3.0 for sepsis (confirmed or suspected infection and SOFA score ≥ 2 points) (32). The exclusion criteria were: (1) pregnant patients; (2) patients with a history of chronic liver disease; (3) blood dialysis patients; (4) those with chronic kidney disease; (5) patients with hematological diseases and those taking anticoagulant medications; (6) patients with incomplete clinical data. This study was approved by the Ethics Committee of Drum Tower Clinical Medical College Affiliated with Nanjing University (File Number:2022-038-02).

2.2 Data collection

The patient demographic characteristics and laboratory data were collected, based on the patient's first examination on admission to the ICU. General data: age and gender; underlying diseases: diabetes, hypertension, chronic liver disease, history of chronic kidney disease with hemodialysis, anticoagulation therapy; origins of sepsis; mechanical ventilation (MV); scores: Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE II) score; died in ICU; laboratory indicators: white blood cell (WBC) count, platelet count (PLT), prothrombin time (PT), activated partial prothrombin time (APTT), international normalized ratio (INR), D-Dimer, fibrinogen (FIB), C-reactive protein (CRP), creatinine (Cr), blood urea nitrogen (BUN), albumin (ALB) level, total bilirubin (TB), serum sodium, serum calcium, serum potassium, and serum phosphorus.

2.3 Definition SIC and serum sodium level

The diagnosis of SIC was based on the SIC score, which were assessed using the PT-INR, PLT, and SOFA score. If the sum of points ≥ 4 and the sum of PT-INR and PLT points > 2 were obtained, the patient was diagnosed with SIC (Table 1). the serum sodium concentration was categorized into three groups according to the definitions of previous studies: hypernatremia (>145 mmol/L), normal sodium level (135–145 mmol/L), and hyponatremia (<135 mmol/L) (33, 34).

2.4 Statistical methods

The SPSS 25.0 software was used for statistical analysis. For comparisons between two groups, independent samples *t*-tests were

TABLE 1 Diagnostic scores of SIC.

Categories	0 point	1 point	2 points
PT-INR	≤1.2	>1.2	>1.4
Platelet count ($\times 10^9$/L)	≥150	<150	<100
SOFA score	0	1	≥2

PT, prothrombin time; INR, international standard ratio; SOFA, sequential organ failure score.

used for measurement data that conformed to normal distribution, expressed as mean ± standard deviation; conversely, nonparametric tests were used, expressed as the median (interquartile spacing). Pearson's chi-square test or continuous calibration chi-square test was used to compare categorical variables, expressed as percentages (%). We analyzed whether the level of serum sodium was independently associated with SIC by utilizing single- and multifactors logistic regression analysis. We included sex, age, and indicators with *p*-values less than 0.05 in the comparison of baseline data between the two groups in via logistic regression analysis. However, considering the covariance between BUN and Cr, we did not include BUN in the logistic regression analysis. Based on the results we constructed receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC), which was aimed at assessing the efficiency of the serum sodium concentration to predict SIC. One-way ANOVA was used for analysis of variables for more than two groups and for measurement data that conformed to a normal distribution. Correlation between serum sodium levels with SIC scores were analyzed via Pearson's correlation analysis. Spearman's correlation analysis was used to process the correlation between serum sodium levels and coagulation parameters The linear-by-linear association was used to analyze whether serum sodium levels were associated with clinical outcomes. A p-value < 0.05 for all the statistical results was considered to indicate statistical significance.

3 Results

3.1 Flowchart of patients meeting inclusion/exclusion criteria for the study

A total of 178 patients were included, of which, 2 pregnant patients, 10 patients with hematological diseases and taking anticoagulant medications, 11 patients with chronic hypohepatia, 7 blood dialysis patients (of whom 5 had been excluded due to a history of chronic liver and kidney diseases), 13 chronic renal insufficiency patients, and 15 patients with incomplete clinical data were excluded. In the end, the data analysis covered 125 patients in total. Sixty two patients were diagnosed with SIC based on the diagnostic criteria, while 63 patients did not meet the criteria (Figure 1).

3.2 Comparison of general information between the SIC and non-SIC groups

The result showed no statistical difference was observed between the two groups in age, gender, underlying diseases, origins of sepsis, needing mechanical ventilation, WBC count, CRP, and ALB levels ($p > 0.05$). However, serum sodium level in the SIC group increased significantly (median, SIC, 144.8 vs. non-SIC, 139.8, $p < 0.001$), while calcium, potassium, and phosphorus levels exhibited no difference between the two groups. Additionally, Cr and TB levels in the SIC group were significantly higher than those in the non-SIC group (median: Cr; SIC, 103.5 vs. non-SIC, 61, $p = 0.001$; TB; SIC, 18.85 vs. non-SIC, 12.6, $p = 0.014$). Moreover, SOFA score and APACHE II score in the SIC group were also significantly higher than those in the non-SIC group (median; SOFA; SIC, 8.5 vs. non-SIC, 6, $p = 0.003$; APACHEII; SIC, 23.95 vs. non-SIC, 20.43, $p = 0.009$), which indicated patients in the SIC group had higher severity (Table 2).

3.3 Relationship between serum sodium level and SIC

The age and sex, as well as SOFA score, Cr, TB, and Na^+ level, were included in the single-factor logistic regression analysis. These indicators were then included in a multi-factor logistic regression analysis. The results showed that Cr (OR, 1.006; 95% CI, 1.010 ~ 1.001; $p = 0.011$) and serum sodium level (OR, 1.127; 95% CI, 1.051 ~ 1.208; $p = 0.001$) were independently correlated with SIC (Table 3).

3.4 ROC curve analysis of serum sodium level to predict SIC

We conducted a ROC curve. The result showed that serum sodium level had a predictive value for the occurrence of SIC (AUC = 0.697, 95% CI, 0.605–0.789, $p < 0.001$). The best cut-off value for predicting SIC was 144.65 mmol/L, with a sensitivity of 53.2% and a specificity of 84.1% (Figure 2).

3.5 Correlation between serum sodium level and SIC score

According to the SIC scores, we created 5 groups (2 points, 3 points, 4 points, 5 points, and 6 points) and compared differences in serum sodium among groups. We also analyzed the correlation between serum sodium level and SIC score. Based on the results, we drew a boxplot and a scatter diagram. The number of patients in each group was 27, 36, 28, 15, and 19, respectively. Compared to the 5 and 6 points groups, the level of serum sodium in 3 points group was significantly lower (mean, 5 points group, 146.41 vs. 3 points group, 143.27, $p = 0.026$; 6 points group, 147.53 vs. 3 points group, 143.27, $p = 0.002$), whereas the 2 points group exhibited a statistical difference when compared to serum sodium level in 6 points groups (mean, 6 points group, 147.53 vs. 2 points group, 139.99, $p = 0.009$) (Figure 3A). There was a correlation between serum sodium level and SIC score ($r = 0.373$, $p < 0.001$) (Figure 3B). The higher the SIC score, the higher the serum sodium level.

3.6 Correlation between serum sodium level and coagulation parameters

Based on the diagnostic criteria of hypo- and hypernatremia, 125 patients were divided into hyponatremia, normal Na level, and hypernatremia groups. The number of patients in each group was 13, 74, and 38, respectively. A correlation analysis was conducted. The results showed higher serum sodium level displayed a significant correlation with lower PLT level (Figure 4A, $r = -0.270$, $p = 0.002$), higher PT level (Figure 4B, $r = 0.245$, $p = 0.006$), higher INR level (Figure 4D, $r = 0.244$, $p = 0.007$), and lower FIB level (Figure 4F, $r = -0.290$, $p = 0.001$), but not with APTT (Figure 4C, $r = 0.022$, $p = 0.808$) and D-dimer levels (Figure 4E, $r = -0.009$, $p = 0.924$).

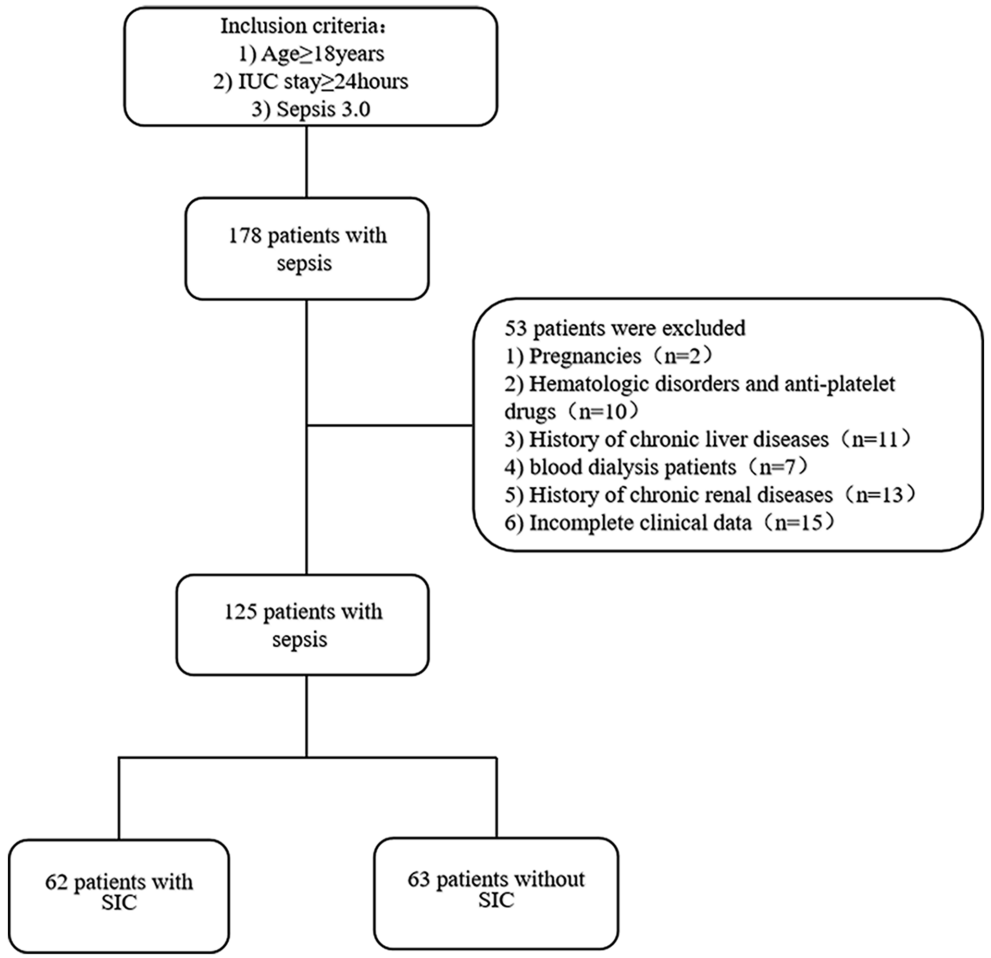

FIGURE 1
Flow chart of patients with inclusion/exclusion criteria for this study. A total of 178 patients were collected. We excluded 53 patients according to the exclusion criteria. Finally, 125 patients were categorized into SIC (n = 62) or non-SIC groups (n = 63) using the diagnostic criteria for sepsis-related coagulation disorders.

3.7 Correlation of serum sodium level with clinical outcomes

The linear-by-linear association was used to evaluate whether the clinical outcomes of patients with sepsis correlate with the serum sodium level. The patients were divided into hyponatremia, normal Na level, and hypernatremia groups as per the serum sodium levels. The in-ICU mortality of each group was 3, 22, and 15, while the number of patients needing mechanical ventilation in each group was 7, 46, and 23, respectively. Our results showed that the in-ICU mortality rate of patients with sepsis correlated with an increased serum sodium level (Figure 5A, p = 0.014), but not with mechanical ventilation (Figure 5B, p = 0.810).

4 Discussion

In this study, we explored the correlation between the level of serum sodium and the SIC. We analyzed the relationship between serum sodium and SIC score. The present study showed a positive correlation between serum sodium levels and SIC scores. An increase in serum sodium levels was independently associated with the development of SIC.

Although there are no studies on the relationship between serum sodium and coagulation disorders, studies have shown that serum sodium concentrations are related to the eGC. The serum sodium concentration in the body plays an important role in maintaining eGC stability. The eGC, a layer of negatively charged villus-like structures covering the endothelial surface of blood vessels, attracts circulating Na + ions in the vascular cava (35) and plays a beneficial role in sodium buffering *in vivo* (36). Consequently, the glycocalyx serves as a significant extrarenal regulator of extracellular sodium and serve as a reservoir for substantial sodium storage (37). When the body experiences sodium overload, it disrupts Na + homeostasis. This alteration causes a transition in endothelial cells from releasing sodium to absorbing sodium (28), leading to damaged in vascular endothelium. This, in turn, results in a reduction in the release of nitric oxide (NO). NO can dilate blood vessels, inhibit platelet activation, prevent platelet aggregation, adhesion, and prevent thrombosis (38, 39). Martin et al. (17) subjected human umbilical vein endothelial cells (HUVECs) to sodium (Na) concentrations of 134 mEq/L (control medium), 150 mEq/L, and 160 mEq/L,

TABLE 2 Comparison of demographic characteristics and laboratory indicators between the SIC and Non-SIC.

Projects	SIC (n = 62)	Non-SIC (n = 63)	p-value
Age, years, mean (SD)	63.1 ± 15.31	60.79 ± 16.98	0.428
Sex, male, n (%)	37 (59.70)	40 (63.50)	0.661
SOFA score, median (IQR)	8.5 (5, 13)	6 (4, 8)	0.003*
APACHEII score, mean (SD)	23.95 ± 8.47	20.43 ± 6.34	0.009*
Basic disease, *n* (%)			
Hypertension	24 (38.7)	25 (39.7)	0.911
Diabetes	19 (30.6)	15 (23.8)	0.391
Cardiovascular	9 (14.5)	12 (19)	0.498
Tumor	12 (19.4)	8 (12.7)	0.310
Origin of sepsis, *n* (%)			
Lung	28 (45.2)	36 (57.1)	0.180
Abdomen	12 (19.4)	13 (20.6)	0.858
Urinary tract	7 (11.3)	3 (4.8)	0.310
Skin or soft tissue	5 (8.1)	3 (4.8)	0.697
Central nervous system	3 (4.8)	5 (7.9)	0.732
Other	7 (11.3)	3 (4.8)	0.310
Mechanical ventilation, n (%)	41 (66.1)	35 (55.6)	0.226
Died in ICU, n (%)	24 (38.7)	16 (25.4)	0.111
Laboratory indicator, median (IQR)			
WBC (10*9/L)	9.85 (5.53, 15.23)	11 (8.7, 15.4)	0.162
CRP (mg/L)	106.8 (50.30, 196.28)	98.3 (53.4, 161.5)	0.811
Creatinine (μmol/L)	103.5 (61.25, 214.25)	61 (45, 124)	0.001*
BUN (mmol/L)	12.4 (8.18, 21.20)	8.5 (6.6, 13.6)	0.002*
Total bilirubin (μmol/L)	18.85 (11.73, 37.88)	12.6 (7.9, 26.5)	0.014*
Albumin (g/L)	31.05 (29.25, 34.45)	31.4 (29.2, 35.3)	0.925
Serum sodium (mmol/L)	144.8 (140.43, 149.23)	139.8 (136.7, 143.1)	< 0.001*
Serum calcium (mmol/L)	2.09 (1.88, 2.20)	2.13 (1.94, 2.27)	0.258
Serum potassium (mmol/L)	4 (3.75, 4.60)	4.02 (3.65, 4.29)	0.174
Serum phosphorus (mmol/L)	1.125 (0.73, 1.39)	0.89 (0.73, 1.17)	0.142

SOFA, Sequential Organ Failure Assessment; APACHEII, Acute Physiology and Chronic Health Status Assessment System II; WBC, white blood cell count; CRP, C-reactive protein; BUN, blood urea nitrogen; *$p < 0.05$.

TABLE 3 Logistic regression analysis of coagulation dysfunction associated with sepsis.

Variables	Single-factor logisitic analysis		Multi-factor logisitic analysis	
	OR value (95% CI)	p value	OR value (95% CI)	p value
Ages	1.009 (0.987 ~ 1.031)	0.424		
Sex	0.851 (0.414 ~ 1.751)	0.661		
SOFA score	1.149 (1.052 ~ 1.254)	0.002*		
APACHEII score	1.066 (1.014 ~ 1.121)	0.012*		
Creatinine (μmol/L)	1.006 (1.002 ~ 1.010)	0.006*	1.005 (1.001 ~ 1.010)	0.012*
Total bilirubin (μmol/L)	1.006 (0.995 ~ 1.016)	0.297		
Serum sodium (mmol/L)	1.121 (1.054 ~ 1.193)	< 0.001*	1.125 (1.050 ~ 1.207)	0.001*

SOFA, Sequential Organ Failure Assessment; APACHEII, Acute Physiology and Chronic Health Status Assessment System II; *$p < 0.05$.

respectively. Then they found that excessive sodium concentrations all resulted in a significant increase in the shedding of eGC damage markers. They also measured glycocalyx thickness and found that the thickness of the cellular glycocalyx was significantly reduced by a factor of two under the Na 160 mEq/L concentration compared to the control group under Na 134 mEq/L. A study by Zheng et al. (40)

reported that, compared to the normal chow (NC) diet group, the NC diet with 4% salt (NC4%) induced microcirculatory disturbances and glycocalyx degradation in mice. Glycocalyx damage is closely associated with the development of coagulation dysfunction, which has also been reported in several papers (41–43). These findings may laterally indicate that elevated serum sodium levels impair eGC, which in turn affects coagulation.

We investigated the relationship between serum sodium levels and coagulation parameters. The findings revealed that the higher serum sodium levels were associated with activation of the coagulation state, primarily manifesting as reduced platelet counts, prolonged PT, increased INR, and diminished FIB levels. Various mechanisms have been proposed to elucidate the coagulation dysfunction that could be related to increased serum sodium. The blood coagulation factor Xa (FXa) is an important serine protease in the coagulation cascade that plays a vital role in physiological hemostasis. However, excessive thrombin levels lead to the transformation of soluble fibrinogen into the insoluble fibrous protein, thus, resulting in thrombus formation (44–47). Relative studies suggested that thrombin displays better catalysis in the process of clotting in the presence of Na^+ (48–51). Rezaie and He (52) also proved that Na^+ can effectively activate thrombin which may relate to that it can bind to the 225 s loop residue of Try conformation of FXa. Moreover, Dmitrieva and Burg (26) cultured HUVECs in a high-sodium environment with different osmotic pressures and found that the secretion of vWF displayed a sodium-dependent increase while the high-sodium environment stimulated increased NFAT5 production. The vWF is secreted by endothelial cells and can bind to blood platelets, which is crucial for thrombus formation; the increased NFAT5 activity also contributes to increased vWF production in endothelial cells. Furthermore, Dmitrieva and Burg (26) revealed that when compared to the renal cortex, the vWF proteins and interstitial sodium chloride levels in the renal medulla were significantly higher. This indicated that the elevation of extracellular sodium within the physiological range is sufficient to increase vWF levels, thereby enhancing its coagulation ability and the risk of thrombus formation. Moreover, we found that the increased serum sodium levels were related to the decreased blood platelets and fibrinogen levels, which was consistent with the above-mentioned studies.

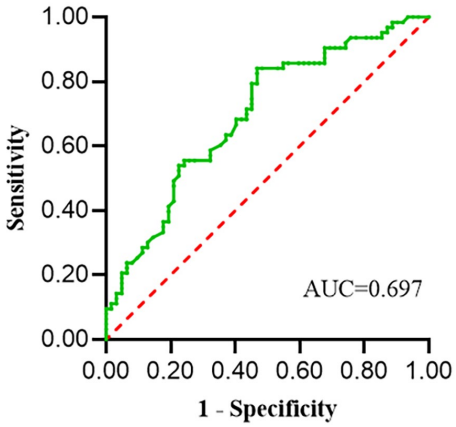

FIGURE 2
ROC curve analysis of serum sodium levels to predict SIC. The sensitivity and specificity of serum sodium to predict SIC were 53.2 and 84.1%, respectively; the critical value was 144.65 mmol/L; the area under the curve was 0.697 ($p < 0.001$); 95% confidence interval: 0.605–0.789.

We also analyzed the relationship between serum sodium level and clinical outcomes in patients with sepsis. The results showed that the higher the serum sodium level was, the greater the mortality rate was for patients with sepsis in the ICU. In addition, the ROC curve showed that a serum sodium concentration of 144.65 mmol/L had predictive value for the occurrence of SIC. Li et al. (53) found that higher serum sodium level was associated with an increased mortality rate in patients with sepsis in a large-sample, multicenter study. Thongprayoon et al. (54) also reported that borderline hypernatremia (143–147 mmol/L) was associated with an increased hospital mortality rate in a study on serum sodium and the risk of death in hospital patients. All of these support the finding that elevated serum sodium levels are associated with severity in septic patients.

In addition, another new finding of our study was that Cr was also independently associated with SIC. However, the association between Cr and coagulation has not been determined. Cr serves as a predictor of renal function. The kidney is one of the organs most likely to

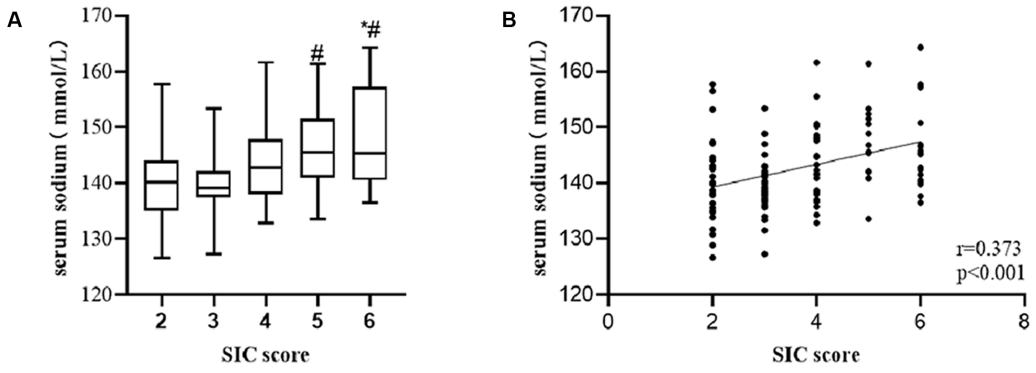

FIGURE 3
Among patient with sepsis, serum sodium level was significant higher in patients in the group with higher SIC score compared to those in the group with lower SIC score **(A)** (*p-value < 0.05, comparison vs. 2 points group; #p-value < 0.05, comparison vs. 3 points group). There was a positive correlation of serum sodium level with SIC score **(B)**.

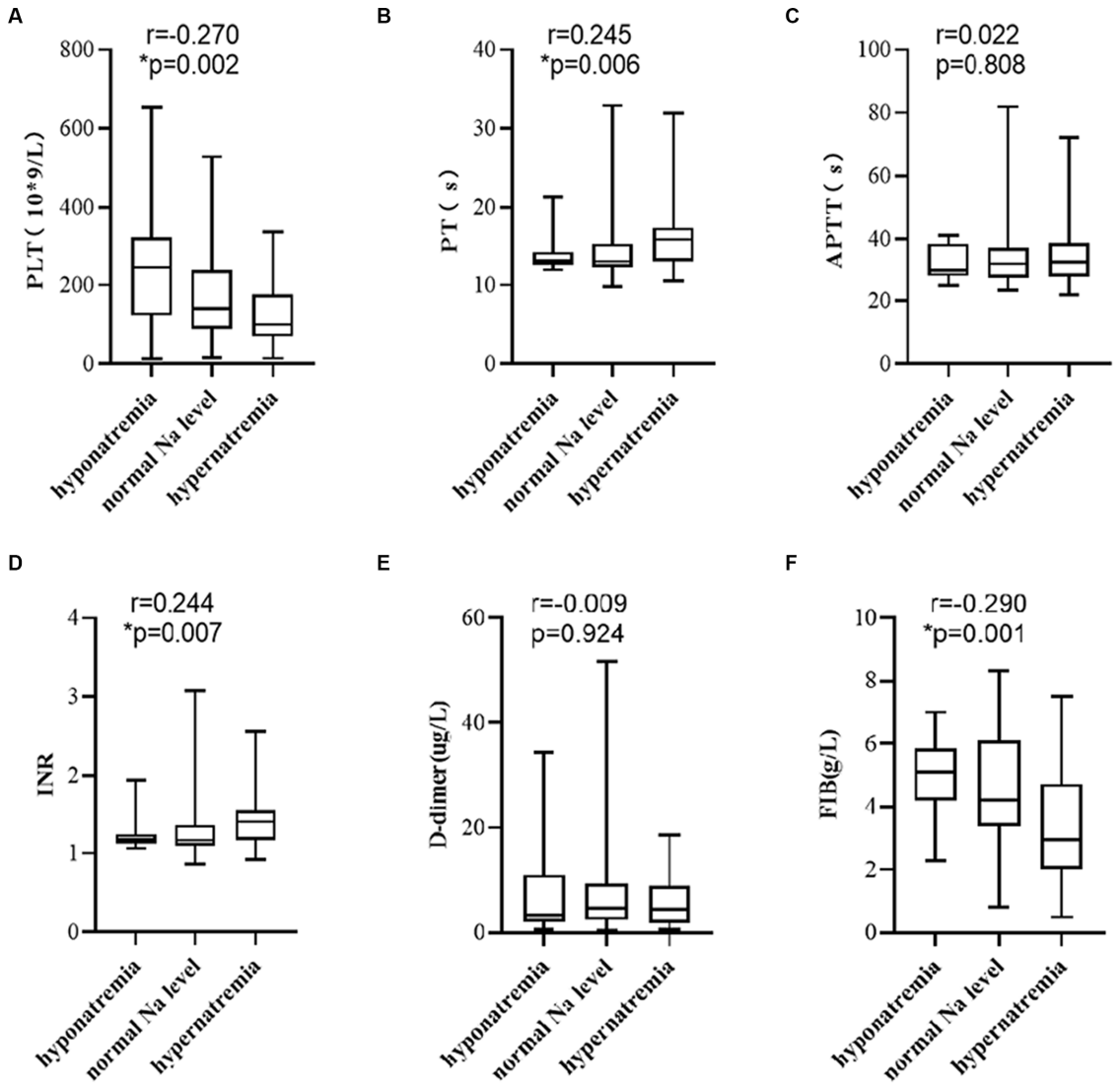

FIGURE 4
Elevated serum sodium level was associated with **(A)** PLT, **(B)** PT, **(D)** INR, and **(F)** FIB, but not with **(C)** APTT, and **(E)** D-dimer. *p*-values by Spearman's correlation analysis test.

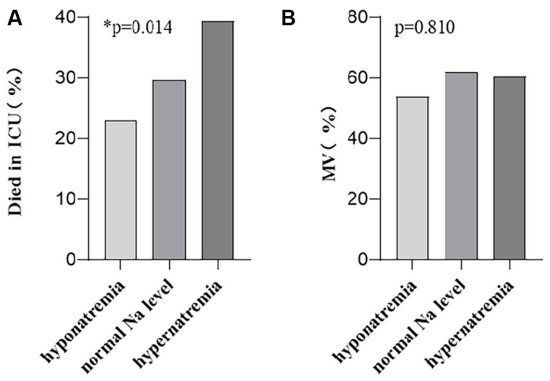

FIGURE 5
Higher serum sodium levels were associated with **(A)** an increased in-ICU mortality rate, but not with **(B)** the needing of mechanical ventilation therapy. *p*-values by linear-by-linear association test.

be involved when an organism suffers from an infection. Therefore, we speculate that Cr may be associated with sepsis complicated by acute kidney loss. One study showed that coagulation function was significantly abnormal in patients with SAKI compared with patients without AKI, as evidenced by thrombocytopenia, elevated INR, and prolonged PT (55). This may be related to the fact that coagulation activation crosstalks with an inflammatory response to form extensive microthrombi, resulting in renal ischemic injury (56).

To the best of our knowledge, this study is not only the first study to investigate the correlation between serum sodium level and coagulation dysfunction in sepsis patients, but also the first study on the relationship between serum sodium level and coagulation function. However, this study has several limitations: first, it was a retrospective single-center study with a small sample size; second, our patient population was skewed toward elderly patients; and third, the causality and mechanism of action could not be proven. Therefore, a large sample size is needed to validate our findings further. Further

studies are needed in the future to reveal the specific mechanism of action involved in the relationship between serum sodium level and SIC.

In conclusion, our retrospective analysis results suggested that an increase in the serum sodium level was independently associated with an increased occurrence of SIC and was also associated with an increase in-ICU mortality rate in septic patients. Higher serum sodium levels may lead to glycocalyx injury and exacerbate coagulation dysfunction. Therefore, we should pay attention to the serum sodium level in sepsis patients and further explore the molecular mechanisms underlying the relationship between the serum sodium and coagulation function to provide potential targets for improving coagulation function in sepsis patients.

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 humans were approved by Ethics Committee of Nanjing Drum Tower Hospital, The Affiliated Hospital School of Nanjing University Medical School, Nanjing, China. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because this is a retrospective analysis.

Author contributions

YH: Conceptualization, Methodology, Visualization, Writing – original draft. JD: Conceptualization, Methodology, Visualization, Writing – original draft. MC: Supervision, Visualization, Writing – review & editing. SH: Data curation, Writing – review & editing. BZ: Data curation, Writing – review & editing. YW: Data curation, Writing – review & editing. JL: Data curation, Writing – review & editing. XL: Project administration, Writing – review & editing. WY: Project administration, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the State Key Laboratory of Pharmaceutical Biotechnology, Department of Critical Care Medicine, Nanjing Drum Tower Hospital, The Affiliated Hospital School of Nanjing University Medical School [grant numbers 81927808]; Jiangsu Funding Program for Excellent Postdoctoral Talent Program [grant numbers 2022ZB689]; Fundings for Clinical Trials from the Affiliated Drum Tower Hospital, Medical School of Nanjing University [grant numbers 2021-LCYJ-PY-40].

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 08 January 2024
DOI 10.3389/fmed.2023.1275605

OPEN ACCESS

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RECEIVED 10 August 2023
ACCEPTED 20 December 2023
PUBLISHED 08 January 2024

CITATION
Yin Q, Yu B, Hao H, Li G, Sun J, Kong H and Deng L (2024) A biased coin up-and-down sequential allocation trial to determine the ED90 of intrathecal sufentanil combined with ropivacaine 2.5 mg for labor analgesia. *Front. Med.* 10:1275605. doi: 10.3389/fmed.2023.1275605

A biased coin up-and-down sequential allocation trial to determine the ED90 of intrathecal sufentanil combined with ropivacaine 2.5 mg for labor analgesia

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Purpose: To determine the 90 percent effective dose (ED90) of intrathecal sufentanil combined with ropivacaine 2.5 mg for labor analgesia and observe its safety for parturients and neonates.

Methods: We conducted a prospective, double-blind, biased coin up-and-down study. We injected a fixed 2.5 mg ropivacaine combined with a designated dose of sufentanil intrathecally to observe the labor analgesic effect. The initial dose of sufentanil was assigned 1.0 μg, and the remaining doses were assigned as per the biased coin up-and-down method. The criterion of successful response was defined as VAS ≤ 30 mm after intrathecal injection at 10 min. Safety was evaluated in terms of maternal and neonatal outcomes.

Results: The ED90 dose of intrathecal sufentanil combined with ropivacaine 2.5 mg (0.1%, 2.5 mL) was 2.61 μg (95% CI, 2.44 to 2.70 μg) by isotonic regression. No respiratory depression, hypotension, or motor block was observed. Thirty-one (77.5%) parturients complained of pruritus, and 14 (35.0%) suffered nausea and vomiting. Three neonates reported a 1 min Apgar score of ≤7, and none reported a 5 min Apgar score of ≤7.

Conclusion: The ED90 of intrathecal sufentanil combined with ropivacaine 2.5mg for labor analgesia was 2.61μg. The dose is safe for parturients and neonates.

KEYWORDS

sufentanil, intrathecal, ED90, labor analgesia, biased coin up-and-down

1 Introduction

Neuraxial analgesia is the most effective and prevailing way to provide labor pain relief. Epidural technique and combined spinal–epidural (CSE) technique are both recommended by guideline (1). Existing evidence suggests that compared with the epidural technique, the CSE technique demonstrated several potential advantages, including more rapid onset of

analgesia, less need for analgesic rescue, lower incidence of urinary retention, and reduced rate of instrumental delivery (2). In the CSE technique, intrathecal injection of low-dose local anesthetics combined with lipophilic opioids can safely achieve adequate analgesia without motor block and offer rapid onset and high maternal satisfaction (3, 4).

Studies have explored the optimal dose of intrathecal sufentanil for labor analgesia. In the early years, Herman et al. (5) established the effective dose (ED) 50 and ED95 for intrathecal sufentanil alone in laboring parturients were 2.6 [95% confidence interval (CI), 1.8–3.2] and 8.9 (7.5–11.5) μg, respectively, when a successful response was determined as an absolute VAS ≤ 25 mm. Wong et al. (6) reported the optimal dose of intrathecal sufentanil in combination with 2.5 mg bupivacaine was 2.5 μg, which provided analgesia comparable to higher doses and a lower incidence of nausea and vomiting and less severe pruritus. In recent years, ropivacaine has been increasingly used in labor analgesia due to its properties of a better separation between sensory and motor block and a lower systemic toxicity than bupivacaine (7, 8). However, the optimum dose of sufentanil with ropivacine was not well clarified. We designed a biased coin up-and-down sequential allocation trial to determine the ED90 of intrathecal sufentanil combined with ropivacaine 2.5 mg for labor analgesia.

2 Materials and methods

2.1 Study design and ethics

We conducted a prospective, double-blind, sequential allocation trial. The research protocol was approved by the Research Ethics Committee at Peking University First Hospital Ningxia Women's and Children's Hospital in Yinchuan, China (KJ-LL-2021-42, approval date November 25, 2021). The study was registered in Chinese Clinical Trial at chictr.org.cn (identifier: ChiCTR2300068408). Written informed consent was obtained from all participants. Our study used the CONSORT reporting guidelines (9).

2.2 Patients

The inclusion criteria included: (i) age 18–35 years; (ii) American Society of Anesthesiologists (ASA) physical status I – II; (iii) gestational age ≥ 37 weeks; (iv) nulliparous women with singleton pregnancy; (v) cervical dilatation between 2 and 4 cm; (vi) cephalic presentation; and (vii) no head pelvic asymmetry. The exclusion criteria included: (i) participants with pregnancy-induced hypertension; (ii) any contraindication for spinal or/and epidural analgesia; (iii) body temperature ≥ 37.5°C; and (iv) allergy to local anesthetics or opioids. The dropout criteria were: (i) puncture failure; (ii) accidental dural puncture; (iii) unilateral block; (iv) epidural catheter unintentionally entered the intrathecal cavity or blood vessel; and (v) epidural catheter detachment or blocked during labor analgesia.

2.3 Management of labor analgesia

Baseline maternal heart rate, non-invasive blood pressure, oxygen saturation, and fetal heart rate were measured between two uterine contractions. Baseline maternal visual analog score (VAS) was recorded during uterine contraction (VAS 0–100 mm, where 0 = painless and 100 = unbearable severe pain).

An intravenous catheter was established, and 500 mL of 0.9% saline was started. The parturient was positioned in a lateral decubitus position and routinely sterilized. The epidural space was identified at L3-L4 interspace via the midline approach with an 18-G, 8-cm Tuohy epidural needle using a loss of resistance to saline technique. A needle-through-needle technique was performed using a 25-G, 12-cm Whitacre spinal needle placed into the shaft of the previously sited epidural needle with confirmation of free-flow cerebrospinal fluid. A designated dose of sufentanil combined with 0.1% ropivacaine 2.5 mg was injected into the intrathecal space. After administration, the spinal needle was pulled out. A 19-G multiport wire-reinforced epidural catheter was inserted 5 cm into the epidural space. Maternal VAS scores were assessed at 5 and 10 min after intrathecal injection. After negative aspiration for cerebrospinal fluid and blood, all parturients received a 1% lidocaine test dose of 3 mL. Patient-controlled epidural analgesia (PCEA) was initiated immediately after VAS assessment at 10 min with the following parameters: ropivacaine 1 mg/mL combined with sufentanil 0.5 μg/mL, background infusion at 6 mL/h, demand dose of 8 mL, lockout interval of 30 min, and hourly limit of 28 mL.

Maternal VAS scores, heart rate, non-invasive blood pressure, respiration, oxygen saturation, and fetal heart rate were monitored after labor analgesia. When maternal systolic blood pressure was <90 mm Hg, a dose of 6 mg ephedrine was administered; when maternal heart rate was <50 beats/min, a dose of 0.2–0.5 mg atropine was administered. Intrapartum fever was defined as maternal body temperature ≥ 38°C during labor analgesia (10). Urinary retention was defined as the implantation of a catheter or a disposable catheter when urine cannot be voided on its own during delivery (11). Motor block was assessed using a Modified Bromage Score (12). Four levels of maternal satisfaction assessment were graded as Very satisfied, fairly satisfied, not sufficiently satisfied, and not at all satisfied (13).

2.4 Biased-coin design up-down sequential method

Based on the biased coin up-and-down (BCUD) and our pilot study, the initial dose of sufentanil (Jiangsu Enhua Medicine Co, Ltd.) was set at 1.0 μg. Sufentanil dose for the subsequent subject was determined according to the responses of the previous subject using the BCUD with a possible increment or decrement of 0.25 μg. If the labor analgesia failed, the dose of sufentanil was increased by 0.25 μg in the subsequent parturient. If the labor analgesia succeeded, the next parturient would receive either the same dose (probability of 0.89) or a dose that was reduced by 0.25 μg (probability of 0.11).

Abbreviations: ASA, American Society of Anesthesiologists; BCUD, biased coin up-and-down; bpm, beats per minute; CI, confidence interval; CSE, combined spinal–epidural; DBP, diastolic blood pressure; ED, effective dose; FHR, fetal heart rate; HR, heart rate; IQR, interquartile range; PAVA, Pooled Adjacent Violators Algorithm; PCEA, patient-controlled epidural analgesia; SBP, systolic blood pressure; SD, standard deviation; VAS, visual analog score.

The criteria used for determining a response were as follows: (i) successful labor analgesia: VAS ≤ 30 mm after intrathecal injection at 10 min; and (ii) failed labor analgesia: VAS > 30 mm after intrathecal injection at 10 min.

The biased coin up-and-down sequential allocation was carried out using a computer-generated list of random responses prepared by our statistician using Excel 2016 (Microsoft, Redmond, WA, USA). A research assistant used this list to provide the sufentanil dose for the next parturient. The anesthesiologists, nurses, and parturients remained blinded to the dose throughout the entire research process.

2.5 Endpoints of the study

Our primary endpoint was determining the ED90 of intrathecal sufentanil combined with ropivacaine 2.5 mg for labor analgesia. Our secondary outcomes were: (i) The visual analog scores at 5 min (T1), 10 min (T2), 15 min (T3), 30 min (T4), and 60 min (T5) after intrathecal injection, and at full cervical dilation (T6); (ii) Maternal adverse outcomes during labor analgesia, including pruritus, nausea and vomiting, urinary retention, respiratory depression, hypotension, intrapartum fever, and motor block, delivery mode, and abnormal fetal heart rate. (iii) Neonatal outcomes, including Apgar scores at 1 and 5 min after birth.

2.6 Sample size

The unknown distribution of data of the BCUD study prevents the development of rigorous rules to calculate the necessary sample size for the estimation of ED90. Pace et al. (14) suggested that including at least 20–40 patients will provide stable estimates of the target dose for the most realistic scenarios. We planned to enroll participants who met the inclusion and exclusion criteria and stopped when 40 patients had completed the study.

2.7 Statistical analysis

When ED90 is determined ($\tau = 0.9$), the probability $(B) = (1-\tau)/\tau = (1-0.9)/0.9 = 0.1/0\ 0.9 \approx 0.11$, where B is the target probability percentage. If a failure is observed, the dose is always stepped up for the subsequent participant. If the dose is successful, the following patient received the next lower dose with a probability of $B \approx 0.11$ (1/9) or the same dose with a probability of $1 - B = 0.89$ (8/9). The success rate after adjusting the results is estimated by the Pooled Adjacent Violators Algorithm (PAVA).

The ED90 of sufentanil was calculated by isotonic regression, and the 95% (CI) was obtained with 2000 bootstrapped samples. Normal distribution data were presented as mean (standard deviation) and were compared using *t*-test between the two groups. Non-normal distribution data were presented as median (interquartile range) and were compared using Mann–Whitney *U* test. Categorical data were presented as number of patients (percentage) and were analyzed using the χ^2 test. The statistical software used was R for Windows version 3.4.4 and SPSS for Windows version 24.0 (SPSS Inc., Chicago, Illinois).

3 Results

3.1 Participants statistical

We screened 51 women who met the inclusion criteria from November 25, 2021, to December 31, 2022. Among them, one was excluded for contraindication to spinal or/and epidural analgesia, three for body temperature ≥ 37.5°C, and five for participants with pregnancy-induced hypertension. The remaining 42 women were enrolled. Two women were dropped out for unilateral block and difficulty with puncture. Finally, a total of 40 women were included in the analysis (Figure 1). The demographics and labor characteristics of maternal subjects are shown in Table 1.

3.2 ED90 and 95% CI of sufentanil

Figure 2 showed the effective and ineffective responses of 40 consecutive women to different intrathecal doses of sufentanil during labor. The doses ranged from 1.0 to 2.75 μg. Table 2 showed the observed and PAVA-adjusted response rates for each sufentanil dose level. With isotonic regression, the ED90 dose of intrathecal sufentanil combined with ropivacaine 2.5 mg (0.1%, 2.5 mL) was 2.61 μg (95% CI, 2.44–2.70 μg).

3.3 VAS scores at different time points

Figure 3 showed the mean VAS scores before labor analgesia (T0), at 5 min (T1), 10 min (T2), 15 min (T3), 30 min (T4), 60 min (T5) after intrathecal injection, and at full cervical dilation (T6).

3.4 Maternal outcomes

Table 3 showed the main outcomes of the parturients. Thirty-one (77.5%) parturients complained of pruritus, and 14 (35.0%) suffered nausea and vomiting. Six (15.0%) reported urinary retention, and two (5.0%) were diagnosed with intrapartum fever. No respiratory depression or hypotension was recorded. No women had any degree of motor block. Among all the parturients, 33 had a vaginal delivery and 7 had a cesarean section finally.

3.5 Neonatal outcomes

Table 4 showed the primary outcomes of newborns. Three neonates reported a 1 min Apgar score of ≤7, none reported a 5 min Apgar score of ≤7.

4 Discussion

Our study demonstrated that the optimal dose of intrathecal sufentanil in combination with ropivacaine 2.5 mg to provide effective analgesia for 90% of women was 2.61 (95% CI, 2.44–2.70) μg. The incidence of maternal adverse effects was very low. All newborns were safe.

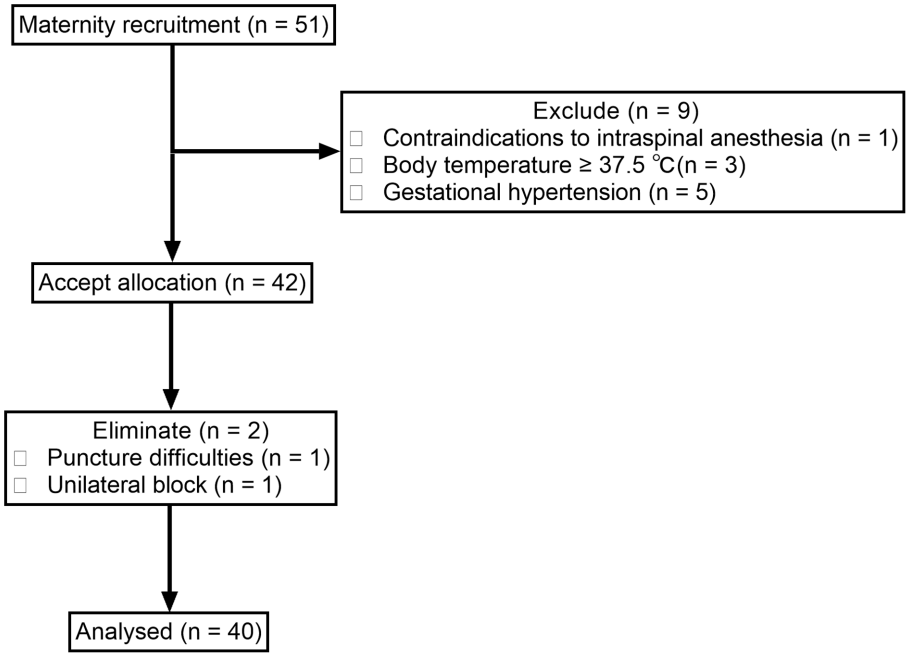

FIGURE 1
Flowchart of the study.

TABLE 1 Demographics and clinical characteristics of maternal participants.

Variables	All (*N* = 40)
Demographics	
Age, year	26.6 ± 3.2
Height, cm	161.2 ± 4.4
Weight, kg	70.2 ± 7.4
Body mass index, kg/m^2	27.0 ± 2.4
Clinical characteristics	
Gestation, weeks	39.7 ± 0.8
Cervical dilatation at recuitment, cm	2.0 (2.0–2.8)
Baseline HR, bpm	86 ± 13
Baseline SBP, mm Hg	128 ± 10
Baseline DBP, mm Hg	78 ± 8
Baseline Fetal HR, bpm	141 ± 7
Baseline body temperature, °C	36.6 ± 0.3
VAS before analgesia, mm	80 (70–90)

Data are presented as mean ± SD or median (IQR). bpm, beats per minute; DBP, diastolic blood pressure; HR, heart rate; IQR, interquartile range; SBP, systolic blood pressure; SD, standard deviation; VAS, visual analog score.

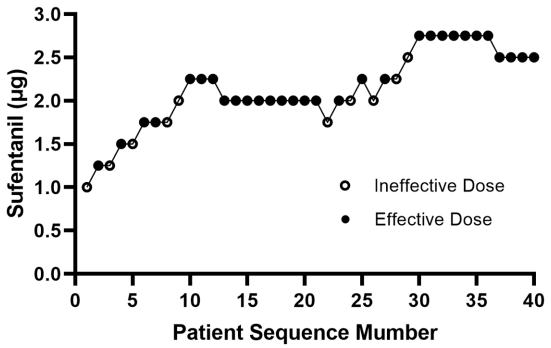

FIGURE 2
Maternal dose-allocation response sequence.

A fixed intrathecal ropivacaine dose of 2.5 mg was determined based on previous studies. Li et al. (3) injected 5 mL of 0.1% ropivacaine with sufentanil 2.5 μg into the subarachnoid space, reporting the symptoms of warmth and numbness within 3 min were both 100%. However, 77.55% of parturients were found to have a motor block, indicating an overdose of intrathecal drugs. Camorcia et al. (15) found the intrathecal minimum local analgesic dose was 3.64 (95% CI, 3.33 to 3.96) mg for ropivacaine in labor analgesia to achieve an efficacy of VAS score decreased to 10 mm or less within 30 min. Ortner et al. (16) reported the ED 50 of ropivacaine was 4.6 (95% CI, 4.28–5.31) mg when the analgesic effectiveness was defined as a VAS score less than 100 mm at 15 min after intrathecal injection. Adding sufentanil 1.6 and 2.2 μg significantly decreased the ED 50 of ropivacaine to 2.1 mg and 1.9 mg, respectively (16). Given combined sufentanil and ropivacaine for spinal analgesia in our study and the criterion we set for block success was VAS ≤ 30 mm after intrathecal injection at 10 min, we fixed intrathecal ropivacaine dose of 2.5 mg, the same with Levin et al. (17) and Hughes et al. (18) studies.

In our study, 75% of parturients' VAS score dropped to below 30 mm, and the mean VAS score was 16.5 mm at 10 min after intrathecal injection, indicating a faster onset of analgesia than

TABLE 2 Observed and Pooled Adjacent Violators Algorithm-adjusted response rates.

Assigned dose, μg	No. of patients, N	No. of successes, N	Observed response rate, %	PAVA-adjusted response rate[a], %	Pruritus, N (%)	Nausea and vomiting, N (%)	Abnormal fetal heart rate, N (%)	Cesarean delivery, N (%)	1 min Apgar score ≤ 7, N (%)
1.00	1	0	0.0	0.0	1 (100.0)	1 (100)	0 (0.0)	0 (0.0)	0 (0.0)
1.25	2	1	50.0	50.0	1 (50.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)
1.50	2	1	50.0	50.0	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1.75	4	2	50.0	50.0	3 (75.0)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)
2.00	13	10	76.9	76.9	9 (69.0)	6 (46.0)	2 (15.0)	1 (8.0)	1 (8.0)
2.25	6	5	83.3	81.8	6 (100.0)	3 (50.0)	1 (17.0)	1 (17.0)	1 (17.0)
2.50	5	4	80.0	81.8	3 (60.0)	1 (20.0)	0 (0.0)	2 (40.0)	0 (0.0)
2.75	7	7	100.0	100.0	5 (71.0)	3 (43.0)	1 (14.0)	1 (14.0)	1 (14.0)

PAVA, Pooled Adjacent Violators Algorithm.
[a] PAVA-Adjusted Response Rates were estimated using the weighted isotonic regression method.

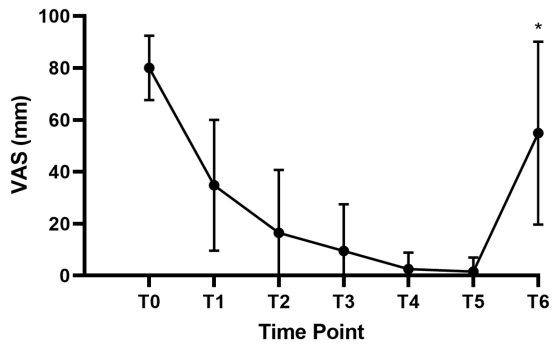

FIGURE 3
VAS scores of parturients at time points. VAS, visual analog score; T0, Before labor analgesia; T1, 5 min after intrathecal injection; T2, 10 min after intrathecal injection; T3, 15 min after intrathecal injection; T4, 30 min after intrathecal injection; T5, 60 min after intrathecal injection; T6, At the time of full cervical dilation. *T6 only included 33 women with vaginal delivery.

TABLE 3 Maternal outcomes.

Variables	All (*N* = 40)
Pruritus	31 (77.5)
Nausea and vomiting	14 (35.0)
Urinary retention	6 (15.0)
Respiratory depression	0 (0.0)
Hypotension	0 (0.0)
Intrapartum fever	2 (5.0)
Abnormal fetal heart rate[a]	5 (12.5)
Modified Bromage score[b]	
0	40 (100.0)
1	0 (0.0)
2	0 (0.0)
3	0 (0.0)
Delivery mode	
Cesarean delivery	7 (17.5)
Vaginal delivery	33 (82.5)
Maternal satisfaction	
Very satisfied	29 (72.5)
Fairly satisfied	11 (27.5)
Not sufficiently satisfied	0 (0.0)
Not at all satisfied	0 (0.0)

Data are presented as N (%).
[a] Abnormal fetal heart rate (FHR) was defined as late deceleration (FHR < 100 bpm after a contraction) or bradycardia (FHR < 100 bpm for more than 90 s).
[b] Modified Bromage score (0 = full flexion of knees and ankles, 1 = partial flexion of knees, full flexion of ankles, 2 = inability to flex knees and partial flexion of ankles, and 3 = inability to flex knees and ankles).

traditional epidural technique (19, 20) and dural puncture epidural technique (20). No adverse effects, such as hypotension, respiratory depression, motor block, or patient discomfort, were observed after subarachnoid administration.

Compared with epidural labor analgesia, combined spinal-epidural labor analgesia was associated with a higher risk of nonreassuring fetal heart rate (21). A meta-analysis indicated the average incidence of abnormal fetal heart rate was 11.8% in parturients receiving CSE analgesia, which was comparable with our study (5/40, 12.5%). Among the five cases in our study, four recovered in a very short period of time, and one performed an emergency cesarean section due to fetal bradycardia. The overall cesarean section rate was basically consistent with previous reports (22, 23). From the results in Table 2, we have not found any close relationship between the incidences of abnormal fetal heart and cesarean section and the dose of sufentanil.

Intrathecal injection of opioids is the main culprit causing pruritus. Our study showed 77.5% of participants had suffered pruritus, similar to previously reported studies (24, 25). However, most symptoms were mild and transient and did not require pharmacological treatment. Herman et al. reported the incidence of pruritus in parturients receiving intrathecal opioids during labor displayed a dose–response in relationship identical to that seen for analgesia (26). However, no dose–response relationship was found in our study. It may be due to a small sample size of each group. The

TABLE 4 Neonatal outcomes.

Variables	All (N = 40)
1 min Apgar score	9 (9–9)
5 min Apgar score	10 (10–10)
1 min Apgar score ≤ 7	3 (7.5)
5 min Apgar score ≤ 7	0 (0.0)

Data are presented as median (IQR) or N (%). IQR, interquartile range.

incidence of nausea and vomiting in our study was 35%, similar to previously reported studies (27).

There are some limitations in our study. Firstly, our results may not be applicable to either multiparous women or nulliparous women in advanced labor. Secondly, the ED90 of sufentanil observed in our study may only be valid for combining with ropivacaine 2.5 mg, since there is a pharmacologic synergistic interaction between intrathecal opioid and local anesthetic given intrathecally for labor analgesia (28). Thirdly, we did not measure the maternal sensory block level. However, no parturient developed respiratory depression in our study indicating no high block level occurred. We will include maternal sensory block level assessment in further study.

5 Conclusion

The ED90 of intrathecal sufentanil combined with ropivacaine 2.5 mg for labor analgesia was 2.61 (95% CI, 2.44 to 2.70) μg. The dose is safe for parturients and neonates.

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 humans were approved by Research Ethics Committee at Peking University First Hospital Ningxia Women's and Children's Hospital in Yinchuan, China (KJ-LL-2021-42, approval date November 25, 2021). The studies were conducted in accordance with the local legislation and institutional requirements. The 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

QY: Conceptualization, Methodology, Project administration, Writing – review & editing. BY: Conceptualization, Methodology, Writing – review & editing. HH: Methodology, Writing – original draft. GL: Formal analysis, Writing – review & editing. JS: Writing – review & editing. HK: Conceptualization, Methodology, Project administration, Writing – original draft. LD: Conceptualization, Methodology, Project administration, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded by the Scientific Research Seed Fund of Peking University First Hospital (number: 2021SF25) and the Youth Clinical Research Project of Peking University First Hospital (number: 2021CR19).

Acknowledgments

The authors gratefully acknowledge Tao Xu. MD (Department of Anesthesiology, the International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China) for his help in statistical analysis.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 31 January 2024
DOI 10.3389/fmed.2024.1346855

OPEN ACCESS

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RECEIVED 30 November 2023
ACCEPTED 15 January 2024
PUBLISHED 31 January 2024

CITATION
Sun S, Liu H, Liang Q, Yang Y, Cao X and Zheng B (2024) Association between acetaminophen administration and clinical outcomes in patients with sepsis admitted to the ICU: a retrospective cohort study. *Front. Med.* 11:1346855. doi: 10.3389/fmed.2024.1346855

Association between acetaminophen administration and clinical outcomes in patients with sepsis admitted to the ICU: a retrospective cohort study

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Background: Sepsis, affecting over 30 million people worldwide each year, is a key mortality risk factor in critically ill patients. There are significant regional discrepancies in its impact. Acetaminophen, a common over-the-counter drug, is often administered to control fever in suspected infection cases in intensive care units (ICUs). It is considered generally safe when used at therapeutic levels. Despite its widespread use, there's inconsistent research regarding its efficacy in sepsis management, which creates uncertainties for ICU doctors about its possible advantages or harm. To address this, we undertook a retrospective cohort study utilizing the MIMIC-IV database to examine the correlation between acetaminophen use and clinical outcomes in septic patients admitted to the ICU.

Methods: We gathered pertinent data on sepsis patients from the MIMIC-IV database. We used propensity score matching (PSM) to pair acetaminophen-treated patients with those who were not treated. We then used Cox Proportional Hazards models to examine the relationships between acetaminophen use and factors such as in-hospital mortality, 30-day mortality, hospital stay duration, and ICU stay length.

Results: The data analysis involved 22,633 sepsis patients. Post PSM, a total of 15,843 patients were matched; each patient not receiving acetaminophen treatment was paired with two patients who received it. There was a correlation between acetaminophen and a lower in-hospital mortality rate (HR 0.443; 95% CI 0.371–0.530; $p < 0.001$) along with 30-day mortality rate (HR 0.497; 95% CI 0.424–0.583; $p < 0.001$). Additionally, it correlated with a decrease in the duration of hospitalization [8.4 (5.0, 14.8) vs. 9.0 (5.1, 16.0), $p < 0.001$] and a shorter ICU stay [2.8 (1.5, 6.0) vs. 3.1 (1.7, 6.5); $p < 0.05$].

Conclusion: The use of acetaminophen may lower short-term mortality in critically ill patients with sepsis. To confirm this correlation, future research should involve multicenter randomized controlled trials.

KEYWORDS

acetaminophen, sepsis, mortality, critical care, MIMIC-IV

1 Introduction

Sepsis is a life-threatening condition arising from an abnormal response to infection, which results in organ dysfunction. It remains a significant cause of death among critically ill patients (1, 2). Even though sepsis-related mortality has reduced recently, it still impacts over 30 million people every year, potentially leading to 6 million deaths (3, 4). Alarmingly, remarkable disparities exist between regions. Patients in low to middle-income countries face higher mortality rates from sepsis than those in developed countries (5, 6). Consequently, sepsis treatment and management persist to be significant obstacles.

Acetaminophen, also known as an over-the-counter medication, is deemed safe at therapeutic doses. It exhibits pain-relieving and fever-reducing properties similar to aspirin (7, 8). Nowadays, it is standard in the intensive care unit (ICU) to use acetaminophen to reduce body temperature for patients presenting with fever and potential infections (9, 10). Most patients diagnosed with sepsis show symptoms of fever (11, 12). In severe sepsis cases, hemolysis occurs, leading to the production of free hemoglobin, reactive oxygen species, and lipid peroxidation, which ultimately cause cell damage (13, 14). Study outcomes have demonstrated that acetaminophen reduces free radicals in iron protoporphyrin-free hemoglobin and hinders lipid peroxidation (15, 16). Thus, employing acetaminophen may be beneficial to sepsis patients. However, its use in sepsis treatment does not have universal agreement within the scholarly community. Some experts champion the idea of reducing body temperature, identifying fever as a harmful factor (17). Conversely, there's a belief among others that fever during an infection can enhance survival (18, 19). Moreover, studies indicate no impact on the number of ICU-free days when acetaminophen is administered early to treat fever resulting from a probable infection (20).

Due to the lack of high-level evidence, ICU physicians currently face uncertainty regarding the benefits, effectiveness, or potential harm of acetaminophen treatment for fever in cases of sepsis (21). To address this uncertainty, we conducted a retrospective cohort study based on the MIMIC-IV database. The aim was to assess the association between acetaminophen use and in-hospital mortality, 30-day mortality, length of hospital stay, and ICU stay in sepsis patients. To be more specific, our hypothesis posits that compared to patients not using acetaminophen, the use of acetaminophen can lower short-term mortality.

2 Materials and methods

We utilized Navicat Premium v16.1.7 to gather data from the MIMIC-IV database v2.2, specifically focusing on sepsis patients who either did or did not use acetaminophen. This publicly accessible database provides real-world data on more than 73,000 patients who were admitted to the ICU at Beth Israel Deaconess Medical Center between 2008 and 2019 (22). Author Shilin Sun secured authorization to utilize this database (Certification Number: 12281929). All reporting in this study adheres to the guidelines stipulated by the Strengthening the Reporting of Observational Studies in Epidemiology (23).

2.1 Study population

We undertook a retrospective analysis of sepsis patients, setting these inclusion criteria: (1) patients must be at least 18 years old, and (2) patients must meet Sepsis-3 criteria — i.e., have a Sequential Organ Failure Assessment (SOFA) score of two or more due to a confirmed or suspected infection (1, 24). We identified infections by referencing International Classification of Diseases (ICD-9 and ICD-10) codes (25, 26). Every patient started with a default SOFA score of zero (27).

The exclusion criteria included: (1) patients younger than 18 years old, and (2) for patients with multiple ICU visits, only data from their first ICU admission were considered (28).

2.2 Acetaminophen use

The researchers examined the use of acetaminophen among patients within the first 48 h of ICU admission, using data extracted from the MIMIC-IV database (29).

2.3 Covariates

We used a predetermined set of covariates based on well-known predictors of sepsis outcomes (28, 30, 31). These factors included heart rate, mean arterial pressure (MAP), temperature, respiratory rate, SPO_2, PaO_2/FiO_2, glucose levels, white blood cell (WBC) count, serum creatinine (SCr) levels, hemoglobin levels, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), bilirubin, SOFA score, simplified acute physiology score (SAPS) II, infection site, and several comorbidities, like myocardial infarction, congestive heart failure, dementia, cerebrovascular disease, chronic pulmonary disease, mild liver disease, renal disease. Moreover, the use of medication such as statins, aspirin, vasopressin, continuous renal replacement therapy (CRRT) and acetaminophen route was considered. Important information from hospital admission records, including demographic characteristics, marital status, insurance details, and admission type, were also factored in. These variables comprehensively cover patient health behaviors, potentially revealing confounding effects in those treated with acetaminophen (32).

2.4 Outcome

This study primarily focuses on in-hospital mortality, with additional outcomes being 30-day mortality the duration of hospital and ICU stays.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BPM, representing beats per minute; MAP, denoting mean arterial pressure; MIMIC, which stands for Medical Information Mart for Intensive Care; PSM, reflecting propensity score matching; SOFA, signifying Sequential Organ Failure Assessment; SAPS, representing simplified acute physiology score; ICU, which stands for intensive care unit; and WBC, an abbreviation for white blood cell.

2.5 Statistical analysis

Variables of continuous nature with normal distribution were expressed as mean ± standard deviation, and an independent-samples *t*-test was used for group comparisons. On the other hand, skewed continuous variables were shown as median (IQR) and compared using the Mann-Whitney U test between groups. Categorical variables were represented by numbers and percentages, with comparisons between groups performed using the chi-squared test or Fisher's exact test, as necessary.

In our research, we applied propensity score matching (PSM) to tackle confounding factors in the original group. This required performing a greedy nearest neighbor match with a 0.2 standard deviation caliper of the logit for the prospective propensity score (33). We employed k-nearest neighbor imputation (KNN) with a k value of 10 for imputing the matching baseline variables (34). We matched patients at a 1:2 ratio, pairing each non-acetaminophen-treated patient within 48 h of ICU admission with two treated patients. To assess the PSM's effectiveness in reducing differences between the groups, we calculated the standardized mean difference (SMD).

We used a multivariate Cox regression model to adjust for confounding variables. These variables were selected based on the results of a univariate analysis with a *p*-value less than 0.05 and potential confounders recognized by our team's clinical expertise. This method was applied to estimate the correlation between acetaminophen use and mortality risk (35, 36).

In our subgroup analysis, we investigated how factors such as age, sex, ethnicity, marital status, insurance, admission type, infection site, comorbidities, medication history, and intervention usage might affect the correlation between acetaminophen use and in-hospital mortality rates.

The statistical analyses were completed using IBM SPSS Statistics version 26.0 and R 4.2.2 software. A *p*-value below 0.05 was deemed statistically significant.

3 Results

3.1 Population

The study incorporated 22,633 patients diagnosed with sepsis per the Sepsis-3 definition. Among these, 15,146 (66.9%) were recognized as acetaminophen users. The patient selection process is visually represented in Figure 1.

Table 1 illustrates notable discrepancies in various foundational characteristics between the two patient groups from the original sample. These include differences in admission type, body temperature, respiratory rate, SPO_2, PaO_2/FiO_2, glucose levels, SCr, ALT, AST, ALP, bilirubin, SOFA score, SAPS II score, infection site, cerebrovascular disease presence, medication usage, and interventions.

After PSM, 9,267 patients treated with acetaminophen were matched with 6,576 patients who did not receive acetaminophen treatment. After matching, there was a good balance in baseline characteristics between the two groups, with all variables having a SMD of less than 10% (Figure 2).

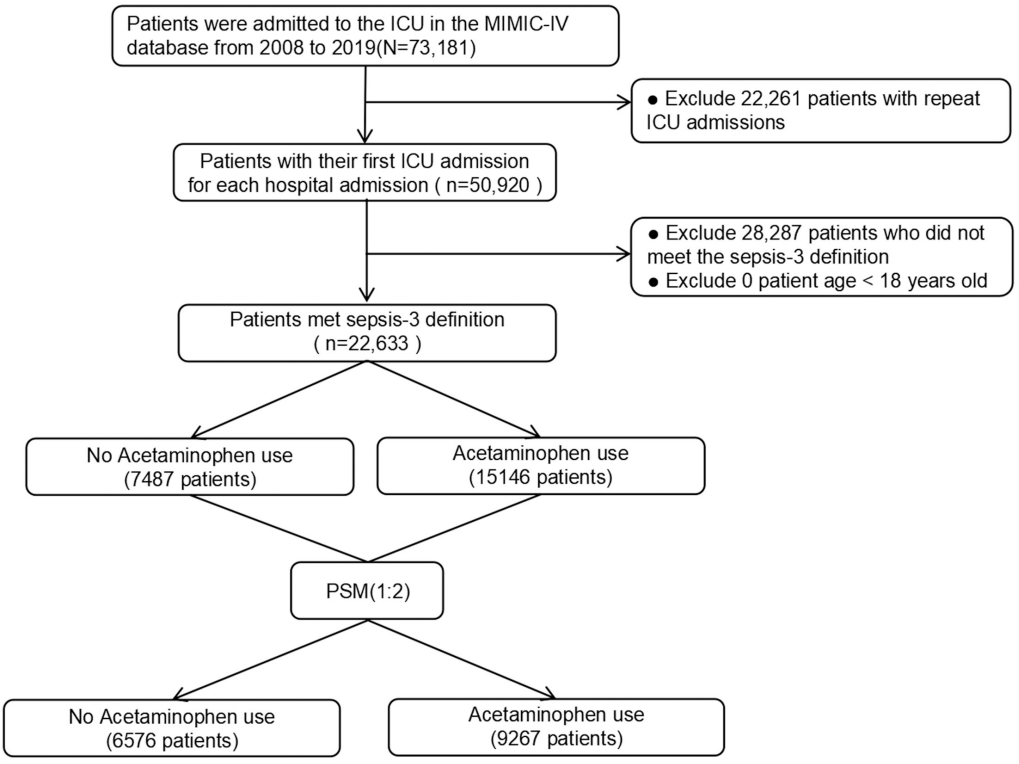

FIGURE 1
The flow chart of the study.

TABLE 1 Baseline characteristics between groups before and after PSM.

Variables	Before matching				After matching			
	Total	Acetaminophen use	No acetaminophen use	SMD$^{\Delta}$	Total	Acetaminophen use	No acetaminophen use	SMD$^{\Delta}$
n (%)	22,633	15,146 (66.9)	7,487 (33.1)		15,843	9,267	6,576	
Age (years)[a]		65.05 ± 16.35	65.12 ± 16.35	0.004		65.65 ± 16.80	65.67 ± 16.31	−0.021
Female, *n* (%)	9,556	6,340 (41.9)	3,216 (43.0)	0.022	6,975	4,122 (44.5)	2,853 (43.4)	−0.028
Ethnicity, white, *n* (%)	15,162	10,280 (67.9)	4,882 (65.2)	−0.056	10,542	6,202 (66.9)	4,340 (66.0)	−0.019
Marital, status, *n* (%)								
Married	10,122	6,995 (46.2)	3,127 (41.8)	−0.09	6,687	3,903 (42.1)	2,784 (42.3)	0.015
Single/divorced	7,457	4,859 (32.1)	2,598 (34.7)	0.055	5,415	3,157 (34.1)	2,258 (34.3)	0.002
Other	5,054	3,292 (21.7)	1,762 (23.5)	0.042	3,741	2,207 (23.8)	1,534 (23.3)	−0.02
Insurance, *n* (%)								
Medicaid	1,629	993 (6.6)	636 (8.5)	0.07	1,187	663 (7.2)	524 (8.0)	0.014
Medicare	10,475	6,896 (45.5)	3,579 (47.8)	0.045	7,696	4,495 (48.5)	3,201 (48.7)	−0.014
Other	10,529	7,257 (47.9)	3,272 (43.7)	−0.085	6,960	4,109 (44.3)	2,851 (43.4)	0.006
Admission type, *n* (%)								
Elective	5,524	4,514 (29.8)	1,010 (13.5)	−0.478	2,527	1,561 (16.8)	966 (14.7)	0.012
Emergency	17,109	10,632 (70.2)	6,477 (86.5)	0.478	13,316	7,706 (83.2)	5,610 (85.3)	−0.012
Vital signs								
Heart rate (BPM)[a]	86.80 ± 18.98	86.50 ± 15.46	87.39 ± 16.97	0.052	87.12 ± 16.86	86.91 ± 16.23	87.12 ± 16.86	0.004
MAP (mmHg)[a]	79.59 ± 10.33	79.46 ± 9.87	79.84 ± 11.20	0.034	80.00 ± 11.07	80.30 ± 10.45	80.00 ± 11.07	−0.029
Temperature (°C)[b]	37.39 (37.00, 37.90)	37.44 (37.06, 38.10)	37.22 (36.94, 37.67)	−0.485	37.33 (37.00, 37.89)	37.33 (37.00, 37.89)	37.28 (36.94, 37.72)	−0.069
Respiratory rate (BPM)[a]	19.62 ± 4.06	19.40 ± 3.91	20.07 ± 4.31	0.154	19.96 ± 4.22	19.80 ± 4.04	19.95 ± 4.22	0.008
SPO_2 (%)[b]	97.24 (95.79, 98.52)	97.34 (95.95, 98.53)	97.02 (95.40, 98.52)	−0.154	97.07 (95.64, 98.41)	97.07 (95.64, 98.40)	97.04 (95.48, 98.53)	−0.018
PaO_2/FiO_2[b]	257 (203, 315)	261 (207, 318)	249 (192, 307)	−0.132	256 (202, 309)	256 (202, 309)	252 (196, 308)	−0.012
Laboratory tests								
Glucose (mg/dL)[b]	131 (114, 159)	130 (115, 153)	137 (112, 174)	0.183	133 (113, 162)	133 (113, 161)	135 (111, 171)	0.034
WBC ($x10^9$)[b]	12 (9, 16)	12 (9, 16)	12 (8, 16)	−0.014	12 (9, 16)	12 (9, 16)	12 (8, 16)	−0.002
SCr (mg/dL)[b]	1.05 (0.75, 1.60)	1.00 (0.75, 1.40)	1.20 (0.80, 2.00)	0.238	1.05 (0.75, 1.60)	1.05 (0.75, 1.60)	1.15 (0.80, 1.90)	0.036
Hemoglobin (g/L)[a]	10.69 ± 2.01	10.72 ± 1.95	10.64 ± 2.14	−0.035	10.69 ± 2.12	10.76 ± 2.05	10.69 ± 2.12	−0.017
Platelets ($x10^{12}$)[b]	180 (129, 246)	179 (133, 240)	184 (120, 257)	0.026	190 (135, 257)	190 (135, 257)	189 (126, 260)	−0.038
ALT (IU/L)[b]	31 (20, 60)	29 (20, 50)	37 (21, 93)	0.179	31 (20, 58)	31 (20, 58)	34 (20, 77)	0.056
AST (IU/L)[b]	46 (31, 90)	44 (31, 75)	55 (31, 140)	0.193	46 (30, 85)	46 (30, 85)	50 (29, 114)	0.055
ALP (IU/L)[b]	75 (60, 105)	71 (58, 95)	86 (66, 125)	0.218	78 (62, 108)	78 (62, 108)	83 (64, 119)	0.028
Bilirubin (μmol/L)[b]	0.73 (0.50, 1.15)	0.70 (0.50, 1.00)	0.80 (0.50, 1.80)	0.252	0.70 (0.50, 1.10)	0.70 (0.50, 1.10)	0.76 (0.50, 1.45)	0.063

(*Continued*)

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TABLE 1 (Continued)

Variables	Before matching				After matching			
	Total	Acetaminophen use	No acetaminophen use	SMD[Δ]	Total	Acetaminophen use	No acetaminophen use	SMD[Δ]
Severity of illness								
SOFA score[b]	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 5.00)	0.239	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 5.00)	0.072
SAPS II score[a]	39.58 ± 14.49	37.87 ± 13.58	43.01 ± 15.64	0.329	41.60 ± 14.80	39.53 ± 14.19	41.60 ± 14.80	0.067
Infection site (%)								
Respiratory system	10,544	6,527 (43.1)	4,017 (53.7)	0.212	8,268	4,779 (51.6)	3,489 (53.1)	−0.004
Digestive system	3,479	2,197 (14.5)	1,282 (17.1)	0.069	2,480	1,403 (15.1)	1,077 (16.4)	0.013
Urogenital system	3,728	2,669 (17.6)	1,059 (14.1)	−0.1	2,484	1,505 (16.2)	979 (14.9)	−0.017
Cardiovascular system	1,210	1,045 (6.9)	165 (2.2)	−0.32	424	264 (2.8)	160 (2.4)	0.009
Other	3,672	2,708 (17.9)	964 (12.9)	−0.149	2,187	1,316 (14.2)	871 (13.2)	0.006
Comorbidity disease, *n* (%)								
Myocardial infarct	3,792	2,574 (17.0)	1,218 (16.3)	−0.02	2,609	1,525 (16.5)	1,084 (16.5)	0.004
Congestive heart failure	6,356	4,108 (27.1)	2,248 (30.0)	0.063	4,755	2,734 (29.5)	2,021 (30.7)	0.001
Dementia	1,034	693 (4.6)	341 (4.6)	−0.001	826	501 (5.4)	325 (4.9)	−0.019
Cerebrovascular disease	3,169	2,285 (15.1)	884 (11.8)	−0.102	2,171	1,344 (14.5)	827 (12.6)	−0.036
Chronic pulmonary disease	5,820	3,709 (24.5)	2,111 (28.2)	0.082	4,374	2,523 (27.2)	1,851 (28.1)	−0.001
Mild liver disease	3,249	1,403 (9.3)	1,846 (24.7)	0.357	2,499	1,229 (13.3)	1,270 (19.3)	0.08
Renal disease	4,791	2,969 (19.6)	1,822 (24.3)	0.11	3,702	2,119 (22.9)	1,583 (24.1)	−0.006
Medications use, *n* (%)								
Aspirin	7,431	5,953 (39.3)	1,478 (19.7)	−0.491	3,795	2,382 (25.7)	1,413 (21.5)	−0.013
Statin	7,229	5,791 (38.2)	1,438 (19.2)	−0.483	3,837	2,439 (26.3)	1,398 (21.3)	−0.033
Interventions, *n* (%)								
Vasopressin	2,422	1,314 (8.7)	1,108 (14.8)	0.172	1,738	935 (10.1)	803 (12.2)	0.036
CRRT	1,199	525 (3.5)	674 (9.0)	0.193	880	432 (4.7)	448 (6.8)	0.046
Acetaminophen route, *n* (%)								
PO/NG	11,007	11,007 (72.7)	–	–	7,999	7,999 (86.3)	–	–
IV	3,160	3,160 (20.9)	–	–	1,258	1,258 (13.6)	–	–
PR	979	979 (6.5)	–	–	10	10 (0.1)	–	–

[a]Descriptive statistics were calculated using the mean (standard deviation), mean ± SD.
[b]Descriptive statistics were calculated using the median (interquartile range, IQR),[median (IQR)].
[Δ]Standardized mean difference.

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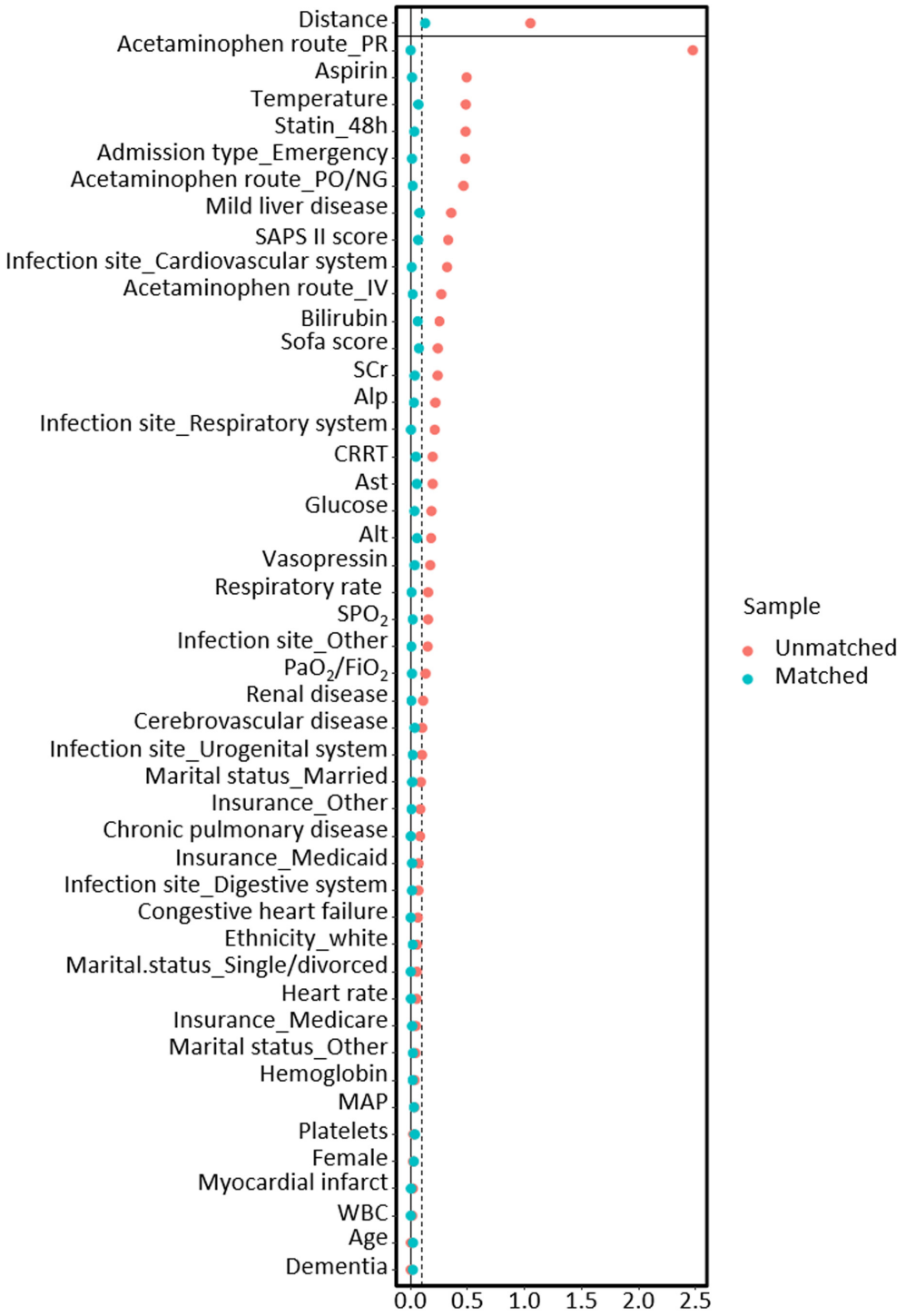


FIGURE 2
The relationship between SMD and all covariates before and after propensity score matching models.

3.2 Association between acetaminophen utilization and clinical outcomes

In the initial group, we noticed a link between acetaminophen use and a lower in-hospital death rate (HR 0.432; 95% CI 0.405–0.462; $p < 0.001$). This correlation stayed statistically significant even after adjusting for possible confounding factors (HR 0.512; 95% CI 0.448–0.585; $p < 0.001$). We also evaluated the effect of acetaminophen use on 30-day mortality, overall hospital stay duration, and length of ICU stay. The data showed that usage of acetaminophen led to a lower 30-day death rate (HR 0.582; 95% CI 0.518–0.655; $p < 0.001$), shorter hospital stay [7.9 (5.0, 13.8) vs. 9.1 (5.1, 16.6), $p < 0.001$], and shorter ICU stay [2.6 (1.4, 5.3) vs. 3.2 (1.7, 6.7); $p < 0.001$] (Table 2).

TABLE 2 Association between acetaminophen use and clinical outcomes in sepsis patients.

	No acetaminophen use	Acetaminophen use	*P*-value	HR	Lower 95% CI	Upper 95% CI
Pre-matched cohort	*n* = 7,487	*n* = 15,146				
Primary outcome						
In-hospital mortality, *n* (%)[a]	1,767 (23.6)	1,684 (11.1)	< 0.001	0.512	0.448	0.585
Secondary outcomes						
30-day mortality, *n* (%)[a]	2,110 (28.2)	2,145 (14.2)	< 0.001	0.582	0.518	0.655
Length of hospital stay (day), [median (IQR)]	9.1 (5.1, 16.6)	7.9 (5.0, 13.8)	< 0.001	1.762	1.398	2.125
Length of ICU stay (day), [median (IQR)]	3.2 (1.7, 6.7)	2.6 (1.4, 5.3)	< 0.001	0.631	0.449	0.813
Post-matched cohort	*n* = 6,576	*n* = 9,267				
Primary outcome						
In-hospital mortality, *n* (%)[a]	1,361 (20.7)	1,271 (13.7)	< 0.001	0.443	0.371	0.530
Secondary outcomes						
30-day mortality, *n* (%)[a]	1,655 (25.2)	1,634 (17.6)	< 0.001	0.497	0.424	0.583
Length of hospital stay (day), [median (IQR)]	9.0 (5.1, 16.0)	8.4 (5.0, 14.8)	< 0.001	1.024	0.617	1.431
Length of ICU stay (day), [median (IQR)]	3.1 (1.7, 6.5)	2.8 (1.5, 6.0)	0.036	0.218	0.015	0.422

[a]Adjusted for all the factors (acetaminophen use, age, sex, ethnicity, marital status, insurance, admission type, temperature, heart rate, MAP, respiratory rate, SPO_2, Glucose, WBC, SCr, hemoglobin, platelets, SAPSII score, SOFA score, PaO_2/FiO_2, ALT, AST, ALP, bilirubin, acetaminophen route, infection site, vasopressin use, CRRT use, aspirin use, statin use, myocardial infarct, congestive heart failure, dementia, cerebrovascular disease, chronic pulmonary disease, Mild liver disease, renal disease). HR, hazard ratio; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range.

After using PSM, we found consistent results with the PSM group, demonstrating that administering acetaminophen was connected to lower in-hospital mortality (HR 0.443; 95% CI 0.371–0.53; $p < 0.001$). Also, the acetaminophen administration was linked to lower 30-day mortality (HR 0.497; 95% CI 0.424–0.583; $p < 0.001$). It further led to shorter hospital [8.4 (5.0, 14.8) vs. 9.0 (5.1, 16.0), $p < 0.001$] and ICU stays [2.8 (1.5, 6.0) vs. 3.1 (1.7, 6.5); $p < 0.05$] (Table 2).

3.3 Subgroup analysis

Figure 3's study suggests that the lower in-hospital mortality rate associated with acetaminophen is linked to various factors like age, sex, ethnicity, and admission type. It also correlates with the presence of certain conditions, such as myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, and renal disease. Acetaminophen usage in the form of aspirin, statins, and vasopressors also seemed to influence the lower mortality rate.

Furthermore, other elements such as marital status (married or other), insurance type (medicare or other), infection site (respiratory, digestive or urogenital system, among others), lack of dementia and mild liver disease, and the non-use of CRRT also showed a correlation with lower in-hospital mortality rates.

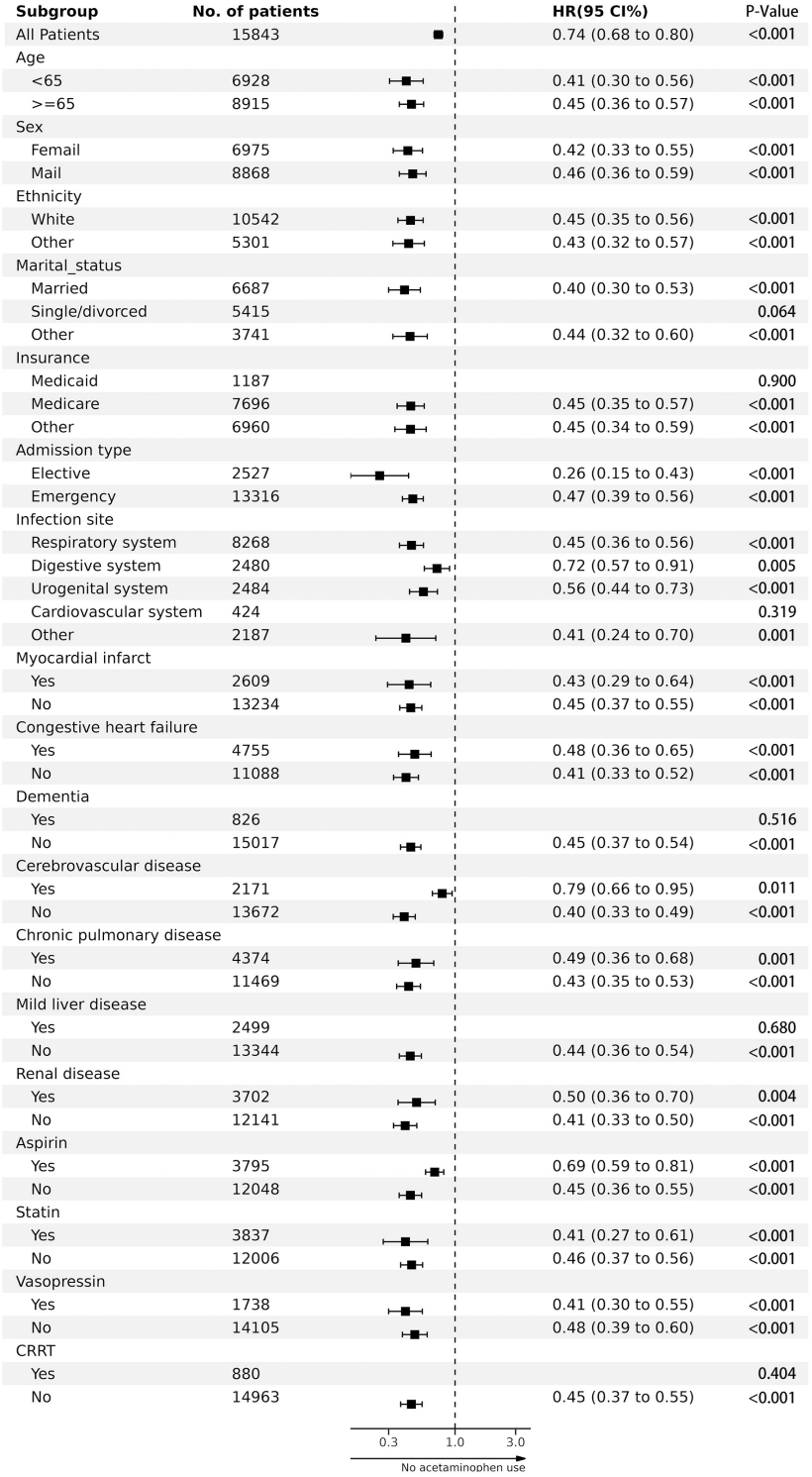
4 Discussion

Our research reveals that administering acetaminophen has a link to a lower in-hospital mortality in patients with critical sepsis. The outcomes from this group also imply that acetaminophen can potentially lower 30-day mortality from sepsis and expedite hospital discharge and ICU discharge. These results maintain their strength even following adjustments for risk factors and the application of PSM for comparison. Our findings endorse the use of acetaminophen in sepsis treatment, suggesting a promising therapeutic option for clinical practice and inviting further research in this area.

Our study aligns with early clinical trials suggesting that acetaminophen could improve lipid peroxidation and kidney function in septic patients (37). An earlier observational study found a correlation between acetaminophen use and decreased in-hospital deaths in critically unwell septic patients. This implies a protective effect by reducing oxidative damage caused by cell-free hemoglobin (38). Moreover, some researchers have noted that giving acetaminophen within the first 24 h of ICU admission can lessen oxidative damage and enhance kidney function in severely septic adults. This is particularly true when cell-free hemoglobin is detectable in the blood plasma (14) .

A controlled study examined 700 patients with fever, indicating that the early use of acetaminophen to treat potential infection neither impacted the length of ICU stays nor affected survival rates at the 28-day and 90-day milestones (20). However, our research, unlike the study mentioned above, focused specifically on sepsis patients. This approach provided a clearer view of acetaminophen's role in sepsis management. The study concluded that administrating acetaminophen to sepsis patients can shorten time spent in the ICU and lower short-term mortality rates.

In a cohort study of 606 sepsis patients, researchers observed a notable link between the use of acetaminophen and increased



Subgroup	No. of patients	HR(95 CI%)	P-Value
All Patients	15843	0.74 (0.68 to 0.80)	<0.001
Age			
<65	6928	0.41 (0.30 to 0.56)	<0.001
>=65	8915	0.45 (0.36 to 0.57)	<0.001
Sex			
Femail	6975	0.42 (0.33 to 0.55)	<0.001
Mail	8868	0.46 (0.36 to 0.59)	<0.001
Ethnicity			
White	10542	0.45 (0.35 to 0.56)	<0.001
Other	5301	0.43 (0.32 to 0.57)	<0.001
Marital_status			
Married	6687	0.40 (0.30 to 0.53)	<0.001
Single/divorced	5415		0.064
Other	3741	0.44 (0.32 to 0.60)	<0.001
Insurance			
Medicaid	1187		0.900
Medicare	7696	0.45 (0.35 to 0.57)	<0.001
Other	6960	0.45 (0.34 to 0.59)	<0.001
Admission type			
Elective	2527	0.26 (0.15 to 0.43)	<0.001
Emergency	13316	0.47 (0.39 to 0.56)	<0.001
Infection site			
Respiratory system	8268	0.45 (0.36 to 0.56)	<0.001
Digestive system	2480	0.72 (0.57 to 0.91)	0.005
Urogenital system	2484	0.56 (0.44 to 0.73)	<0.001
Cardiovascular system	424		0.319
Other	2187	0.41 (0.24 to 0.70)	0.001
Myocardial infarct			
Yes	2609	0.43 (0.29 to 0.64)	<0.001
No	13234	0.45 (0.37 to 0.55)	<0.001
Congestive heart failure			
Yes	4755	0.48 (0.36 to 0.65)	<0.001
No	11088	0.41 (0.33 to 0.52)	<0.001
Dementia			
Yes	826		0.516
No	15017	0.45 (0.37 to 0.54)	<0.001
Cerebrovascular disease			
Yes	2171	0.79 (0.66 to 0.95)	0.011
No	13672	0.40 (0.33 to 0.49)	<0.001
Chronic pulmonary disease			
Yes	4374	0.49 (0.36 to 0.68)	0.001
No	11469	0.43 (0.35 to 0.53)	<0.001
Mild liver disease			
Yes	2499		0.680
No	13344	0.44 (0.36 to 0.54)	<0.001
Renal disease			
Yes	3702	0.50 (0.36 to 0.70)	0.004
No	12141	0.41 (0.33 to 0.50)	<0.001
Aspirin			
Yes	3795	0.69 (0.59 to 0.81)	<0.001
No	12048	0.45 (0.36 to 0.55)	<0.001
Statin			
Yes	3837	0.41 (0.27 to 0.61)	<0.001
No	12006	0.46 (0.37 to 0.56)	<0.001
Vasopressin			
Yes	1738	0.41 (0.30 to 0.55)	<0.001
No	14105	0.48 (0.39 to 0.60)	<0.001
CRRT			
Yes	880		0.404
No	14963	0.45 (0.37 to 0.55)	<0.001

FIGURE 3
The association between acetaminophen adminstration and in-hospital mortality in subgroups.

mortality among those who had a fever (39). What makes our study unique is our wider scope. We did not focus solely on fever patients but on various forms of sepsis for all reasons. We utilized the Sepsis-3 criteria to define sepsis, incorporating a more diverse range of subjects for a complete depiction of the sepsis patient population. Unlike past results, our study indicates a significant correlation between the use of acetaminophen and a reduction in mortality.

In a past study, researchers examined 46 pediatric sepsis patients aged 7 to 18. They found no link between acetaminophen use and increasing organ dysfunction or mortality rates (40). Unlike this study, our research primarily targets adult patients due to the

higher occurrence of sepsis in adults versus children. Moreover, our study involves a larger sample size, rendering our results more clinically relevant.

Research indicates that the common anti-inflammatory and antioxidant medication, acetaminophen, shows noteworthy potential in treating sepsis (13). Essentially, acetaminophen might provide a safeguard by minimizing oxidative damage instigated by cell-free hemoglobin. It can connect to ferrous iron (Fe^{4+}) in cell-free hemoglobin at clinically relevant doses, altering it to a less reactive ferric iron (Fe^{3+}) (38, 41, 42). In lab tests, some studies have suggested that acetaminophen eases sepsis-induced cognitive impairment by reducing iron-induced cell death via the GPX4 and FSP1 signal pathways (43, 44). Other research hints that it reduces the effect of endotoxins on pulmonary circulation in sedated pigs, which could be crucial in severe systematic inflammation (45). Moreover, the CYP3A5 gene has been proposed as a potential significant biomarker for acetaminophen metabolism. Understanding certain genotypes linked to acetaminophen reactions could lead to more tailored treatment methods for handling sepsis and septic shock (46). Looking forward, more research is required to understand the molecular mechanics and biochemical responses of acetaminophen in sepsis treatments, gathering evidence for its positive effects in clinical contexts.

While this study offers significant findings, it is not without constraints. First, as with all retrospective analyses, potential confounding elements like a patient's underlying medical conditions, lifestyle, and personal habits could influence results. We minimized these influences by adjusting for possible confounders using PSM. Second, our study only considered drugs like acetaminophen, disregarding other treatment interventions. The multi-faceted nature of sepsis treatment warrants further research comparing different methods. Third, our analysis only included patients treated with acetaminophen within 48 h of admission, leaving the effects of delayed use uncertain. More research is needed in this area. Fourth, the MIMIC-IV database, which does not record death causes, has some data limitations, hampering our ability to conduct a competing risk analysis. Lastly, our study is single-center, necessitating validation through multicenter trials. Given these constraints, future research should explore acetaminophen's exact role in sepsis treatment and provide more comprehensive analyses to confirm our findings.

5 Conclusion

Acetaminophen use may be linked to lower short-term mortality in critically ill septic patients, according to our study's findings. This implies that the careful use of acetaminophen can benefit such patients. However, more comprehensive studies, like multicenter randomized controlled trials, are needed to validate and confirm this correlation further.

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 humans were approved by the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

SS: Conceptualization, Data curation, Writing – original draft, Writing – review & editing. HL: Data curation, Writing – original draft. QL: Conceptualization, Writing – review & editing, Writing – original draft. YY: Data curation, Writing – original draft. XC: Data curation, Writing – original draft. BZ: Data curation, Writing – original draft.

Funding

The authors declare financial support was received for the research, authorship, and/or publication of this article. This research was supported by The National Natural Science Foundation of China (General Program, Grant No. 81974557) and The National Natural Science Foundation of China (General Program, Grant No. 82374400).

Acknowledgments

We express our gratitude to Dr. Yang Qilin from The Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China, and Dr. Liu Ming from Heilongjiang University of Chinese Medicine, Harbin, Heilongjiang, China, for their valuable assistance in reviewing this manuscript.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 31 January 2024
DOI 10.3389/fmed.2024.1342568

OPEN ACCESS

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RECEIVED 22 November 2023
ACCEPTED 15 January 2024
PUBLISHED 31 January 2024

CITATION
Shi X, Yang L, Bai W, Jing L and Qin L (2024) Evaluating early lymphocyte-to-monocyte ratio as a predictive biomarker for delirium in older adult patients with sepsis: insights from a retrospective cohort analysis.
Front. Med. 11:1342568.
doi: 10.3389/fmed.2024.1342568

Evaluating early lymphocyte-to-monocyte ratio as a predictive biomarker for delirium in older adult patients with sepsis: insights from a retrospective cohort analysis

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Background: This study aims to explore the value of the Lymphocyte-to-Monocyte Ratio (LMR) in predicting delirium among older adult patients with sepsis.

Methods: Retrospective data were obtained from the MIMIC-IV database in accordance with the STROBE guidelines. Patients aged 65 and above, meeting the Sepsis 3.0 criteria, were selected for this study. Delirium was assessed using the Confusion Assessment Method for the ICU (CAM-ICU). Demographic information, comorbid conditions, severity of illness scores, vital sign measurements, and laboratory test results were meticulously extracted. The prognostic utility of the Lymphocyte-to-Monocyte Ratio (LMR) in predicting delirium was assessed through logistic regression models, which were carefully adjusted for potential confounding factors.

Results: In the studied cohort of 32,971 sepsis patients, 2,327 were identified as meeting the inclusion criteria. The incidence of delirium within this subgroup was observed to be 55%. A univariate analysis revealed a statistically significant inverse correlation between the Lymphocyte-to-Monocyte Ratio (LMR) and the risk of delirium ($p < 0.001$). Subsequent multivariate analysis, which accounted for comorbidities and illness severity scores, substantiated the role of LMR as a significant predictive marker. An optimized model, achieving the lowest Akaike Information Criterion (AIC), incorporated 17 variables and continued to demonstrate LMR as a significant prognostic factor ($p < 0.01$). Analysis of the Receiver Operating Characteristic (ROC) curve indicated a significant enhancement in the Area Under the Curve (AUC) upon the inclusion of LMR ($p = 0.035$).

Conclusion: The Lymphocyte-to-Monocyte Ratio (LMR) serves as a significant, independent prognostic indicator for the occurrence of delirium in older adult patients with sepsis. Integrating LMR into existing predictive models markedly improves the identification of patients at elevated risk, thereby informing and potentially guiding early intervention strategies.

KEYWORDS

lymphocyte-to-monocyte ratio, delirium, sepsis, older adult, predictive modeling, MIMIC-IV

1 Introduction

Sepsis, which manifests as life-threatening organ dysfunction due to a dysregulated host response to infection, annually impacts millions worldwide and is a principal cause of deteriorating global health (1). It has been established that advanced age correlates with an elevated risk of sepsis and an increased mortality rate among septic patients (2), with older adults accounting for over half of all severe sepsis incidents (3). Delirium, marked by an acute reduction in cognitive capabilities, constitutes a frequent, grave, and often lethal challenge, affecting as many as 50% of hospitalized older individuals (4). Evidence suggests that individuals aged 65 years or older are at heightened risk for sepsis-associated delirium (SAD), which is closely linked with the severity of their septic condition (5). Delirium not only commonly complicates the clinical picture for older adult patients with sepsis but also significantly contributes to extended hospital stays, increased fatality rates, and escalated healthcare expenditures (6). Moreover, the incidence of delirium bears a direct relation to the long-term prognosis of patients, with severe instances potentially culminating in enduring cognitive impairment or mortality.

Contemporary studies have established that the emergence of sepsis-associated delirium (SAD) is multifactorial, involving neuroinflammatory responses, microcirculatory impairments, metabolic anomalies, and neurotransmitter dysregulation (7). The prevailing diagnostic approach for SAD employs clinical tools such as the Confusion Assessment Method (CAM) and the Delirium Rating Scale (DRS) (8). These tools are designed to facilitate prompt delirium detection by clinicians, though their deployment in high-paced clinical environments may be constrained by requirements for specialized training and time commitment. Additionally, assessing patients with unstable levels of consciousness poses considerable difficulty. Research identifying delirium predictors has linked factors such as advanced age, pre-existing cognitive deficits, infection severity, and specific laboratory measures—including white blood cell count and serum creatinine levels—to the likelihood of delirium onset (9). Despite these insights, the field still faces a deficit of biomarkers that possess both high sensitivity and specificity for delirium prediction (10). The innovation and application of objective, precise assessment instruments and biomarkers, coupled with a deeper understanding of SAD's pathophysiology, are imperative for enhancing the clinical prognosis of older adult patients with sepsis.

Recent investigations have brought the lymphocyte-to-monocyte ratio (LMR) to the fore as a biomarker with promising utility in indicating immune status. LMR is posited to forecast acute inflammatory responses and the advent of sepsis (11). It is posited that a balance between adaptive and innate immune responses is crucial in the etiology of sepsis-induced delirium (12). Employing retrospective data from the MIMIC-IV database, this study evaluated LMR's predictive efficacy for delirium in septic senior patients. The aim was to ascertain LMR's viability as a non-invasive, cost-efficient, and easily accessible biomarker for the precocious identification of delirium in this patient population.

2 Materials and methods

2.1 Data source

Open-source medical information was employed from the Medical Information Mart for Intensive Care (MIMIC-IV version 2.2) database for this investigation. The MIMIC-IV repository encompasses extensive, high-quality patient data spanning from 2008 to 2019, sourced from the Beth Israel Deaconess Medical Center (13). The database amalgamates diverse clinical datasets including case histories, pharmacotherapy records, laboratory findings, patient demographics, and diagnostic codes based on the International Classification of Diseases. The principal investigator (Xiaopeng Shi) successfully completed the requisite online training under the auspices of the National Institutes of Health's collaborative institutional training initiative. Subsequent to this training, authorization was secured from the Institutional Review Board of the Massachusetts Institute of Technology for database access and data retrieval from MIMIC-IV (Certification number 38652558). Both the Massachusetts Institute of Technology (No. 0403000206) and the Beth Israel Deaconess Medical Center (2001-P-001699/14) provided ethical approval for the database's research utilization. The manuscript conforms to the STROBE guidelines, which delineate standards for reporting observational studies (14).

2.2 Patients

The results of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) assessments, used to evaluate the presence of delirium, are recorded in the MIMIC-IV database. This method includes criteria such as acute onset with marked fluctuations in consciousness, inattention, disorganized thinking, and acute changes in the level of consciousness. A positive delirium diagnosis was established if the criteria (1) + (2) + (3) or (1) + (2) + (4) were satisfied. Patients were subsequently stratified into either the delirium or non-delirium cohort, contingent upon any positive CAM-ICU assessment during their ICU tenure.

2.3 Study settings

Inclusion criteria were anchored to the 2016 Sepsis 3.0 definition and diagnostic benchmarks promulgated by the American Society of Critical Care Medicine and the European Society of Intensive Care Medicine, delineating Sepsis 3.0 as an infection conjoined with a Sequential Organ Failure Assessment (SOFA) score of 2 or higher (15). Only the data from the first ICU admission were considered for patients with multiple hospital stays.

The study excluded individuals under the age of 65, patients who either died or left the ICU within 48 h of admission, and those with primary diseases causing brain injury, such as ischemic or hemorrhagic stroke, psychiatric disorders, or dementia. Additionally, patients diagnosed with malignant tumors and those who did not undergo a delirium assessment were also excluded.

2.4 Data collection

Data were extracted from the MIMIC-IV database using structured query language with PostgreSQL. The following information was retrieved: (1) demographic data: age, sex, and height; (2) comorbidities: chronic pulmonary disease, diabetes, chronic liver disease, and chronic renal disease; (3) severity of illness scores on the first day in the ICU: Acute Physiology Score III (APSIII), Logistic Organ Dysfunction System (LODS), Oxford Acute Severity of Illness

Score (OASIS), Glasgow Coma Scale (GCS), and Charlson Comorbidity Index (CCI); (4) vital signs on the first day of ICU admission: heart rate (HR), respiratory rate (RR), mean arterial pressure (MAP), temperature (T), mechanical ventilation status, and peripheral oxygen saturation (SpO2); (5) laboratory results on the first day of ICU admission: hemoglobin, platelet count, white blood cell count (WBC), albumin, anion gap, bicarbonate, blood urea nitrogen (BUN), calcium, sodium, potassium, international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), SpO2, glucose, and lactate.

2.5 Statistical analysis

The distribution of continuous variables was appraised using the Shapiro–Wilk test, revealing non-normality. Accordingly, such variables are delineated as medians with interquartile ranges (IQR), and were compared via the Mann–Whitney U test or Wilcoxon rank-sum test, contingent upon their suitability. Categorical variables are expressed as counts (percentages) and were subjected to the chi-square test or Fisher's exact test, as dictated by the dataset's characteristics.

In the univariate analysis phase, LMR served as the exclusive predictor in the logistic regression model's construction. For the multivariate analysis, the models were sequentially enriched with additional variables: Model 1, the foundational model, incorporated solely LMR; Model 2 integrated various vital signs and comorbidities, refining Model 1; Model 3 appended laboratory results to the previously adjusted Model 2; and Model 4, adjusted for the elements in Model 3, included a variety of scoring metrics. To avert multicollinearity, neither monocytes nor lymphocytes were included in these models. Furthermore, a backward stepwise logistic regression approach (Model 5) was executed to procure the most parsimonious model, as indicated by the minimum Akaike Information Criterion (AIC) (16). The presence of collinearity among continuous variables was gauged using the variance inflation factor (VIF) (17), with any variable exhibiting a VIF exceeding 5 being excluded from the final model (18). Additionally, the relationship between LMR and delirium was graphically depicted using restricted cubic splines. The prognostic power of LMR for predicting the presence of delirium was quantified by calculating the sensitivity and specificity, and by constructing ROC curves for regression models, both inclusive and exclusive of LMR. The enhancement of predictive performance by LMR was measured by the area under the ROC curve (AUC), with the DeLong method applied to assess any significant shifts in AUC resultant from LMR inclusion. All statistical analyses were performed using R version 4.3.2, and $p < 0.05$ was considered statistically significant.

3 Results

3.1 Baseline characteristics

A total of 32,971 sepsis patients were retrieved from the MIMIC IV 2.2 database. Based on the exclusion criteria, 30,644 patients were excluded. Ultimately, 2,327 older adult patients with sepsis were included in this study, as shown in Figure 1. The median age of the included patients was 76.71 years (IQR: 70.4–83.44), with 55% being male. There were 1,281 cases of delirium, resulting in a delirium incidence of 55% among the older adult patients with sepsis. Compared to patients without delirium, those with delirium had higher APSIII, LODS, and OASIS scores, as well as increased heart rate, respiratory rate, and temperature; a higher proportion required mechanical ventilation, and there were higher rates of chronic renal and liver failure, as well as a higher comorbidity index. Additionally, these patients exhibited increased white blood cell counts, higher anion gaps, and elevated levels of blood urea nitrogen, creatinine, monocytes, neutrophils, ALT, AST, TBIL, while bicarbonate, sodium, platelet counts, and lymphocytes were lower, along with a decreased GCS score and lower LMR, as detailed in Table 1.

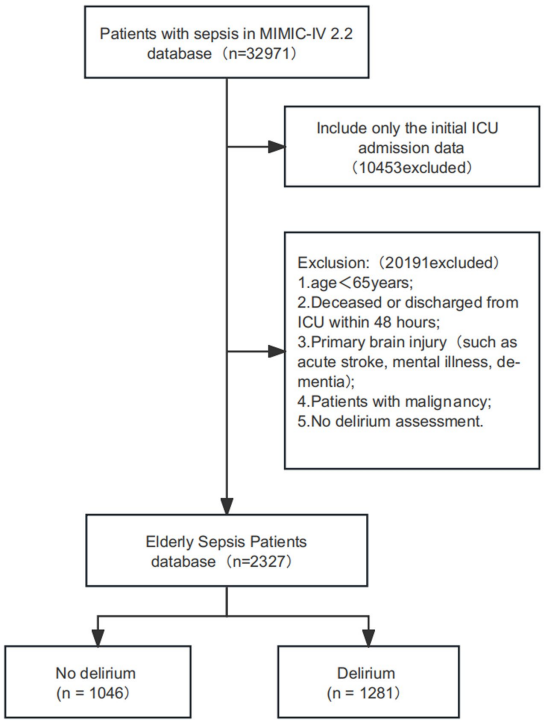

FIGURE 1
Flow chart for patient selection. ICU: intensive care unit; MIMIC-IV: medical information mart for intensive care IV.

3.2 Association between LMR and delirium incidence

Univariate logistic regression analysis (Model 1) revealed that each incremental increase in LMR was inversely correlated with the likelihood of delirium onset, evidenced by a decrease of 0.12845 in the log-odds ratio, a result bearing statistical significance ($p < 0.001$). Subsequent multivariate logistic regression models (Models 2, 3, and 4) upheld the significance of LMR as a predictive factor, even when accounting for the influence of additional variables. In the culminating model (optimal_model), a unit augmentation in LMR was significantly associated with a reduction of 0.09911 in the log-odds ratio for the occurrence of delirium ($p < 0.001$). Additional variables, inclusive of

TABLE 1 Baseline characteristics of the included patients.

Baseline variables	Total (*n* = 2327)	No delirium (*n* = 1046)	Delirium (*n* = 1281)	*p*-value
Age (years), median (Q1,Q3)	76.71 (70.4, 83.44)	76.62 (70.4, 83.78)	76.82 (70.38, 83.22)	0.955
Height(cm), Median (Q1,Q3)	169.76 (165, 173)	169.76 (165, 170)	169.76 (163, 173)	0.67
Male, n (%)	1288 (55)	568 (54)	720 (56)	0.38
Severe score (median [Q1,Q3])				
APSIII	49 (38, 63)	44 (35, 57)	54 (42, 67)	< 0.001
LODS	6 (4, 8)	5 (3, 7)	7 (5, 9)	< 0.001
OASIS	35 (30, 41)	33 (27, 38)	37 (32, 43)	< 0.001
GCS	15 (14, 15)	15 (14, 15)	15 (13, 15)	< 0.001
CCI	6 (4, 7)	5 (4, 7)	6 (4, 7)	< 0.001
Vital signs, median [IQR]				
HR(beats/minute)	83.33 (74.42, 95.14)	81.82 (74.13, 92.66)	84.52 (74.54, 97.24)	0.001
MAP (mmHg)	73.42 (68.31, 79.26)	73.13 (68.21, 78.29)	73.89 (68.42, 80.07)	0.021
RR (breath/minute)	19.2 (17.09, 22.15)	18.74 (16.76, 21.69)	19.59 (17.39, 22.4)	< 0.001
Temperature (°C)	36.85 (36.6, 37.06)	36.78 (36.57, 36.94)	36.91 (36.64, 37.15)	< 0.001
Ventilation, *n* (%)	1528 (66)	517 (49)	1011 (79)	< 0.001
Spo2 (%)	97.23 (95.66, 98.51)	97.18 (95.67, 98.43)	97.29 (95.66, 98.59)	0.223
Comorbidity, *n* (%)				
COPD	773 (33)	332 (32)	441 (34)	0.185
DM	837 (36)	364 (35)	473 (37)	0.308
CKD	708 (30)	295 (28)	413 (32)	0.039
CLD	84 (4)	25 (2)	59 (5)	0.006
Laboratory parameters (median [Q1,Q3])				
Hemoglobin (g/dL)	9.5 (8.1, 11.05)	9.5 (8.1, 10.9)	9.6 (8.1, 11.2)	0.135
Platelet (K/uL)	152 (109, 211.5)	145.5 (108, 203)	157 (109, 220)	0.012
WBC (K/uL)	15.1 (11.2, 20.2)	14.9 (10.8, 19.6)	15.5 (11.4, 20.4)	0.019
Albumin (g/dL)	3.06 (3, 3.1)	3.06 (3.06, 3.06)	3.06 (2.9, 3.2)	0.303
Aniongapp (mEq/L)	17 (14, 20)	16 (14, 19)	18 (15, 21)	< 0.001
Bicarbonate (mEq/L)	24 (21, 26)	24 (22, 26)	23 (21, 26)	0.014
BUN (mg/dL)	28 (19, 46)	26 (17.25, 40)	31 (20, 51)	< 0.001
Calcium (mg/dL)	8.51 (8.1, 8.9)	8.5 (8.1, 8.88)	8.51 (8.1, 9)	0.031
Creatinine (mg/dL)	1.3 (0.9, 2.1)	1.2 (0.9, 1.8)	1.4 (1, 2.3)	< 0.001
Sodium (mEq/L)	140 (137, 143)	140 (138, 143)	140 (137, 142)	< 0.001
Potassium (mEq/L)	4.6 (4.2, 5.1)	4.6 (4.2, 5)	4.6 (4.2, 5.2)	0.004
Monocytes (K/uL)	0.62 (0.38, 0.97)	0.57 (0.35, 0.86)	0.67 (0.4, 1.08)	< 0.001
Lymphocytes (K/uL)	1.15 (0.72, 1.74)	1.24 (0.77, 1.93)	1.09 (0.68, 1.61)	< 0.001
Neutrophils (K/uL)	10.56 (7.34, 14.97)	10.07 (7.11, 14.24)	10.93 (7.51, 15.71)	< 0.001
INR	1.4 (1.2, 1.76)	1.45 (1.2, 1.7)	1.4 (1.2, 1.8)	0.781
PT (sec)	15.7 (13.3, 19.1)	15.8 (13.62, 18.88)	15.5 (13.1, 19.9)	0.58
PTT (sec)	35.6 (29.7, 49.95)	35.4 (29.8, 49.45)	35.8 (29.6, 50.4)	0.895
ALT (U/L)	84 (23, 290.34)	210 (27, 290.34)	52 (21, 290.34)	< 0.001
AST (U/L)	137 (35, 469.08)	294.5 (42.25, 469.08)	92 (33, 469.08)	< 0.001
TBIL (mg/dL)	1.5 (0.6, 2.36)	2.36 (0.7, 2.36)	1.1 (0.5, 2.36)	< 0.001
Glucose (mg/dL)	136 (118.05, 166.23)	132.65 (117.83, 155.81)	139.5 (118.4, 173.75)	< 0.001
NLR	9.13 (5.14, 16.02)	7.92 (4.67, 13.92)	10.13 (5.8, 17.6)	< 0.001

(Continued)

TABLE 1 (Continued)

Baseline variables	Total (n = 2327)	No delirium (n = 1046)	Delirium (n = 1281)	p-value
PLR	176 (103.96, 302.44)	152.77 (94.02, 274.31)	195.45 (117.43, 326.67)	< 0.001
LMR	1.83 (1, 3.32)	2.25 (1.18, 3.95)	1.57 (0.9, 2.87)	< 0.001
Lactate (mmol/L)	3.1 (1.8, 3.4)	3.2 (1.9, 3.4)	3 (1.8, 3.8)	0.887

SOFA: sequential organ failure assessment; APSIII: acute physiology score III; LODS: logistic organ dysfunction system; OASIS: oxford acute severity of illness score; GCS: Glasgow coma scale; CCI: Charlson comorbidity index DM: diabetes mellitus; COPD: chronic obstructive pulmonary diseases; CKD: chronic kidney disease; CLD: chronic liver disease; HR: heart rate; RR: respiratory rate; MAP: mean arterial pressure; BUN: blood urea nitrogen; WBC: white blood cell count; INR: international normalized ratio; PT: prothrombin time; PTT: partial thromboplastin time; ALT: alanine aminotransferase; AST: aspartate aminotransferase; TBIL: total bilirubin; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; LMR: lymphocyte to monocyte ratio.

TABLE 2 The correlation between lymphocyte-to-monocyte ratio (LMR) and the occurrence of delirium in older adult patients with sepsis.

	Univariable analysis model 1	Multivariable analysis model 2	Multivariable analysis model 3	Multivariable analysis model 4
OR (95% CI)	0.8795 (0.8495, 0.9095)	0.8991 (0.8678, 0.9305)	0.9033 (0.8696, 0.9374)	0.9104 (0.8751, 0.9462)
p-value	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$

HR, MAP, body temperature, CLD, platelet count, WBC, anion gap, bicarbonate, BUN, sodium, PTT, TBIL, SpO2, and scores from SOFA, LODS, OASIS, and GCS, were assimilated into the final model. While a robust negative association between LMR and delirium was discernible in the foundational model, the introduction of further variables led to a progressive elevation of the OR, indicating a diluted impact of LMR on delirium manifestations. Nevertheless, as model complexity intensified, the correlation between LMR and delirium attenuated, with the OR converging towards unity (Table 2).

Utilizing backward stepwise logistic regression, a model was identified with the minimum Akaike Information Criterion (AIC) value, concluding at 2853. This model was constructed by integrating 17 variables. Among these variables, it was found that LMR (OR = 0.9056, $p < 0.01$), heart rate (HR, OR = 0.9927, $p = 0.0218$), mean arterial pressure (MAP, OR = 1.0273, $p < 0.01$), body temperature (OR = 1.6826, $p < 0.01$), chronic liver disease (CLD, OR = 1.7491, $p = 0.0401$), anion gap (OR = 1.0346, $p = 0.0026$), sodium levels (OR = 1.034, $p = 0.001$), total bilirubin (TBIL, OR = 0.961, $p = 0.0398$), Sequential Organ Failure Assessment score (SOFA, OR = 1.0559, $p = 0.0401$), Logistic Organ Dysfunction Score (LODS, OR = 1.1872, $p < 0.01$), Oxford Acute Severity of Illness Score (OASIS, OR = 1.0451, $p < 0.01$), and Glasgow Coma Scale score (GCS, OR = 1.0635, $p = 0.001$) exhibited significant independent correlations with an elevated risk of delirium onset (Table 3).

TABLE 3 Variables selected through stepwise logistic regression analysis.

	OR	95%CI	p-value
LMR	0.9056	0.8712–0.9406	<0.01
HR	0.9927	0.9865–0.9989	0.0218
MAP	1.0273	1.0163–1.0387	<0.01
Temperature	1.6826	1.4182–2.0050	<0.01
CLD	1.7491	1.0368–3.0284	0.0401
Platelet	1.00096	0.99998–1.00196	0.0566
WBC	0.9921	0.9817–1.0025	0.1357
Aniongap	1.0346	1.0122–1.0580	0.0026
Bicarbonate	1.0185	0.9969–1.0407	0.0952
BUN	0.9966	0.9924–1.0009	0.1246
Sodium	1.034	1.0136–1.0550	0.001
PTT	0.9973	0.9946–1.0001	0.0569
TBIL	0.961	0.9215–0.9956	0.0398
Spo2	1.054	1.0088–1.1014	0.0189
SOFA	1.0559	1.0027–1.1125	0.0401
LODS	1.1872	1.1318–1.2461	<0.01
OASIS	1.0451	1.0304–1.0602	<0.01
GCS	1.0635	1.0250–1.1034	0.001

The analysis utilized restricted cubic splines to characterize the preoperative LMR's association with delirium incidence. As demonstrated in Figure 2, the relationship between LMR and the odds ratio (OR) for delirium was found to be non-linear. When LMR was lower, there was a correspondingly higher OR, which sharply decreased with an increase in LMR, indicating an inverse correlation between LMR and delirium risk. However, at higher levels of LMR, the OR for delirium began to ascend slowly, potentially indicating that an excessively elevated LMR is associated with an augmented risk of delirium.

Receiver Operating Characteristic (ROC) curves were generated within the optimal model framework to evaluate the prognostic utility for delirium, both with the inclusion of the Lymphocyte-to-Monocyte Ratio (LMR) and without. The area under each curve (AUC) served as a quantitative measure of each model's predictive efficacy. The integration of LMR into the model was associated with a marginal enhancement in AUC, and the comparative analysis of the ROC curves demonstrated statistical significance (DeLong, $p = 0.035$), as depicted in Figure 3.

4 Discussion

This study conducted an in-depth analysis of the delirium incidence within the older adult patients with sepsis population. Our data reveals a 55% incidence of delirium among these patients, in contrast to the 17.7

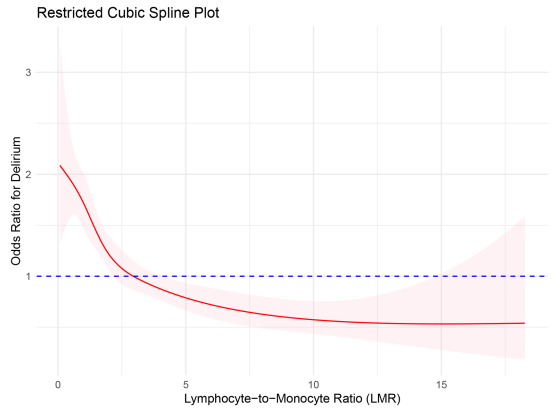

FIGURE 2
Restricted spline curve for the relationship between LMR and delirium in older adult patients with sepsis. The red bold line represents the odds ratio, and the shaded area represents the 95% confidence interval.

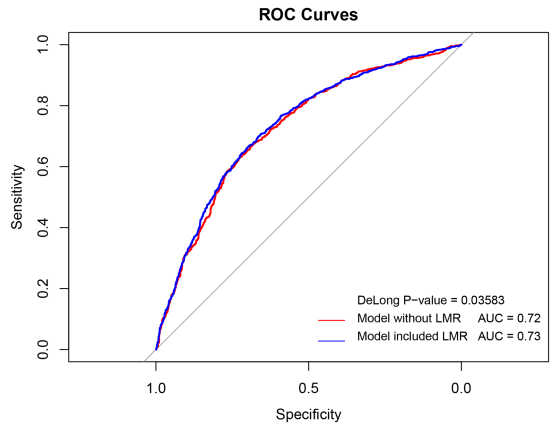

FIGURE 3
ROC curves for Multivariate Model Predictions of delirium in older adult patients with sepsis with and without LMR. ROC: receiver operating characteristic curve; AUC: area under the receiver operating characteristic curve; OR: odds ratio.

to 48% range reported in intensive care units (ICU) for sepsis-associated delirium (SAD) (9), with some studies indicating rates up to 70% (19). Additionally, another multicenter study documented acute mental status changes in 307 of 1,333 patients with severe sepsis (23%) (20). The variation in reported incidence rates may stem from differences in patient demographics, severity of sepsis, delirium diagnostic criteria, and methods of data collection and analysis. Our findings highlight the clinical importance of delirium in older adult patients with sepsis and identify multiple biomarkers and clinical parameters associated with an increased incidence of delirium, suggesting the need for heightened vigilance and comprehensive assessment in this vulnerable group to mitigate the impact of delirium on morbidity and mortality.

The mechanisms through which sepsis incites delirium are not fully understood, yet current research implicates a complex interplay of neuroinflammation, impaired cerebral perfusion, blood–brain barrier compromise, and neurotransmitter transport dysfunction. It has been observed that sepsis-induced endothelial cell activation escalates systemic inflammatory markers such as IL-1β, IL-6, and TNF-α, as well as the production of reactive oxygen species, factors that may accelerate the onset of sepsis-associated delirium (SAD) (12). Notably, the criteria for defining and applying SAD risk factors vary across studies. Ely et al. (21) found that over half of non-sedated septic patients exhibited SAD, correlating with bacteremia, and elevated levels of blood urea nitrogen and bilirubin. Ai Yuhang et al. (22) noted SAD in a subset of ICU patients, marked by heightened APACHE II scores. In contrast, Pandharipande et al. recognized SAD in a majority of their study cohort, with age and functional dependency as contributing risks (5). The single-center nature of these studies, however, introduces limitations such as small sample sizes and inadequate consideration of ICU-specific risk factors. Ebersoldt et al.'s multicenter research corroborated advanced age as an independent risk factor for SAD (23). These factors, while potentially central to SAD's pathophysiology, await further investigation to establish causality (24).

In this study, we observed a significant inverse correlation between the lymphocyte-to-monocyte ratio (LMR) and the risk of delirium. This finding, not widely reported in the literature, suggests that LMR could serve as a potential biomarker for predicting and monitoring delirium risk in older adult patients with sepsis. Our multivariate logistic regression model further substantiated the significant association between increased LMR and reduced delirium risk, even after adjusting for other known risk factors. While aligning with literature on the close link between delirium and poor outcomes in sepsis patients, our data suggests that LMR may possess greater predictive value. This could be attributed to the use of an updated database, a broader patient cohort, and a more sophisticated statistical model. Hence, our findings underscore the potential significance of LMR as a novel biomarker for predicting delirium in sepsis and its potential direct impact on clinical management of sepsis patients.

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is the most widely utilized tool, designed specifically for the ICU setting and proven to be highly specific in assessing delirium among critically ill patients. However, significant heterogeneity in CAM-ICU results across different study settings has been noted, with potential low sensitivity in real-world clinical practice (25). The incidence of delirium varies greatly among ICU patient populations, possibly due to predisposing risk factors such as age and depression (26). The CAM-ICU faces challenges in assessing patients with fluctuating consciousness levels and in the absence of definitive diagnostic criteria for SAD. In this scenario, the LMR emerges as an objective biomarker, offering a novel approach. Its utility is underscored by its independence from subjective patient responses and variations in consciousness, rendering it particularly beneficial for patients who are unsuitable for traditional delirium assessments. Moreover, LMR's ability to reflect the body's inflammatory and immune status is potentially closely linked to the pathophysiological mechanisms involved in mental disorder development. This connection is crucial, given the established association between delirium and disruptions in inflammatory and immune responses. Consequently, LMR acts as a pivotal indicator of a patient's risk of delirium. Its proficiency in mirroring these systemic states provides vital insights into the likelihood of a patient being at high risk for SAD, thereby aiding in the prompt identification and intervention. These characteristics elevate LMR as an indispensable tool in delirium assessment, significantly enhancing the capacity for early detection and effective management of patients predisposed to this intricate condition.

The development of delirium is a multifaceted and complex process influenced by a myriad of biological and environmental factors. The lymphocyte-to-monocyte ratio (LMR), while showing promise as a predictive tool for delirium in older adult patients with sepsis, requires further empirical validation to ascertain its efficacy and reliability comprehensively. This need for additional substantiation is crucial, considering the multifactorial nature of delirium. Moreover, LMR's effectiveness may vary across different clinical scenarios due to factors such as inflammation levels, comorbidities, and treatment approaches, which can significantly impact its predictive accuracy. Therefore, future research should concentrate on integrating LMR with other biomarkers to achieve a more holistic understanding of delirium's pathophysiology. Such integration aims to refine the assessment and management of delirium, potentially leading to enhanced patient outcomes, particularly in complex cases influenced by interrelated factors. In summary, while LMR is a valuable indicator for predicting delirium, its application should be cautiously considered alongside other clinical assessments, acknowledging its limitations and the necessity for further research to confirm its clinical utility.

5 Conclusion

In the cohort of older adult patients with sepsis, this study has identified the lymphocyte-to-monocyte ratio (LMR) as a substantial independent predictor of delirium. Retrospective analyses have uncovered a significant inverse relationship between LMR and the risk of delirium, where each increment in LMR correlates with a reduced risk. The integration of LMR into multivariate predictive models markedly improves the detection of patients with a heightened risk for delirium, thus potentially informing early interventions. The findings advocate for the clinical utility of LMR in refining delirium risk assessment and management strategies in the geriatric sepsis population, warranting further investigation into its broader clinical efficacy.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because the requirement for individual patient consent was waived because the project does not impact clinical care and all patient confidential information was anonymized, therefore, the patient's consent is not required. All methods were carried out by relevant guidelines and regulations. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because the institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The requirement for individual patient consent was waived because the project does not impact clinical care and all patient confidential information was anonymized, therefore, the patient's consent is not required. All methods were carried out by relevant guidelines and regulations.

Author contributions

XS: Data curation, Methodology, Writing – original draft. LY: Methodology, Visualization, Writing – review & editing. WB: Software, Validation, Writing – review & editing. LJ: Formal analysis, Software, Writing – review & editing. LQ: Project administration, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 07 February 2024
DOI 10.3389/fmed.2024.1321599

OPEN ACCESS

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RECEIVED 14 October 2023
ACCEPTED 15 January 2024
PUBLISHED 07 February 2024

CITATION
Chen W, Peng M, Ye Z, Ai Y and Liu Z (2024) The mode and timing of administrating nutritional treatment of critically ill elderly patients in intensive care units: a multicenter prospective study.
Front. Med. 11:1321599.
doi: 10.3389/fmed.2024.1321599

The mode and timing of administrating nutritional treatment of critically ill elderly patients in intensive care units: a multicenter prospective study

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Introduction: Critically ill patients are more susceptible to malnutrition due to their severe illness. Moreover, elderly patients who are critically ill lack specific nutrition recommendations, with nutritional care in the intensive care units (ICUs) deplorable for the elderly. This study aims to investigate nutrition treatment and its correlation to mortality in elderly patients who are critically ill in intensive care units.

Method: A multiple-center prospective cohort study was conducted in China from 128 intensive care units (ICUs). A total of 1,238 elderly patients were included in the study from 26 April 2017. We analyzed the nutrition characteristics of elderly patients who are critically ill, including initiated timing, route, ways of enteral nutrition (EN), and feeding complications, including the adverse aspects of feeding, acute gastrointestinal injury (AGI), and feeding interruption. Multivariate logistic regression analysis was used to screen out the impact of nutrition treatment on a 28-day survival prognosis of elderly patients in the ICU.

Result: A total of 1,238 patients with a median age of 76 (IQR 70–83) were enrolled in the study. The Sequential Organ Failure (SOFA) median score was 7 (interquartile range: IQR 5–10) and the median Acute Physiology and Chronic Health Evaluation (APACHE) II was 21 (IQR 16–25). The all-cause mortality score was 11.6%. The percentage of nutritional treatment initiated 24h after ICU admission was 58%, with an EN of 34.2% and a parenteral nutrition (PN) of 16.0% in elderly patients who are critically ill. Patients who had gastrointestinal dysfunction with AGI stage from 2 to 4 were 25.2%. Compared to the survivors' group, the non-survivors group had a lower ratio of EN delivery (57% vs. 71%; p =0.015), a higher ratio of post-pyloric feeding (9% vs. 2%; p =0.027), and higher frequency of feeding interrupt (24% vs. 17%, p =0.048). Multivariable logistics regression analysis showed that patients above 76years old with OR (odds ratio) 2.576 (95% CI, 1.127–5.889), respiratory rate>22 beats/min, and ICU admission for 24h were independent risk predictors of the 28-day mortality study in elderly patients who are critically ill. Similarly, other independent risk predictors of the 28-day mortality study were those with an OR of 2.385 (95%CI, 1.101–5.168), lactate >1.5mmol/L, and ICU admission for 24h, those with an OR of 7.004 (95%CI, 2.395–20.717) and early PN delivery within 24h of ICU admission, and finally those with an OR of 5.401 (95%CI, 1.175–24.821) with EN delivery as reference.

Conclusion: This multi-center prospective study describes clinical characteristics, the mode and timing of nutrition treatment, frequency of AGI,

and adverse effects of nutrition in elderly ICU patients. According to this survey, ICU patients with early PN delivery, older age, faster respiratory rate, and higher lactate level may experience poor prognosis.

KEYWORDS

enteral nutrition, parenteral nutrition, elderly, intensive care units, mortality

1 Introduction

With the global increase in elderly patients who are critically ill, hospital admissions also increased, especially at the peak of the COVID-19 infection (1). With increasing aging, symptoms of critical illness in elderly people become more significant, alongside poor clinical outcomes attributed to several intensive care unit (ICU) factors (2). With the onset of organ degradation and poor immune function in elderly patients, malnutrition contributes significantly to poor clinical outcomes, including increased incidence of infections, length of hospital and ICU stay, and risk of mortality, among others (3).

Malnutrition is defined as the state of insufficient intake or uptake of nutrients, leading to an altered body composition (2). The study by Agarwal et al. evaluated 3,122 patients with a mean age of 64.6 ± 18 years and concluded that participants suffering from malnutrition were 41% (4). In critically ill elderly patients, malnutrition was higher with poor outcomes, increased rates of infections, length of hospital stay, and mortality risks (5). More data are required to evaluate nutrition in critically ill elderly patients.

Most critically ill patients, especially the elderly, require artificial nutrition. It is reported that neither higher nor lower energy intake improves clinical outcomes in critically ill elderly patients (6). However, food intake between 12 and 25 kcal/kg in the first 7–10 days of ICU stay is recommended (7). However, a decrease in fat-free body mass and resting energy expenditure (REE) generally decreases due to aging. Approximately 30 kcal/kg body weight is a recommended rough estimate and general orientation for energy requirements in older persons (8). In addition, for nutrition support therapy, early enteral nutrition (EN) is beneficial for maintaining gut integrity, modulating stress, and regulating the systemic immune system. Due to higher rates of gastrointestinal (GI) dysfunction in elderly critical patients, clinical nutrition therapy has changed substantially.

Owing to poor nutrition recommendations and malnutrition in critically ill elderly patients and the consequent longer hospital stays, poor clinical outcomes, and high mortality risks (9, 10), it is important to develop protocols to improve nutrition treatments in elderly critical patients. This study aims to evaluate the clinical characteristics of nutrition therapy and the impact of nutrition on mortality in elderly critical patients.

2 Materials and methods

2.1 Methods

2.1.1 Study design

A multiple-center prospective observational cohort study was conducted in China from 128 intensive care units (ICUs) in 116 hospitals. The clinical information of patients was collected on the first day of ICU admission, and the nutritional tolerance of the patients was assessed to choose the appropriate nutritional therapy. A follow-up visit was made to assess the survival prognosis of the patients on the 28th day of ICU admission. The aim was to explore the effect of nutrition treatment on 28-day survival outcomes in elderly patients during ICU admission. Patients who were admitted to ICU on 26 May 2017 were screened for eligibility based on the following inclusion criteria: (A) first-time ICU admission patients; (B) above 65 years old and more than 7 days of stay in the ICU; and (C) patients with approximately 2 months without gastrointestinal surgery. The exclusion criteria were as follows: (A) patients with severe cachexia; (B) severe craniocerebral injury patients with lack of consciousness; (C) patients without informed consent; and (D) patients without follow-up within 28 days after ICU admission. The flowchart is shown as a Supplementary Figure S1. A total of 1,238 patients were included in our study. Survival outcomes at day 28 were used as the endpoint, and clinical characteristics and variables were collected and recorded. All data involved in our study were obtained from a customized website and authorized by the ethics committee of Nanjing Hospital (no. 2017NZKY-010-01).

2.2 Data collection

2.2.1 Baseline characteristics

Clinical information was collected on the first day during ICU admission, including age, sex, weight, height, comorbidities, and diagnoses. Vital signs were also collected, including body temperature, mean arterial pressure, heart rate, and respiratory rate. Routine laboratory tests were carried out, including white blood cell (WBC) count, percentage of lymphocytes, platelet, total bilirubin, albumin, creatinine, C-reactive protein (CRP), maximum and minimum blood glucose, oxygenation, and lactate. Acute Physiology and Chronic Health Evaluation II (APACHE II) score and Sequential Organ Failure Assessment (SOFA) score were assessed. All these baseline characteristics were collected on the first day of ICU admission. All clinical data were collected with the informed consent of patients and their families (including the study protocol, study purpose, and study content), and all clinical data were identified to protect patients' privacy.

2.2.1.1 Nutrition-associated parameters

We also extracted some nutrition-related indicators, such as serum albumin levels on the first day of ICU admission. Furthermore, we continuously recorded more specific information related to nutrition treatment during ICU admission, including the initiation of nutritional therapy, the mode of nutritional therapy (enteral,

parenteral, or oral), and the option of enteral nutrition delivery (such as gastric feeding, post-pyloric feeding, percutaneous, or jejunostomy). At the same time, we also conducted detailed assessments of patients' tolerance to enteral nutrition during hospitalization, including nausea, vomiting, aspiration, abdominal pain, abdominal distension, and diarrhea.

2.2.1.2 AGI scale and assessment

Early enteral nutrition in critically ill patients is important for improved rehabilitation and prevention of related complications. According to the ESPEN guidelines of the intensive care unit, critically ill patients admitted to the ICU for more than 48 h are at risk of malnutrition. It was further noted that early enteral nutrition can improve gastrointestinal mucosa and prevent intestinal microbiota translocation, which should be implemented within 3–7 days (11). However, acute gastrointestinal injury (AGI) was common among critically ill patients (12). AGI is mainly manifested as gastric retention or reflux, abdominal distension, diarrhea, gastrointestinal paralysis, abdominal pressure, and gastrointestinal bleeding. Therefore, we conducted a comprehensive assessment of patient tolerance to nutritional therapy on the first day during ICU admission and selected personalized nutritional plans and methods for each patient through consecutive 8 days of evaluation of the patient's gastrointestinal function (the final evaluation, also labeled as the eighth evaluation, was performed on day 10 after admission to the ICU) based on the AGI scale originated from the ESICM Working Group on Abdominal Problems (12).

2.3 Statistical analysis

The collected data were analyzed using SPSS software (version 26.0) and R version 4.0.3. Continuous variables were reported as a median and interquartile range with non-gaussian data distribution confirmed by the Kruskal–Wallis test. Continuous variables were compared using the non-parametric Mann–Whitney test. Categorical variables were compared using the chi-square test.

A receiver operating characteristic (ROC) curve was performed to calculate the threshold for predicting the long-term mortality of each continuous variable with significant differences after univariate logistics regression analysis. Logistic regression was used for univariate and multivariate analysis to calculate mortality predictive values, with odds ratio (OR) and a 95% confidence interval (CI). Variables in the univariate logistics regression analysis were selected using an enter elimination method. Multivariate logistic regression analysis was performed to adjust for several confounders, incorporating all risk factors with a p-value of 0.05. The selection of likelihood ratio (LR) test for maximum partial likelihood estimation (forward: LR) was used to choose independent prognostic factors using odds ratio (OR) and 95% confidence interval. All parameters with a p-value of 0.05 were statistically significant.

3 Results

3.1 Baseline characteristics of participants

In total, 1,238 critically ill elderly patients were enrolled in this study. The overall 28-day survival rate was 88.4% ($n = 1,094$), including 1,094 survivors and 144 non-survivors, of which 804 (65%) patients were male. The median age for patients was 76 years (IQR 70–83), height was 168 cm (IQR 160–173), and weight was 61 kg (IQR 55–70). The median SOFA and APACHE II scores were 7 (IQR 5–10) and 21 (IQR 16–25). The characteristics and variables of the study of the elderly population are presented in Table 1.

TABLE 1 Baseline clinical characteristics in elderly critically ill patients.

Variables	Total (n = 1,238)
Gender, male, n (%)	804 (65)
Age, Median (IQR), years	76 (70, 83)
Height, Median (IQR), cm	168 (160, 173)
Weight, Median (IQR), kg	61 (55, 70)
ICU diagnosis, n (%)	
Sepsis	104 (8)
Sepsis shock	161 (13)
Cardiac arrest	51 (4)
Severe pancreatitis	46 (4)
Cerebral disease	320 (26)
Underlying diseases, n (%)	
Hypertension	338 (27)
Diabetes	188 (15)
Chronic kidney dysfunction	189 (15)
Gastrointestinal tumor	116 (9)
Clinical examination during 24 h ICU admission, Median (IQR)	
Oxygenation index	200 (130, 286.5)
Platelet, × 10^9/L	170 (120, 237)
Total bilirubin, mmol/L	13.9 (8.93, 21.87)
Creatinine, umol/L	89.65 (64.35, 134)
SOFA	7 (5, 10)
APACHE II	21 (16, 25)
Temperature, °C	37 (36.6, 37.98)
Mean arterial pressure, mmHg	80 (70, 96)
Heart rate, beats/min	100 (84.25, 119)
Respiratory rate, beats/min	22 (18, 26)
GCS	9 (6, 14)
WBC, × 10^9/L	11.70 (8.3, 16)
lymphocytes%	7.15 (4, 12.38)
CRP, mmol/L	58.34 (19, 120)
ALB, mg/dl	30.8 (26.9, 35)
Lactate, mmol/L	1.9 (1.2, 3.1)
Glucose_min, mmol/L	6.8 (5.6, 8.5)
Glucose_max, mmol/L	11.3 (8.9, 14.8)
Day28_ICU stay, n (%)	358 (29)
28_day mortality, n (%)	144 (11.6)

IQR, interquartile range; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow coma scale; WBC, white blood cell; CRP, C-reactive protein; ALB, albumin.

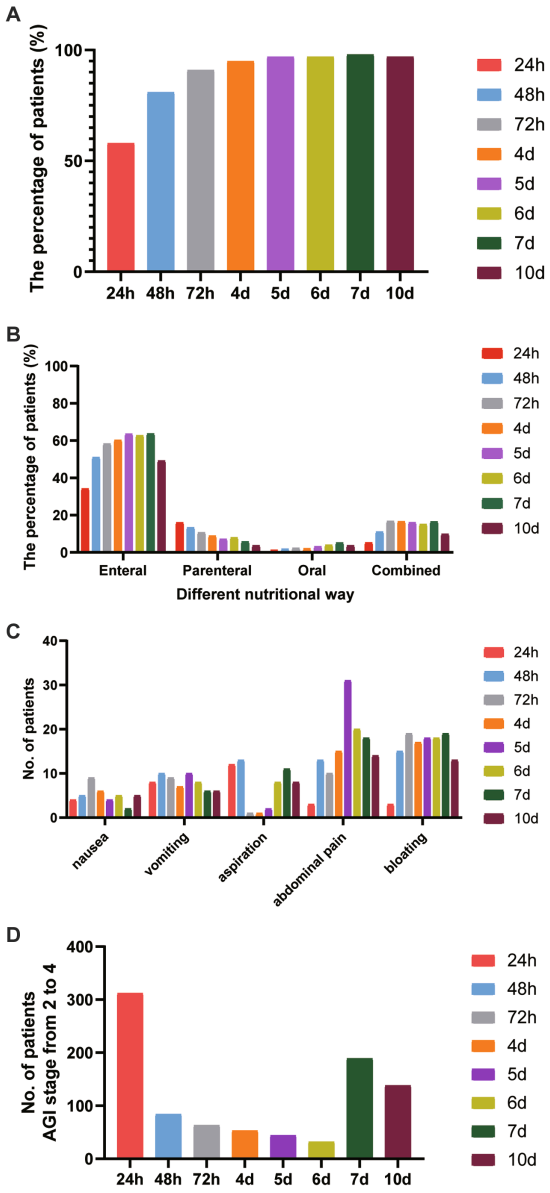

FIGURE 1
The features of nutrition treatment in elderly critically ill patients. **(A)** The percentage of nutrition treatment-initiated timing at different feeding stages from 24 h to day 10 after ICU entry. **(B)** The proportion of nutritional routines at different feeding stages from 24 h to day10 after ICU entry. **(C)** The adverse aspects of feeding treatment at different feeding stages. **(D)** The distribution of the AGI stage with grades of 2 to 4 was shown.

3.2 Features of nutrition treatment in critically ill elderly patients

As shown in Figure 1A, nutrition treatment started within 24 h, 48 h, 72 h, and day 7 after ICU admission were 58% ($n = 722$), 81% ($n = 999$), 91% ($n = 1,130$), and 98% ($n = 1,208$), respectively, in elderly critically ill patients. The ratio of subjects receiving EN within 24 h after ICU admission was 34.2% ($n = 488$). This increased to 51.0% after 48 h and 63.7% after day 7. The percentage of patients receiving PN was 16.0%, 24 h after ICU admission. This decreased to 13.4% after 48 h and 5.8% after day 7. In addition, the percentage of oral treatment 24 h after ICU admission was 1.3%, and EN combined with PN was 5.3% (Figure 1B). The distribution of nutrition treatment is demonstrated in Figure 1B. The mode of EN delivery used was gastric feeding in 85% of patients, post-pyloric feeding in 2% of patients, and PEG/J or jejunostomy feeding in 2% of patients. The infusion style of EN delivery was a continuous pump in 95% of patients and an intermittent pump in 5% of patients.

Figure 1C shows the adverse effects of nutrition treatment, including nausea, vomiting, aspiration, abdominal pain, and bloating at different feeding stages. We found that at an early stage, the frequency of aspiration occurred in 12 elderly patients 24 h after ICU admission and 13 patients after 48 h. The frequency of abdominal pain occurred in 3 patients 24 h after ICU admission, increased to 13 patients after 48 h, and 18 patients on day 7.

In this study, we assessed the AGI grade in elderly critically ill patients from 24 h to day 10 after admission to ICU. The distribution of the AGI stage from 2 to 4 is shown in Figure 1D. After 24 h of ICU admission, 25.2% ($n = 312$) of elderly patients had gastrointestinal dysfunction with AGI stage from 2 to 4. It decreased to 6.8% ($n = 84$) after 48 h and increased to 15.3% ($n = 189$) on day 7 after ICU admission.

3.3 Features of nutrition treatment between survivors and non-survivors groups in critically elderly ill patients

We categorized the elderly patients into two groups according to the mortality 28 days after ICU admission (Table 2). Compared to the survivors' group, the non-survivor group had significant elderly patients (78 years vs. 75 years old; $p = 0.038$), a lower rate of cerebral disease (15% vs. 27%; $p = 0.003$), and a higher rate of gastrointestinal tumor (19% vs. 7%; $p = 0.001$). We also assessed the clinical characteristics 24 h after ICU admission in these two groups, and the results showed that, compared to the survivors' group, the non-survivors group had higher SOFA scores (8.5 vs. 7 years old; $p = 0.01$) and APACHE II score (23 vs. 20; $p = 0.002$); higher frequencies of heart rate (109 vs. 100; $p = 0.027$) and respiratory rate (24 vs. 22; $p = 0.004$); higher levels of serum CRP (82 vs. 55 mg/dL; $p = 0.003$) and serum lactate (2.2 vs. 1.8 mmoL/L; $p < 0.001$); and lower level of serum platelet (158 vs. $172 \times 10^*9$/L; $p = 0.015$) and the percentage of lymphocyte (6.5 vs. 7.3%; $p = 0.033$).

Meanwhile, the features of nutrition treatment were also shown. Compared to the survivors' group, there was a lower ratio of EN delivery (57% vs. 71%; $p = 0.015$), a higher ratio of post-pyloric feeding (9% vs. 2%; $p = 0.027$), and a higher frequency of feeding interrupt (24% vs. 17%; $p = 0.048$) in the non-survivors group.

3.4 Nutrition treatment factors associated with long-term mortality in elderly critical patients

Univariate logistics regression analysis was used to investigate the factors associated with 28-day mortality in critically ill elderly patients. As shown in Table 3, Several factors were significantly associated with long-term mortality. These include age with an OR of 1.047 (95% CI, 1.020–1.075), weight with an OR of 0.975 (95% CI, 0.956–0.995),

TABLE 2 Clinical characteristics in elderly patients are compared for survivor and non-survivor groups.

Variables	Survivor group (n = 1,094)	Non-survivor group (n = 144)	p
Gender, n (%)	704 (64)	100 (69)	0.266
Age, Median (IQR), years	75 (70, 82)	78 (70.75, 84)	0.038
Height, Median (IQR), cm	168 (160, 173)	170 (160, 173)	0.276
Weight, Median (IQR), kg	62 (55, 70)	60 (55, 68)	0.057
ICU diagnosis, n (%)			
Sepsis	92 (8)	12 (8)	1
Sepsis shock	141 (13)	20 (14)	0.839
Cardiac arrest	48 (4)	3 (2)	0.278
Severe pancreatitis	40 (4)	6 (4)	0.944
Cerebral disease	298 (27)	22 (15)	0.003
Underlying diseases, n (%)			
Hypertension	302 (28)	36 (25)	0.575
Diabetes	164 (15)	24 (17)	0.687
Chronic liver dysfunction	40 (4)	6 (4)	0.944
Chronic kidney dysfunction	167 (15)	22 (15)	1
Gastroenteric tumor	98 (7)	18 (19)	0.001
Clinical examination during 24 h ICU admission, Median (IQR)			
SOFA	7 (5, 10)	8.5 (6, 11)	0.010
APACHEII	20 (16, 25)	23 (17, 27)	0.002
Temperature, °C	37 (36.7, 37.98)	37 (36.5, 37.92)	0.492
Mean arterial pressure, mmHg	80 (70, 96)	78.5 (68, 91.25)	0.256
Heart rate, beats/min	100 (84, 118)	109 (86, 121)	0.027
Respiratory rate, beats/min	22 (18, 26)	24 (19, 28.25)	0.004
GCS	9 (6, 13)	8.5 (5, 14)	0.714
Oxygenation index	200 (132, 290)	184 (122, 265)	0.268
Platelet, $\times 10^9$/L	172 (121, 241)	158 (100, 207)	0.015
Total bilirubin, mmol/L	13.9 (8.9, 21.98)	14.35 (9.4, 20.65)	0.769
Creatinine, umol/L	88.5 (64.03, 132)	94.16 (67.75, 156.62)	0.160
WBC, $\times 10^9$/L	11.7 (8.22, 16)	12.15 (8.83, 15.8)	0.720
lymphocytes%	7.3 (4.1, 12.5)	6.5 (3.68, 10.83)	0.033
CRP, mmol/L	55 (18, 117)	82 (33, 149)	0.003
ALB, mg/dl	31 (27, 35.1)	29.56 (25.95, 33.5)	0.026
Lactate, mmol/L	1.8 (1.2, 3)	2.2 (1.6, 4.0)	<0.001
Glucose_min, mmol/L	6.8 (5.6, 8.5)	6.8 (5.68, 8.45)	0.901
Glucose_max, mmol/L	11.3 (8.9, 14.88)	11.5 (8.97, 14.2)	0.962
Nutritional treatment during 24 h ICU admission, n (%)			
AGI with 2 to 4 stages	283 (25.8)	29 (9.3)	0.348
Nutritional therapy initiation	632 (58)	90 (62)	0.321
Nutritional routine			0.015
EN	454 (71)	34 (57)	
PN	172 (27)	26 (43)	
Oral	16 (2)	0 (0)	
The way of EN delivery			0.027
Gastric feeding	442 (97)	30 (88)	

(Continued)

TABLE 2 (Continued)

Variables	Survivor group (n = 1,094)	Non-survivor group (n = 144)	p
Postpyloric feeding	9 (2)	3 (9)	
PEG/J or jejunostomy feeding	5 (1)	1 (3)	
EN delivery infusion way			0.176
Continuous	426 (95)	34 (100)	
Discontinuous	23 (5)	0 (0)	
The adverse aspect of feeding during 24 h ICU admission, n (%)			
Nausea	200 (18)	30 (21)	0.657
Vomiting	69 (6)	13 (9)	0.303
Aspiration	173 (16)	25 (17)	0.722
Abdominal pain	78 (7)	11 (8)	0.654
Bloating	41 (4)	6 (4)	0.267
Tolerability assessment	574 (52)	68 (47)	0.273
Gastric residue, Median (IQR)	80 (0, 300)	280 (0, 300)	0.073
Feeding interrupt, n (%)	188 (17)	35 (24)	0.048

IQR, interquartile range; ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II; GCS, Glasgow Coma Score; WBC, white blood cell; CRP, C-reactive protein; ALB, albumin; AGI, acute gastrointestinal injury; EN, enteral nutrition; PN, parenteral nutrition; PEG/J, percutaneous endoscopic gastrostomy/jejunostomy.

previous gastrointestinal tumor with an OR of 0.412 (95% CI, 0.237–0.716), APACHE II score with an OR of 1.0385 (95% CI, 1.008–1.070), respiratory rate with an OR of 1.036 (95% CI, 1.007–1.067), lactate with an OR of 1.060 (95% CI, 1.010–1.114), and post-pyloric feeding, 24 h after ICU admission, with an OR of 4.911 (95% CI, 1.263–19.096). Also, when using gastric feeding as a reference, and PN delivery 24 h after ICU admission with OR 2.018 (95% CI 1.176–3.463) and EN delivery as reference.

The ROC curves were performed to explore the diagnostic efficiency in continuous variables with a significant difference after univariate logistics regression analysis. As Figure 2 shows, the optimal cutoff value of age median, weight median, APACHE II score median, respiratory rate median, and lactate median was 75.5 years old, 58.4 kg, 22.5, 22.5 beats/min, and 1.595 mmoL/L, respectively.

We then changed the continuous variables with significant differences into dichotomous variables according to the optimal cutoff value. To investigate the independent factors that influenced long-term mortality, all the dichotomous variables with significant differences after univariate logistics regression analysis were entered into the multivariable logistics regression model. Table 4 shows that several factors were significantly independently associated with long-term mortality. These include age above 76 years old with an OR of 2.576 (95% CI, 1.127–5.889), respiratory rate > 22 beats/min, 24 h after ICU admission with an OR of 2.385 (95% CI, 1.101–5.168), lactation >1.5 mmol/L, 24 h after ICU admission with an OR of 7.004 (95% CI, 2.395–20.717). In addition, PN delivery is 24 h after ICU admission with an OR of 5.401 (95% CI, 1.175–24.821) when using EN delivery as reference.

4 Discussion

The multi-center prospective study, which involved 128 ICUs from different hospitals in mainland China, was the first to determine the characteristics of nutrition treatment in elderly critical patients. We included 1,238 elderly critical patients with a median age of 76 years and further investigated the effect of nutrition patterns and nutrition programs on 28-day all-cause mortality in elderly patients who are critically ill. Our data suggested that delivery and therapy of nutrition was an independent risk factor for a 28-day survival and that enteral nutrition could improve the 28-day mortality.

Several previous studies on nutritional therapy in critically ill patients have not reached consistent conclusions due to the heterogeneity of patient's conditions and the complexity of clinical diagnosis and treatment. In a global study involving 880 units in 46 countries, only 10% of patients received enteral feeding on the first day (13). In our study, 24 h after ICU admission, 58% of elderly critical patients had initiated nutrition therapy, including 34.2% with an EN delivery of nutrition. EN should be started within 24 h in critically ill patients who can sustain voluntary ingestion according to clinical practice guidelines (14). Furthermore, we made a personalized nutrition therapy according to the assessment of the nutrition tolerance of each patient according to the AGI scale. Additionally, EN delivery was also involved in our study. In this study, 96% of patients with EN had gastric feeding and 7% experienced AGI stages 3 to 4. We found that a lower rate of EN (57% vs. 71%), higher rates of post-pyloric feeding (9% vs. 2%), and feeding interrupt (9% vs. 2%) were associated with an increased risk of 28-day mortality. When using EN delivery as a reference, 24 h after ICU admission in multivariable analysis, PN delivery, 24 h after ICU admission, was independently associated with long-term mortality. A cohort study involving 3,500 patients showed that within 2 years, enteral nutrition had a better prognosis than PN in patients with and without malignant diseases (15). Multivariable logistics regression analysis showed that age > 76 years during 24 h of ICU admission, respiratory rate > 22 beats/min, lactate >1.5 mmol/L, and early PN feeding delivery at 24 h after ICU admission had

TABLE 3 Univariate logistics regression analysis for the factors that influenced mortality in elderly critically ill patients.

Parameters	OR	95%CI	*p*
Gender	0.905	0.583–1.406	0.657
Age, years	1.047	1.020–1.075	0.001
Height, cm	1.007	0.980–1.034	0.629
Weight, kg	0.975	0.956–0.995	0.014
ICU diagnosis			
Sepsis	1.022	0.481–2.170	0.955
Septic shock	1.064	0.568–1.995	0.847
Cardiac arrest	4.400	0.601–32.200	0.145
Severe pancreatitis	3.945	0.538–28.936	0.177
Cerebral disease	1.702	0.992–2.919	0.054
Underlying diseases			
Hypertension	0.971	0.612–1.543	0.902
Diabetes	0.768	0.449–1.315	0.336
Chronic renal disease	1.301	0.696–2.431	0.410
Gastroenteric tumor	0.412	0.237–0.716	0.002
SOFA	1.037	0.975–1.102	0.249
APACHE II	1.038	1.008–1.070	0.013
Temperature, °C	0.968	0.772–1.213	0.775
Mean arterial pressure, mmHg	0.997	0.987–1.007	0.563
Heart rate, beats/min	1.005	0.996–1.014	0.272
Respiratory rate, beats/min	1.036	1.007–1.067	0.015
Platelet, $\times 10^9$/L	0.999	0.997–1.001	0.347
Total bilirubin, mmol/L	1.001	0.999–1.003	0.562
Creatinine, umol/L	1.000	0.998–1.001	0.575
WBC, $\times 10^9$/L	1.009	0.978–1.041	0.571
Lymphocyte, %	0.981	0.957–1.006	0.129
CRP, mmol/L	1.002	0.999–1.005	0.129
ALB, mg/dl	0.986	0.955–1.018	0.387
Lactate, mmol/L	1.060	1.010–1.114	0.019
Glucose_min, mmol/L	0.987	0.905–1.077	0.774
Glucose_max, mmol/L	1.025	0.984–1.067	0.244
AGI with 1 stage as reference			0.480
AGI with 2 stage	1.243	0.744–2.077	0.406
AGI with 3 stage	1.633	0.714–3.737	0.245
AGI with 4 stage	0.467	0.062–3.493	0.458
Nutritional routine			
EN			0.039
PN	2.018	1.176–3.463	0.011
Oral	0.000	0.000	0.999
The way of EN delivery			
Gastric feeding			0.049
Postpyloric feeding	4.911	1.263–19.096	0.022
PEG/J or jejunostomy feeding	2.947	0.334–26.032	0.331
Abdominal pain	1.514	0.693–3.308	0.298
Bloating	1.677	0.737–3.813	0.218
Gastric residue	1.138	0.554–2.335	0.725
Feeding interrupt	1.080	0.246–4.737	0.919

ICU, Intensive Care Unit; SOFA, Sequential Organ Failure Assessment; APACHE II, acute physiology and chronic health evaluation II; WBC, white blood cell; CRP, C-reactive protein; ALB, albumin; AGI, acute gastrointestinal injury; EN, enteral nutrition; PN, parenteral nutrition; PEG/J, percutaneous endoscopic gastrostomy/jejunostomy.

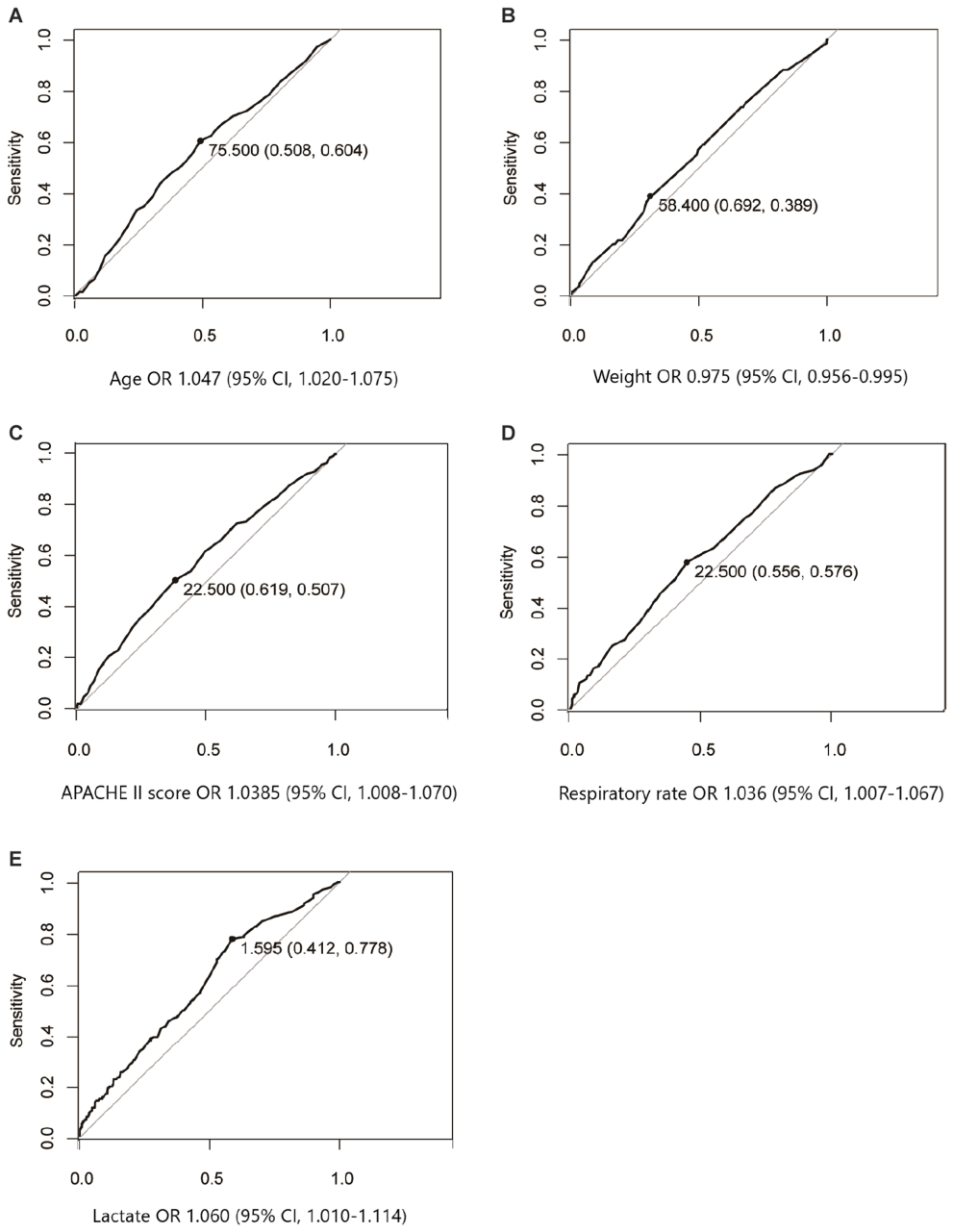

FIGURE 2
ROC curves were performed to explore the diagnostic efficiency in continuous variables that significantly influenced mortality after univariate logistics regression analysis. The optimal cutoff value associated with survival of age median **(A)**, weight median **(B)**, APACHE II score median **(C)**, respiratory rate median **(D)**, and lactate median **(E)** were 75.5 years old, 58.4 kg, 22.5, 22.5 beats/min, and 1.595 mmoL/L, respectively.

independently increased the risk of mortality and were the independent risk factors for mortality in elderly patients who are critically ill when using EN as a reference.

In a worldwide study involving 9,777 critical adult patients from 46 countries and 880 units, oral feeding was very common; 50% of patients had enteral feeding on the first day, which increased to 75% of patients after 5 days, and parenteral nutrition was administered to approximately 10% of patients (13). This indicates that enteral nutrition that leads to AGI in the early stage is relatively common. The conclusion of this study is similar to the current study. In another multinational study conducted in Latin America, EN nutrition therapy occurred in 79.9% of critically ill patients, PN alone (9.4%), and EN + PN (10.7%). Meanwhile, 59.7% of patients received >90% of the estimated daily target within 24 h after ICU admission (16). The conclusion of this study is also similar to the current study. Due to the poor immune function in the elderly, the body condition is complex and diverse, and the nutritional status and gastrointestinal function appear to be impaired, contributing to malnutrition and frailty with poor recovery and even disastrous prognosis in elderly patients who are critically ill (17).

Old age and nutritional status are key factors associated with adverse clinical outcomes (18). Therefore, it is important to clarify the status of nutrition treatment in elderly patients who are critically ill. ESPEN guideline detailed that critically ill elderly patients should

TABLE 4 Multi-logistics regression analysis for the factors that influenced mortality in elderly critically ill patients.

Parameters	OR	95%CI	*p*
Age > 76 years	2.576	1.127–5.889	0.025
Respiratory rate > 22 beats/min at 24 h ICU admission	2.385	1.101–5.168	0.028
Lactate >1.5 mmol/L at 24 h ICU admission	7.044	2.395–20.717	<0.001
EN delivery at 24 h ICU admission			0.038
PN delivery at 24 h ICU admission	5.401	1.175–24.821	0.030
Oral delivery	5.651	0.570–56.018	0.139

ICU, Intensive Care Unit; EN, enteral nutrition; PN, parenteral nutrition.

initiate early EN (within 48 h) rather than delaying it (19). In our multicenter study, 34.2% of elderly patients received EN on the first day, and this percentage increased to 58.3% within 3 days. Parenteral nutrition was prescribed to 16.0% of the patients and decreased to 10.7% within 3 days. The ratio of enteral nutrition was lower than previous studies focused on critically ill elderly patients (13, 20). ESPEN guidelines on clinical nutrition in the intensive care unit recommend an oral diet over EN or PN in critically ill patients who can eat (19). However, in our study, the percentage of oral treatment in elderly patients who are critically ill is very low, which indicates that most elderly patients who are critically ill are unable to provide their nutrition. At the same time, the ratio of PN is higher than that of critically ill adult patients. Approximately 4.16% of the patients in our study had intestinal functional intolerance and required post-pyloric feeding, and 25.2% of patients had AGI at 2 to 4 stages and decreased to 5.1% after 3 days. The rates of feeding complications, including aspiration, were high in elderly patients who were critically ill 24 h after ICU admission, and the symptoms of abdominal problems were high 48 h after ICU admission.

A meta-analysis, including 18 randomized controlled trials focused on the impact of early EN vs. early PN on clinical outcomes in critically ill patients, has concluded that the uses of EN as compared to PN leads to a reduction of infectious complications and shorter ICU stay, but no difference in mortality (21). However, in the NUTRIREA-2 study, compared to early isocaloric PN, early isocaloric EN does not affect the mortality rate or the risk of secondary infections, in adverse, with a greater risk of digestive complications in critically ill adults with shock (22). Therefore, different nutritional support strategies are needed for different critically ill patients (7, 17, 23–25). Nutritional screening in the intensive care unit (ICU) requires an understanding of two key points, the nutritional status and severity of the disease at admission, as well as different treatment measures and the duration of organ support (26). ESPEN guideline for clinical nutrition and hydration in geriatrics has indicated that even short-term starvation in the acutely ill older person leads to loss of lean body mass, which can be critical, especially in older patients, so it has suggested that regardless of the nutritional status and severity of the disease upon admission, if possibly, PN should be initiated immediately in older patients (8). In our study, for those critically ill elderly patients, after multivariable logistics regression analysis, we found that when EN delivery was used as a reference, PN delivery 24 h after ICU admission was the independent risk factor associated with long-term mortality with OR 5.401 (95% CI, 1.175–24.821). The main reasons for the worse impact of early PN on clinical outcomes are that it may bring caloric overfeeding and risk of ICU infection.

A randomized controlled trial by White et al. has compared early post-pyloric versus early gastric feeding in ventilated intensive care patients, and the result showed that early post-pyloric feeding had no advantage over early gastric feeding (27). The results indicated that feeding mode did not affect prognosis but rather complications. Zhu et al. conducted a single-center randomized trial to explore gastric versus post-pyloric feeding in elderly patients (age ≥ 75 years) on mechanical ventilation and found that compared to gastric EN, post-pyloric EN reduced the risk of ventilator-associated pneumonia (VAP), but did not affect mortality (28). Therefore, gastric feeding is recommended as an initial EN delivery in critically ill elderly patients with high-risk factors of aspiration (7, 19, 29, 30). In our multi-center prospective study, we found that the incidence of early post-pyloric feeding in elderly patients who are critically ill is rare regardless of being in the survivor or non-survivor groups (2% vs. 9%). However, the reasons might be that the clinical physician might strictly evaluate EN tolerance in elderly patients who are critically ill while adhering to EN protocols based on current nutrition guidelines and then those with a high risk of aspiration.

Our study has some limitations. First, regardless of the multi-center prospective study with 1,238 elderly patients, this study, in one part, reflects the nutritional status of elderly patients who are critically ill from different ICU units in China. In the other part, the heterogeneity of the study derived from the treatment practices in the population included is very different in different units. So, to identify the effect of nutrition treatment on mortality, we used multivariable logistics regression analysis to control the confounding bias. Second, this study only shows some associations between nutrition treatment and mortality. Therefore, further study needs to delve into the influencing factors of nutritional support and the causes of nutritional intolerance in elderly patients who are critically ill. Our study mainly targeted elderly patients. Age is an important factor in increasing ICU mortality, and nutrition is also one of the most important links. Last but not least, nutritional status at admission is very important, but BMI was not collected in our study design. Therefore, nutritional status at admission may be a potential confounding factor for a 28-day survival prognosis.

5 Conclusion

This multi-center prospective study describes clinical characteristics, the mode and timing of nutrition treatment, frequency of AGI, and adverse effects of nutrition in elderly ICU patients. According to this survey, ICU patients with early PN delivery, older age, faster respiratory rate, and higher lactate level may experience poor prognosis.

Clinical relevancy statement

The status of nutrition treatment and feeding-influenced mortality remains uncertain in elderly patients in the intensive care unit (ICU). Our article describes that in elderly critically ill patients, the proportion of enteral nutrition (EN) delivery at an early stage is low and the choice of early Parenteral nutrition (PN) feeding seems to be associated with disastrous clinical outcomes.

Data availability statement

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

Ethics statement

This study was approved by the medical ethics committee of Nanjing General Hospital of Nanjing Military Command (2017NZKY-010-01). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

WC: Conceptualization, Writing – original draft. MP: Data curation, Methodology, Writing – review & editing. ZY: Data curation, Formal analysis, Writing – review & editing. YA: Data curation, Formal analysis. ZL: Funding acquisition, Software, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by the National Natural Science Foundation of China (grant number 82102282); the Natural Science Foundation of Hunan Province (grant numbers 2022JJ30944, 2022JJ30953); and the China Postdoctoral Science Foundation (grant number 2022M713528).

Acknowledgments

The authors thanked the database and the working group for providing access to our study.

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.2024.1321599/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Flowchart of patient selection.

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 14 February 2024
DOI 10.3389/fmed.2024.1330446

OPEN ACCESS

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RECEIVED 30 October 2023
ACCEPTED 15 January 2024
PUBLISHED 14 February 2024

CITATION
Birnbaums JV, Ozoliņa A, Solovjovs L, Glāzniece-Kagane Z, Nemme J and Logina I (2024) Efficacy of erector spine plane block in two different approaches to lumbar spinal fusion surgery: a retrospective pilot study.
Front. Med. 11:1330446.
doi: 10.3389/fmed.2024.1330446

Efficacy of erector spine plane block in two different approaches to lumbar spinal fusion surgery: a retrospective pilot study

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Background: Erector spine plane block (ESPB) has been widely used in spinal surgery, although there are variable data about its efficacy.

Objectives: This study aimed to evaluate the efficacy of ESPB in elective lumbar spinal fusion surgery patients with two different surgical approaches.

Materials and methods: Retrospectively, 45 elective lumbar transpedicular fusion (TPF) surgery patients undergoing open surgery with different approaches [posterior transforaminal fusion approach (TLIF) or combined posterior and anterior approach (TLIF+ALIF)] were divided into 2 groups: general anesthesia (GA, $n = 24$) and general anesthesia combined with ESPB (GA + ESPB, $n = 21$). The primary outcome was to analyze the efficacy of ESPB in two different surgical approaches in terms of pain intensity in the first 48 h. Secondary: Fentanyl-free patients and opioid consumption in the first 24 h postoperatively. Comparative analysis was performed (SPSS® v. 28.0) ($p < 0.05$).

Results: Out of 45 patients (27 female), 21 received GA + ESPB and 24 received GA. The average age was 60.3 ± 14.3 years. Chronic back pain before the operation was registered in 56% of patients. ESPB was performed in 17 TLIF and in 4 TLIF+ALIF patients. ESPB significantly reduced pain intensity at rest in both surgical approaches 48 h after surgery ($p < 0.05$). The need for postoperative fentanyl infusion was significantly lower in the group treated with GA + ESPB in both surgical approaches than in those who only received GA (29% vs. 77% in TLIF and 0% vs. 80% in TLIF+ALIF); $p = 0.01$ and $p = 0.004$. Additionally, we observed that ESPB provides a good analgesic effect for up to 6.8 ± 3.2 h in the TLIF and 8.9 ± 7.6 h in the TLIF+ALIF approaches. Consequently, ESPB reduced the initiation of the fentanyl compared to GA alone, with a mean difference of 3.2 ± 4.2 h in the TLIF subgroup ($p = 0.045$) and 6.7 ± 5.3 h in TLIF +ALIF ($p = 0.028$). Only in the TLIF+ALIF approach, ESPB reduced the total fentanyl consumption compared to those with GA (1.43 ± 0.45 mg/24 h vs. 0.93 ± 0.68 mg/24 h; $p = 0.015$).

Conclusion: ESPB significantly reduced pain at rest after surgery, the number of patients requiring immediate postoperative fentanyl analgesia, and total fentanyl consumption in both surgical approaches, particularly in TLIF+ALIF. However, the application of ESPB does not always provide completely sufficient analgesia.

10.3389/fmed.2024.1330446

KEYWORDS

ESPB, erector spine plane block, regional anesthesia, postoperative pain, lumbar spinal fusion surgery, pain, ultrasound

1 Introduction

Since the human lifespan is rapidly increasing, there is also an increase in the number of patients with degenerative lumbar spondylosis, which is a cause of chronic back pain in up to 80% of cases (1). Nowadays, surgical interventions are gaining in popularity—spinal fusion operations in the US have increased by 77% in the period from 2002 to 2011 (2), and in the UK, the number of surgeries has increased by 63% from 2005 to 2015 (3).

The main indications for spinal fusion surgery are spinal stenosis, spondylolisthesis, and vertebral instability (4). After surgery, most severe pain is expected in the first 3–5 days postoperatively, with a tendency to progress into chronic pain (1, 5–7). Many spinal surgery patients suffer from chronic pain, depression, and restrictions on physical activities (8). Therefore, appropriate postoperative analgesia, with a reduction in opioid consumption, is of superior importance (9, 10).

Currently, the practice of anesthesiology is focused on opioid-sparing postoperative analgesia to avoid opioid-related side effects (2). Peripheral blocks, including erector spine plane block (ESPB), are essential components of multimodal analgesia, which helps to alleviate pain and increase the patient's comfort (11). It has been widely used in spinal surgery, although there are variable data about its efficacy regarding different surgical approaches, duration of action, and impact on early rehabilitation (12). Recently, a large meta-analysis demonstrated that ESPB used in lumbar spinal surgery was effective in relieving postoperative pain and decreasing the perioperative consumption of opioids (13).

Still, it would be important to understand the impact of the ESPB on pain intensity and opioid consumption after spinal fusion surgeries using two surgical approaches: TLIF and TLIF+ALIF.

In our study, the aim was to look through our first clinical experience with and without ESPB for postoperative analgesia in TPF surgery patients. The primary outcome was to analyze the efficacy of ESPB on pain intensity in the first 48 h for lumbar spinal fusion surgeries with two different surgical approaches. The secondary outcomes were opioid consumption in the first 24 h postoperatively, and the number of fentanyl-free patients was evaluated.

2 Materials and methods

2.1 Study subjects

This is a retrospective cohort study including 45 adult patients who underwent elective lumbar spinal fusion surgery in the Orto Clinic, Riga, Latvia, from 1 November 2019 to 30 April 2022. All spinal fusion surgeries were performed using two surgical approaches: either posterior transforaminal fusion (TLIF) surgery or combined surgery with posterior and anterior (TLIF+ALIF) approaches. The TLIF approach was performed on multiple surgery levels, but the ALIF approach was performed only on the L5-S1 level.

The inclusion criteria were 8 years of age or older, an ASA score of I–III, and elective lumbar spinal fusion surgery under general anesthesia. The exclusion criteria were known allergic reactions to local anesthetics, signs of local or general infection, pregnancy, history of mental disorders, and failed regional block (immediately reported pain intensity NRS > 6 after surgery).

All the ESPBs were performed by the same anesthesiologist for all included patients starting in September 2021, when ESPBs were introduced in the daily practice for TPF lumbar spinal surgeries. Until then, all patients underwent standardized general anesthesia (GA) without ESPB. Consequently, all patients retrospectively were allocated into two groups: the general anesthesia group (GA, $N = 24$) and GA combined with ESPB (GA + ESPB, $N = 21$). Of those who received GA, 13 underwent the TLIF approach, and 11 had the TLIF + ALIF approach. From those, who received GA + ESPB, 17 underwent TLIF, and only 4 underwent the TLIF + ALIF approach. The patient sample size was based on retrospectively available data, and the incidence of the TPF surgery approach was based on surgical indications; therefore, the sample size in the TLIF+ALIF approach receiving GA + ESPB was lower compared to other groups.

2.2 Perioperative care

All patients, with or without ESPB block, received the same standardized GA. It included a premedication of 7.5 mg of oral Midazolam (Dormicum®, F. Hoffman-La Roche AG, Switzerland) for 30 min before transfer to the operating room. Induction of GA was provided with midazolam (Dormicum® 5 mg/mL, F. Hoffmann-La Roche Ltd., Switzerland) 2.5 mg, fentanyl (Fentanyl-Kalceks® 0.05 mg/mL, A/S Kalceks, Latvia) 1.5–2 μg/kg, propofol (Propofol® 10 mg/mL, Fresenius Kabi AG, Germany) 2 mg/kg, and cisatracurium (Nimbex®, 2 mg/mL, Aspen Pharma Ltd., Ireland) 0.2 μg/kg. Then the patient was intubated. Anesthesia was maintained with sevoflurane (Sevorane®, AbbVie S.r.l., Italy) MAC 0.8–1.2, intravenous fentanyl (Fentanyl-Kalceks® 0.05 mg/mL, A/S Kalceks, Latvia) infusion 0.5–1.5 μg/kg/h, and cisatracurium infusion 1–2 μg/kg/min.

For those who received ESPB, after the induction of GA, the patient was intubated and placed in the prone position. Bilateral ultrasound-guided ESPB at the lumbar (L2–L4) level was then performed depending on the spinal fusion level. A high-frequency linear ultrasound transducer was placed in a parasagittal orientation 3 cm laterally from the spinous process. At the spinal lumbar level, the only muscle identified superficial to the hyperdense transverse process is the erector spinae muscle. A 50 mm 22 G ultrasound needle (BRAUN®, Germany) was inserted in-plane in a cephalad-to-caudal direction until bone contact with the top of the transverse process. After slight retraction of the needle, 30 mL of 0.35% bupivacaine

(Bupivacaine-Grindex, 5 mg/mL, Grindex, Latvia) with 200 mcg epinephrine (Adrenaline, 1 mg/mL, Sopharma Ad. Bulgaria) was injected between the transverse process and erector spinae, observing the cephalad to caudal spread of the local anesthetic. The same procedure was repeated on the contralateral side. During surgery, standard monitoring was performed according to the American Society of Anesthesiology standards.

Postoperatively, hemodynamic monitoring was followed regularly. Fluid management and oxygen supply were provided in the postoperative observational surgical unit for the first 24 h. The patient was assessed for pain control at 0, 1, 6, 12, 24, and 48 h after the surgery using the numeric pain rating scale (NRS). According to the local hospital guidelines, intravenous multimodal analgesia was provided with dexketoprofenum (Dolmen®, Berlin-Chemie/Menarini, Germany) 50 mg every 12 h, acetaminophen (Paracetamol, B. Braun Melsungen AG, Germany) 1 g every 6 h, and pregabalin orally (Lyrica®, Pfizer, United States) 150 mg every 24 h. For pain exacerbation, if NRS > 6, a fentanyl infusion of 2 mg/50 mL intravenously was started with a rate of 0.5–1 μg/kg/h depending on the response to analgesia. Afterward, total fentanyl consumption was calculated in the first 24 h after surgery. Thromboprophylaxis was provided with enoxaparin 40 mg (Clexane®, Sanofi-Aventis S.A. Spain) once daily from the first postoperative day.

2.3 Statistical analysis

Statistical analysis was performed using SPSS 26.0 (*Statistical Package for Social Sciences*). The Kolmogorov–Smirnov test was used to evaluate whether datasets conformed to a normal distribution. Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were presented as median ± IQR. Differences in data distribution between the groups were evaluated using a Mann–Whitney U-test for non-parametric datasets and a two-sample *t*-test or ANOVA for datasets conforming with normal distribution. A chi-square test was used for sets of nominal variables. Statistical significance was assumed if the two-tailed $p < 0.05$.

3 Results

3.1 Clinical course

In total, 45 patients 18 (40%) men and 27 (60%) women were included. The mean age was 60.3 ± 14.3 years. All patients were scheduled for elective lumbar spinal fusion surgery. Of those, 30 patients underwent TLIF, of whom 17 received GA + ESPB and 13 received GA. TLIF+ALIF was performed in 15 patients, of whom 4 received GA + ESPB and 11 received GA. In total, 21 (47%) patients received GA + ESPB, and 24 (53%) were included in the GA group. As shown in Table 1, patients undergoing TLIF+ALIF with GA had a higher body mass index (BMI) compared to those receiving GA + ESPB; $p = 0.04$. Analyzed comorbidities and ASA class were similarly distributed between patients with the two lumbar spinal fusion surgical approaches. Chronic pain (> 3 months) was identified before surgery in 56% of all analyzed cases. All patients with the TLIF+ALIF approach in the GA + ESPB group had a history of chronic pain in contrast to patients with the TLIF approach in the GA group ($p = 0.01$). Lumbar spinal fusion surgery is most often performed at one (47%) or two (33%) vertebral levels. Less often, spinal fusion surgery was performed at four or five levels (4.4%).

3.2 Assessment of pain intensity in the first 48 hours postoperatively

As shown in Figures 1, 2, the pain was assessed at 0, 1, 6, 12, 24, and 48 h after the surgery. We found significantly lower pain scores in GA + ESPB vs. GA patients at several time points: 6 h after the surgery, pain at rest was NRS 0 vs. 2.18 ± 1.2; $p < 0.001$ in TLIF patients. Similarly, in TLIF+ALIF surgery patients, the pain score at rest was lower already 1 h after the surgery, NRS 0.94 ± 1.3 vs. 2.5 ± 2.3; $p = 0.04$ in the GA + ESPB group compared to the GA group.

Finally, 12 h after surgery, the mean pain score at rest in the GA + ESPB vs. GA group was lower in both surgery approaches: TLIF approach was 1.54 ± 1.2 vs. 0.5 ± 066; $p = 0.004$ and in the TLIF+ALIF approach was 2 ± 1.2 vs. 0.25 ± 0.5; $p = 0.015$, respectively.

3.3 Opioid consumption in the first 24 hours postoperatively

In total, 73%, or 33 patients out of 45, required additional fentanyl analgesia after surgery without differences according to the type of anesthesia, as reflected in Table 2. Fentanyl immediately after surgery was less often started in those receiving GA + ESPB vs. GA alone, respectively, in 29% vs. 77% (TLIF) and in 0% vs. 82% (TLIF+ALIF); $p = 0.01$ and $p = 0.004$. Additionally, we observed that ESPB provides a good analgesic effect for up to 6.8 ± 3.2 h in the TLIF and 8.9 ± 7.6 h in the TLIF+ALIF approaches. Therefore, patients with ESPB had lower total fentanyl consumption, particularly those undergoing the TLIF+ALIF approach, 1.4 ± 0.45 mg/24 h vs. 0.9 ± 0.7 mg/24 h; $p = 0.01$, as depicted in Table 2.

4 Discussion

In this retrospective pilot study, we demonstrated that ESPB might be suitable for lumbar spinal fusion surgery patients with two different surgical approaches: posterior (TLIF) or combined posterior and anterior (TLIF+ALIF). We observed that ESPB reduces pain at rest in the 48 h postoperative period, providing a good analgesic effect for up to 6.8 ± 3.2 h in the TLIF and 8.9 ± 7.6 h in the TLIF+ALIF approaches. Additionally, it reduces the number of patients requiring immediate postoperative fentanyl analgesia, the initiation of the fentanyl after surgery, and the total fentanyl consumption compared to GA alone in both surgical approaches, particularly in the TLIF+ALIF approach.

Opioid requirement reduction is essential, particularly in spinal surgery patients who might be at high risk of developing chronic back pain syndrome without showing enough satisfaction after surgery. Moreover, the application of opioids is associated with major side effects such as nausea and vomiting, sedation, urinary retention, ileus, and respiratory depression. These side effects promote a longer hospital stay and a longer recovery time. In our study, 56% of patients suffered from chronic back pain (> 3 months) already before surgery (60% with TLIF and 46% with the TLIF+ALIF approach). According

10.3389/fmed.2024.1330446

TABLE 1 Distribution of patients in two lumbar spinal fusion surgery approaches according to the type of anesthesia.

Parameters	Total (n = 45)	TLIF GA (n = 13)	TLIF GA + ESPB (n = 17)	p-value	TLIF+ALIF GA (n = 11)	TLIF+ALIF GA + ESPB (n = 4)	p-value
Sex, female, n (%)	27 (60)	9 (69)	8 (47)	0.2	7 (64)	3 (75)	0.7
BMI, kg/m^2	30 ± 5.4	29.2 ± 5.8	30 ± 4.7	0.7	30.2 ± 5.1	23 ± 6.1	**0.04**
ASA class, n (%)							
I	4 (9)	1 (7.7)	1 (6)	0.8	2 (18)	0	0.4
II	31 (69)	10 (59)	10 (77)	0.3	8 (73)	3 (75)	0.9
III	10 (22)	2 (15.4)	6 (35.3)	0.2	1 (9)	1 (25)	0.4
Comorbidities, n (%)							
None	13 (29)	2 (15)	4 (23.5)	0.6	5 (45.5)	2 (50)	0.9
Arterial hypertension (AH)	7 (16)	2 (12)	2 (15.4)	0.8	2 (18)	1 (25)	0.8
Diabetes mellitus (DM)	2 (4.4)	0	2 (12)	0.2	0	0	–
Rheumatoid arthritis	1 (2.2)	0	0	–	0	1 (25)	0.09
AH + DM	2 (4.4)	1 (8)	1 (6)	0.8	0	0	–
AH + Atherosclerosis + ischemic heart disease	17 (38)	7 (54)	6 (35)	0.3	4 (36)	0	0.16
AH + DM + atherosclerosis + ischemic heart disease	3 (7)	1 (8)	2 (12)	0.7	0	0	–
Chronic pain factors, n (%)							
Chronic pain	25 (56)	7 (54)	11 (65)	0.5	3 (27)	4 (100)	0.01
Adiposity	17 (38)	6 (46)	7 (54)	0.8	4 (36)	0	0.2
Spinal surgery in anamnesis	10 (22)	0	4 (23.5)	0.06	4 (36)	2 (50)	0.6
Anxiety	9 (20)	2 (15)	4 (23.5)	0.6	1 (9)	2 (50)	0.08
Emotional labiality	5 (11)	2 (15)	1 (6)	0.4	1 (9)	1 (25)	0.4
Sleep disorders	4 (9)	1 (8)	1 (6)	0.8	1 (9)	1 (25)	0.4
Depression	6 (13)	1 (8)	2 (12)	0.7	1 (9)	2 (50)	0.08
Surgery levels, n (%)							
Level 1	21 (47)	7 (54)	4 (23.5)	0.09	7 (64)	3 (75)	0.7
Level 2	15 (33)	4 (31)	8 (47)	0.4	3 (27)	0	0.2
Level 3	5 (11)	1 (7)	4 (23.5)	0.25	0	0	–
Level 4	2 (4.4)	1 (8)	0	0.2	1 (9)	0	0.5
Level 5	2 (4.4)	0	1 (6)	0.4	0	1 (25)	0.07

Data are presented as mean ± SD or number (n), percentage (%), and median (interquartile range). yr.: years; kg: kilogram; SAH: subarachnoid hemorrhage; CV, cerebral vasospasm; DCI, delayed cerebral ischemia; BMI, body mass index; GCS, Glasgow coma scale; ICH, intracerebral hemorrhage; ICU, intensive care unit; IQR, interquartile range; NS, not significant. p-value[1] comparing GA and GA + ESPB groups undergoing TLIF surgery; p-value[2] comparing GA and GA + ESPB groups undergoing TLIF + ALIF surgery.

to other studies, for every 10% of the patients suffering from severe pain in the postoperative period, there is a 30% risk of the development of chronic pain (9, 14–22). As a result, multimodal analgesia with the application of regional blocks is gaining in popularity (23–26).

We must say that the applications of ESPB are not always allowed to fully avoid fentanyl administration for postoperative pain control. In total, 33 patients out of 45 required additional fentanyl analgesia after surgery, without differences according to the type of anesthesia. Still, ESPB allowed to reduce the total fentanyl consumption in the 24 h postoperative period with the greatest analgesic effect produced in patients with the TLIF+ALIF approach, where 81% of patients did not require fentanyl in the early postoperative period and it was started on average 8.9 ± 7.6 h after the surgery. Thereby, the total fentanyl consumption in 24 h was considerably lower in the GA + ESPB group compared to GA for those with the TLIF+ALIF approach, with MD 0.5 ± 0.23 mg/24 h; $p = 0.015$.

Interestingly, 29.4% of TLIF patients in the GA+ ESPB group required fentanyl analgesia early after the operation, but after the TLIF +ALIF approach, none of the patients required immediate fentanyl infusion. That might be explained by the small group of patients who received ESPB for TLIF+ALIF surgery.

ESPB might be useful as a part of multimodal analgesia because it also considerably reduces the initiation of fentanyl analgesia immediately after surgery. Similar results were reported by Liang et al. in a 2021 meta-analysis. They demonstrated that patients receiving ESPB in spinal fusion surgeries in the lumbar region less often required rescue analgesia (RR = 0.39, from 0.19 to 0.80, $p = 0.01$). Moreover, rescue analgesia was asked for later compared to patients without ESPB. The application of ESPB prolonged the time until rescue analgesia was started on average for 6.15 h (from 2.19 to 10.12; $p = 0.002$) (27). Our study confirmed this data, where fentanyl analgesia immediately after the surgery was more often started in the

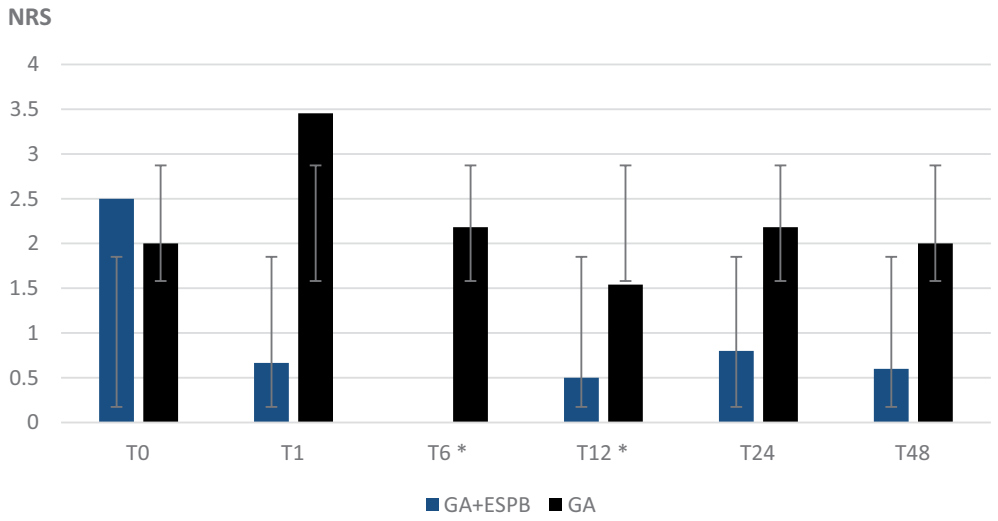

FIGURE 1
Pain score at rest between patients with general anesthesia with and without erector spinae plane block undergoing lumbar spinal fusion surgery with posterior transforaminal fusion approach. GA: general anesthesia; ESPB: erector spinae plane block; NRS: numeric rating scale; T0: before the surgery; T1: 1 h after the surgery; T6: 6 h after the surgery; T12: 12 h after the surgery; T24: 24 h after the surgery; T48: 48 h after the surgery; * – statistically significant difference.

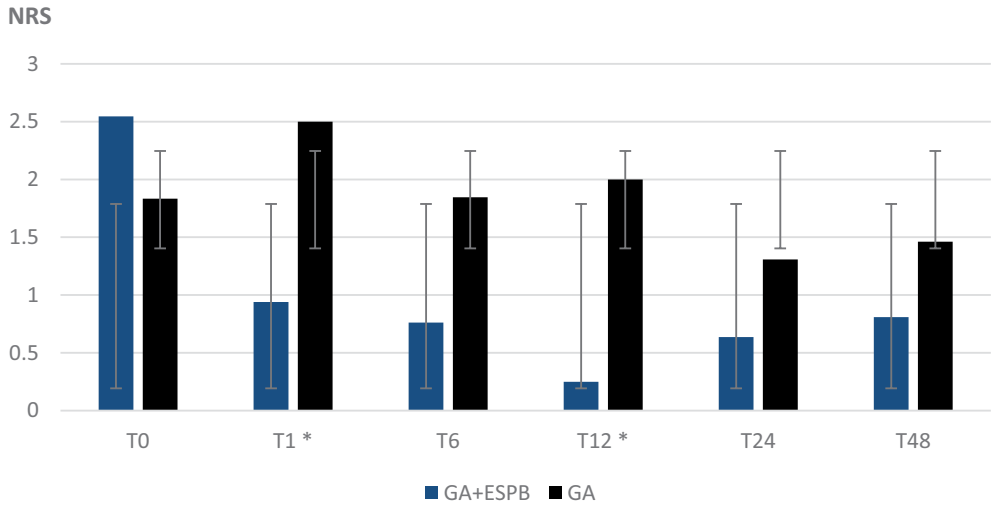

FIGURE 2
Pain score at rest between patients with general anesthesia with and without erector spinae plane block undergoing lumbar spinal fusion surgery with a combined posterior transforaminal and anterior surgical approach. GA: general anesthesia; ESPB: erector spinae plane block; NRS: numeric rating scale; T0: before the surgery; T1: 1 h after the surgery; T6: 6 h after the surgery; T12: 12 h after the surgery; T24: 24 h after the surgery; T48: 48 h after the surgery; * – statistically significant difference.

GA group vs. GA + ESPB group in both the TLIF (77% vs. 29%) and TLIF+ALIF (82% vs. 0%) approaches.

We found that the ESPB reduces total 24 h fentanyl consumption, particularly in TLIF+ALIF approach patients (MD 0.5 mg/24 h). Other studies had shown marked opioid reduction in the ESPB group patients (MD, −18.69; 95% CI, −27.95 to −9.42; $p < 0.0001$) in various spinal surgeries (20, 26–37). However, still great non-homogeneity in results regarding opioid reduction is shown. Wu et al. in 2019 found a small difference in opioid consumption in the first 24 h (MD, −2.6; 95% CI, −4.82 to −0.38; $p < 0.0001$) (27, 38). Our study showed a mean difference in fentanyl consumption of 0.26 mg. When recalculated to intravenous morphine equivalents, it is 1.3 mg. We might conclude that the different types of surgery, such as laminectomy or decompression, require a greater dose of opioids for postoperative analgesia compared with lumbar discectomy (39–44).

We also evaluated pain intensity at rest after surgery in the first 48 h postoperative period. High pain levels are usually expected after spinal fusion surgeries (4). It is reported that the peak in pain intensity after spinal surgeries in the lumbar region is usually felt 4 h after the surgery, and it gradually decreases during the next 72 h (28, 45–48). That is why we aimed to evaluate the pain level in the first 48 h after the surgery. Furthermore, there is no common opinion about when to

TABLE 2 Distribution of opioid consumption in two lumbar spinal fusion surgery approaches according to the type of anesthesia.

Parameters	Total (n = 45)	TLIF GA (n = 13)	TLIF GA + ESPB (n = 17)	p-value	TLIF+ALIF GA (n = 11)	TLIF+ALIF GA + ESPB (n = 4)	p-value
Number of patients requiring fentanyl analgesia, n (%)							
Total, (if NRS > 6)	33 (73)	10 (77)	9 (53)	0.2	11 (100)	3 (75)	0.07
Immediately after surgery	24 (53)	10 (77)	5 (29)	0.01	9 (82)	0	0.004
Later after surgery	9 (20)	0	4 (23.5)	0.02	2 (18)	3 (75)	0.009
Time to rescue fentanyl analgesia, h	7 ± 5	1.2 ± 0	6.8 ± 3.2	0.2	1.5 ± 0.7	8.9 ± 7.6	0.15
Fentanyl consumption, mg/24 h							
Total in 24 h period	1.1 ± 0.5	0.9 ± 0.4	0.9 ± 0.6	0.99	1.4 ± 0.4	0.9 ± 0.7	0.01
Started immediately after surgery	1.2 ± 0.5	0.9 ± 0.4	1.2 ± 0.74	0.2	1.4 ± 0.5	0	0.2
Started later after surgery	0.9 ± 0.5	0	0.6 ± 0.2	0.3	1.5 ± 0.04	0.9 ± 0.7	0.02

Data are presented as mean ± SD or number (n) and percentage (%) and median (interquartile range) GA, general anesthesia; ESPB, erector spine plane block, h, hours; SD, standard deviation; TLIF, transpedicular fixation posterior approach; TLIF + ALIF, combined posterior and anterior approach.

measure pain—at rest or movement (4, 14, 49–54). We found statistically significant differences in the pain intensity between two applied types of anesthesia: 1, 6, and 12 h after surgery. In all included patients, the mean pain intensity at rest in the GA group was NRS 3, but it is important to specify that this pain level in most of the patients (87.5%) was observed when fentanyl analgesia was used. The authors describe ESPB in a wide range of spinal surgeries—decompressions, discectomies, and fusion surgeries—and in some cases, the type of surgery is not always specified (4, 11, 27, 28, 39, 55). Still, there is no clear understanding of the mechanism of action and distribution of local anesthetics after ESPB. Most likely, the analgesic effect is provided by the distribution of the local anesthetic in the dorsal and ventral nerve roots from the interfacial space between the processus transversus and the erector spine muscle group; however, systemic absorption of the local anesthetic cannot be excluded (6, 23, 35, 56–64).

The postoperative pain intensity can be affected not only by surgical trauma but also by risk factors for chronic pain (65–68). Other publications demonstrate that chronic pain before surgery increases the risk of postoperative chronic pain by 2.6 times (9, 24, 69–71). In our study, half of the patients (56%) suffered from chronic back pain (>3 months) already before surgery (60% with the TLIF approach and 46% with the TLIF+ALIF approach), but we did not evaluate the incidence of postoperative chronic pain 3 months after the surgery since the study was retrospectively designed.

The duration of the ESPB depends on the volume and concentration of the local anesthetic, as well as on the application of adjuvants (23, 54, 72–75). Rizkkalla et al., in the meta-analysis (2021) of 15 studies, showed that the duration of ESPB varied from 4 to 72 h and this was influenced by the type of local anesthetic, its volume (20–40 mL), and if the block was unilateral or bilateral (55). In our study, we unified the dose of the local anesthetic and used 30 mL of bupivacaine 0.35% bilaterally, knowing that 20 mL in the lumbar region distributes up to 2–3 levels (76) and the expected duration of the ESPB is 6–8 h after bilateral block with the 20 mL of bupivacaine 0.25% reported by Singh et al. (77). We added 200 μg epinephrin, decreasing the systemic absorption of the local anesthetic (78–81). We observed that our regimen had not affected the prolongation of the block when compared to other studies (55, 77, 82). There is no certainty about the optimal dose of the local anesthetic or volume. Studies show variable doses of the local anesthetic for spinal surgeries: 10–40 mL of ropivacaine, levobupivacaine, bupivacaine (in concentrations 0.5, 0.25%, or 0.375%), and lidocaine (in concentrations 1% or 2%), not exceeding the maximal dose (21, 67, 75).

Since the anatomical structures are being impacted during the spinal surgery, there might be different analgesic effects of ESPB, which can be affected by the changes in the anatomical structures of the spine (3, 83–85). That emphasizes the importance of the evaluation of the sensor block before and after surgery. It might be the restriction of our study that routinely ESPB was performed after induction of anesthesia without the evaluation of a sensor block. Still, we speculate that it might be hard to distinguish if the analgesic effect is always achieved by ESPB or by the systemic absorption of the local anesthetic after surgery (11, 86–88).

We admit as a major limitation of this study that it was a retrospectively designed pilot study to evaluate our first experience with ESPB. Therefore, we were not able to reach equal distributions of different TPF surgery approaches between the GA and GA + ESPB groups. The patient group in the TLIF+ALIF approach receiving GA + ESPB was too small (four patients), which may lead to a type 2 error in statistical analysis. Although we reached a statistically significant difference in 24 h fentanyl consumption in the TLIF+ALIF approach, it is still too early to draw any scientific or clinically relevant conclusions.

In contrast, we did not reach a statistically significant difference in the 24 h fentanyl consumption in the TLIF group, also indicating a too low analyzed patient sample size. Nevertheless, the data were precisely manually collected by going through each medical history, surgery, and anesthesia performed by the same surgeon and the same anesthesiologist, and postoperative care was strongly standardized for all analyzed patients. According to ASA classes and co-morbidities most patients were homogenic, although some heterogenicity was noticed in those with TLIF+ALIF approach and GA + ESPB, these patients more often presented chronic pain, anxiety and depression.

Assuming a medium effect size of 0.5, a significance level of 0.05, a power of 0.80, and a potential attrition rate of 10%, the minimum

sample size required for each group would be approximately 64 participants.

5 Conclusion

Retrospective data from our first clinical experience with ESPB in TPF surgery patients indicate that ESPB might be an effective component of multimodal analgesia in lumbar spinal fusion surgery patients with TLIF or TLIF+ALIF surgical approaches. ESPB significantly reduced pain at rest after surgery, the number of patients requiring immediate postoperative fentanyl analgesia, and total fentanyl consumption in both surgical approaches, particularly in TLIF+ALIF. However, the application of ESPB does not always provide sufficient analgesia to completely avoid fentanyl administration after the surgery in the 24 h postoperative period. Further prospective analysis, including more patients, is necessary to confirm the effectiveness of both TPF approaches.

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 humans were approved by Prof. Olafs Brūvers Theology Asoc. Prof. Santa Purviņa Pharmacology Asoc. Prof. Voldemārs Arnis Rehabilitology Prof. Regīna Kleina Pathology Prof. Guntars Pupelis Surgery Asoc. Prof. Viesturs Liguts Toxicology Doc. Iveta Jankovska orthodontology Doc. Kristaps Circenis Lecturer Ilvija Razgale. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

JB: Methodology, Writing – original draft. AO: Supervision, Conceptualization, Data curation, Methodology, Writing – review & editing. LS: Conceptualization, Formal analysis, Writing – review & editing. ZG-K: Data curation, Writing – original draft. JN: Formal analysis, Writing – original draft. IL: Conceptualization, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The publication has been supported by funding Nr.3-FD.1-1/99/IE24 from Rīgas Stradiņš University.

Acknowledgments

Many thanks to Spinal Surgeon Dr. Gulbis, who performed surgeries for all the patients analyzed in the study. And thanks to the Ortho Clinic for excellent collaboration in conducting this study.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 27 March 2024
DOI 10.3389/fmed.2024.1342752

OPEN ACCESS

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RECEIVED 22 November 2023
ACCEPTED 20 February 2024
PUBLISHED 27 March 2024

CITATION
Bratke S, Schmid S, Ulm B, Jungwirth B, Blobner M and Borgstedt L (2024) Genotype- and sex-specific changes in vital parameters during isoflurane anesthesia in a mouse model of Alzheimer's disease. *Front. Med.* 11:1342752. doi: 10.3389/fmed.2024.1342752

Genotype- and sex-specific changes in vital parameters during isoflurane anesthesia in a mouse model of Alzheimer's disease

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Background: The prevalence of neurodegenerative diseases is increasing as is life expectancy with Alzheimer's disease accounting for two-thirds of dementia cases globally. Whether general anesthesia and surgery worsen cognitive decline is still a matter of debate and most likely depending on the interplay of various influencing factors. In order to account for this complexity, Alzheimer's disease animal models have been developed. The Tg2576 model of Alzheimer's disease is a well-established mouse model exhibiting amyloidopathy and age-dependent sex-specific differences in Alzheimer's disease symptomology. Yet, data on anesthesia in this mouse model is scarce and a systematic comparison of vital parameters during anesthesia with wild-type animals is missing. In order to investigate the safety of general anesthesia and changes in vital parameters during general anesthesia in Tg2576 mice, we did a secondary analysis of vital parameters collected during general anesthesia in aged Tg2576 mice.

Methods: After governmental approval (General Administration of the Free State of Bavaria, file number: 55.2-1-54-2532-149-11) 60 mice at 10-12 months of age were exposed to isoflurane (1.6 Vol%) for 120 min, data of 58 mice was analyzed. During general anesthesia, heart rate, respiratory rate, temperature, isoflurane concentration and fraction of inspired oxygen were monitored and collected. Data were analyzed using univariate and multivariate linear mixed regression models.

Results: During general anesthesia, heart rate decreased in a sex-specific manner. Respiratory rate decreased and body temperature increased dependent on genotype. However, the changes were limited and all vital parameters stayed within physiological limits.

Conclusion: Isoflurane anesthesia in the Tg2576 mouse model is safe and does not seem to influence experimental results by interacting with vital parameters. The present study provides information on appropriate anesthesia in order to advance research on anesthesia and AD and could contribute to improving laboratory animal welfare.

KEYWORDS

Alzheimer's disease, Tg2576, isoflurane, general anesthesia, vital parameters, mouse model, transgenic mice

1 Introduction

According to the World Health Organization (WHO) 55 million people worldwide are currently living with dementia, with Alzheimer's disease (AD) being the underlying cause in 60–80% of all cases. This number of AD patients is projected to increase to 139 million people by 2050 accounting for 1.6 trillion USD in healthcare costs by 2050 (1, 2).

With an increase in life expectancy as well as medical progress, patients with a preexisting cognitive impairment or even a diagnosis of AD might require surgery and thus either general or regional anesthesia. When it comes to general anesthesia (GA), it is still unclear whether general anesthetics aggravate a preexisting cognitive dysfunction or accelerate cognitive decline (3, 4). Investigating the effect of general anesthesia on AD pathology in humans is impeded by confounders such as surgical trauma, comorbidities, preoperative fasting and post-operative complications (5).

To account for these limitations and to advance research on AD pathology, diagnosis and therapy, various AD mouse models have been developed (6). Mice have a complex nervous system with notable homologies to humans in anatomy (7) and function in terms of learning, memory and behavior (8). There are numerous transgenic, knock-in, injection, and neuroinflammation based AD mouse models, representing amyloidopathy, tauopathy or both (6). In our study, the Tg2576 model was used. It overexpresses the human amyloid precursor gene with the KM670/671NL (so called "Swedish mutation") under a viral hamster prion promotor and was first described by Hsiao et al. (9). These animals show first symptoms of cognitive decline at the age of 10 months, with sex specific differences at the age of 12 months, along with amyloid plaques and microglial activation in the neocortex and hippocampus (10, 11).

The monitoring of vital parameters is a standard procedure and ensures adequate and safe anesthesia by detecting and thus preventing hypotension, subsequent cerebral hypoperfusion or hypoxia which can lead to an unfavorable cognitive outcome (12). Although the Tg2576 mouse model has been used for many years and has often been subjected to anesthesia in this context, the authors are not aware of any publications regarding the associated changes in vital parameters (13, 14). In some cases, very limited monitoring was carried out (15, 16). Furthermore, despite the frequent use of isoflurane for general anesthesia in Tg2576 mice, literature on the effects of 120 min of general anesthesia on this mouse model is scarce (15, 17). To our knowledge, a direct comparison between the vital signs of anesthetized wild-type animals and Tg2576 has not yet been carried out systematically. In a previously published study, our group investigated the influence of isoflurane anesthesia on neurocognition, behavior and amyloidopathy in 10 months old Tg2576 mice with respect to sex. Typical symptoms of early stage AD with corresponding histopathological alterations were found, whereas relevant sex-specific differences or an influence of isoflurane on AD symptomology and pathology could not be detected (18). We retrospectively assessed vital parameters during general anesthesia in order to address whether isoflurane affects heart rate, respiratory rate and body temperature dependent on transgenic status or sex. Data were obtained during isoflurane anesthesia in Tg2576 and wild type mice randomized to intervention during the above-mentioned study. Concerning laboratory animal welfare, another aim of this publication was to evaluate the safety and physiological changes of Tg2576 under general isoflurane anesthesia (19).

2 Materials and Methods

This study was carried out in strict accordance with the recommendations of the Federation of European Laboratory Animal Science Associations (FELASA). The following experimental procedures on animals were approved by the Governmental Animal Care Committee (Regierung von Oberbayern, Maximilianstr. 39, 80538 Munich, Germany, Chair: Dr. B. Wirrer, Registration number: 55.2-1-54-2532-67-2016, July 28th, 2016). All efforts were made to minimize suffering. Animal welfare was assessed daily.

2.1 Mouse model

We used the B6; SJL-Tg (APPSWE) 2576Kha mouse model of AD, also referred to as Tg2576. With the approval of Taconic (Taconic Europe, Lille Skensved, Denmark), male Tg2576 mice were crossed with female C57B6/SJL mice (The Jackson Laboratory, Bar Harbor, ME, USA) in a separate breeding facility. The genotype was confirmed by PCR, using DNA from tail tissues (Charles River Laboratories, Sulzfeld, Germany). Mice homozygous for the rd1-mutation were excluded from the analysis as these mice are blind. At least 14 days prior to anesthesia, cognitive and behavioral

testing, mice were transferred to a test facility for acclimatization. Mice were housed under standard laboratory conditions (specific pathogen free environment, 12 h light/12 h dark cycle, 22°C, 60% humidity and free access to water and standard mouse chow) (11, 18).

Mice were randomly assigned to the experimental groups regarding isoflurane anesthesia or sham procedure using a computer-generated randomization list (18).

2.2 General anesthesia

For induction of general anesthesia mice were placed in an acrylic glass chamber that had been pre-flushed with 4.5 Vol% isoflurane (Isofluran Baxter vet, Deerfield, IL, USA; Vaporizer: Draeger, Lübeck, Germany) and 50% oxygen. After loss of postural reflexes, mice were placed in sternal recumbency on a warming pad. General anesthesia was maintained for 120 min with 1.6 Vol% isoflurane (MAC 1.0) and a fraction of inspired oxygen of 50% (FiO2 0.5) administered via a nose chamber. Mice breathed spontaneously with an applied positive end-expiratory pressure of 5 mbar. Anesthetic depth was monitored every 15 min using the tail clamp test (20). Eye lubricant (Bepanthen®, Bayer Vital GmbH, 51368 Leverkusen, Germany) was applied and animals were individually covered with compresses (Vliwasoft®, Lohmann & Rauscher GmbH & Co. KG, 56567 Neuwied, Germany).

After 120 min mice were placed in the acrylic glass chamber again with 50% oxygen now without isoflurane until full recovery from anesthesia. Afterward the animals were weighed and placed in single cages. During general anesthesia respiratory rate, heart rate (both via subcutaneous electrocardiogram), gas concentrations, and rectal temperature were measured (Datex Ohmeda S/5 Anesthesia Monitor F-CM1-05 with MNESTPR Modul, Datex-Ohmeda GmbH, Duisburg, Germany).

2.3 Statistical analysis

All analyses were conducted with RStudio 2023.09.1 (RStudio, Boston, MA, USA) running R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

Categorical values are presented as absolute and relative numbers, continuous variables with median and interquartile range (IQR). For group comparisons Mann-Whitey *U*-tests and Kruskal-Wallis tests with Bonferroni's corrected *post-hoc* tests were used. To assess changes in vital parameters during the time of anesthesia in combination with the possibly influencing factors sex and genotype, linear mixed regression models were calculated. An alpha of 5% was seen as significant.

3 Results

A total of 60 mice (median weight 28.1 g) underwent general anesthesia for 120 min (Table 1). Incomplete recordings in two mice due to a technical failure at the start of the experiments led to the exclusion of these animals from further analyses concerning general anesthesia. Therefore 58 animals in total with a median age of 10.5 months were analyzed, of which 27 (46.6%) were male. Genotype was equally distributed (Table 1).

TABLE 1 Depiction of experimental groups.

	n = 58
Sex, n (%)	
Male	27 (46.6)
Female	31 (53.4)
Genotype, n (%)	
Tg2576	29 (50.0)
WT	29 (50.0)
Combination of sex and genotype, n (%)	
m_Tg2576	14 (24.1)
m_WT	13 (22.4)
f_Tg2576	15 (25.9)
f_WT	16 (27.6)
RD1 status, n (%)	
Heterozygous	31 (53.4)
WT	27 (46.6)
Age (months), Median (IQR)	10.5 (10–12)

3.1 Heart rate

The median heart rate was 466 (434–499) beats per minute (bpm) in all animals during general anesthesia, without significant sex- or genotype-specific differences in univariate analyses (Table 2). Anesthesia time [min], had a significant influence on heart rate [−0.26 (−0.38 to −0.13); $p < 0.001$, Table 3] as heart rate decreased over time in univariate analyses (Figures 1A, B).

Overall, females had a significantly lower heart rate compared to males [−35 (−65 to −5.6) bpm; $p = 0.020$, Table 3] without a significant influence of genotype [−11 (−41 to 19); $p = 0.47$, Table 3 and Figures 1C, D].

There was a significant interaction between anesthesia time and sex with a positive value for females over time [0.42 (0.25 to 0.59); $p < 0.001$, Table 3]. The heart rate in female mice was lower at the beginning and increased over the course of anesthesia (Figures 1C, D).

The combination of sex and genotype showed a significantly negative influence of female sex in both Tg2576 [−63 (−106 to −21); $p = 0.003$] and WT [−48 (−90 to −6.2); $p = 0.025$] on heart rates (Table 3) compared to male Tg2576 as the heart rates of male Tg2576 remained above those of the other experimental groups throughout general anesthesia.

Anesthesia time had a significantly positive effect on the combination of sex and genotype in male WT [0.28 (0.03 to 0.53); $p = 0.026$], female Tg2576 [0.61 (0.37 to 0.84); $p < 0.001$] and female WT [0.52 (0.28 to 0.76); $p < 0.001$, Table 3].

Female Tg2576 had a significantly lower heart rate [−63 (−108 to −19); $p = 0.005$, Table 4] than male Tg2576.

The combination of anesthesia time and female sex showed a significantly positive influence on heart rate in Tg2576 [0.61 (0.35

TABLE 2 Univariate analysis of vital parameters stratified by sex and genotype.

	Overall, *N* = 58					
Heart rate, median (IQR)	466 (434–499)					
Respiratory rate, median (IQR)	104 (93–115)					
Body temperature, median (IQR)	36.8 (36.5–37.6)					
	Sex					
	Male, *N* = 27	Female, *N* = 31	*p*-value			
Heart rate, median (IQR)	454 (432–507)	468 (438–492)	0.97			
Respiratory rate, median (IQR)	103 (92–114)	106 (93–117)	0.58			
Body temperature, median (IQR)	36.8 (36.7–37.8)	36.8 (36.4–37.6)	0.39			
	Genotype					
	Tg2576, *N* = 29	WT, *N* = 29	*p*-value			
Heart rate, median (IQR)	476 (442–500)	454 (430–493)	0.48			
Respiratory rate, median (IQR)	96 (89–109)	111 (100–121)	**0.005**			
Body temperature, median (IQR)	36.7 (36.3–37.2)	37.2 (36.8–38.1)	**0.022**			
	Combination of sex and genotype					
	Male Tg2576, *N* = 14	Male WT, *N* = 13	Female Tg2576, *N* = 15	Female WT, *N* = 16	*p*-value	
Heart rate, median (IQR)	476 (445–503)	436 (421–510)	476 (438–492)	466 (445–492)	0.69	
Respiratory rate, median (IQR)	94 (90–107)	112 (103–120)	96 (87–112)	111 (100–121)	**0.039**	
Body temperature, median (IQR)	36.8 (36.5–37.2)	37.0 (36.8–38.1)	36.4 (36.3–37.2)	37.2 (36.7–37.8)	0.093	
	Post hoc					
	Male Tg2576 male WT	Male Tg2576 female Tg2576	Male Tg2576 female WT	Male WT female Tg2576	Male WT female WT	Female Tg2576 female WT
Heart rate, median (IQR)						
Respiratory rate, median (IQR)	<0.001	0.41	<0.001	<0.001	1	<0.001

Body temperature, median (IQR). Significance level was set at $p < 0.05$.

to 0.86); $p < 0.001$, Table 4] and WT [0.24 (0.02 to 0.45); $p = 0.032$, Table 4].

In male mice, WT genotype had a significantly positive influence on heart rate [0.29 (0.03 to 0.54); $p = 0.027$] when assessing the combination of anesthesia time and genotype (Table 4).

3.2 Respiratory rate

The median respiratory rate was 104 (93–115) breaths per minute in all animals during general anesthesia (Table 2).

Univariate comparisons showed a significant difference between genotype [Tg2576 96 (89–109) and WT 111 (100–121); $p = 0.005$, Table 2] and between the combination of sex and genotype [male Tg2576 94 (90–107), male WT 112 (103–120), female Tg2576 96 (87–112), female WT 111 (100–121); $p = 0.039$, Table 2] in median respiratory rates.

Overall, WT animals had a significantly higher respiratory rate throughout general anesthesia [12 (3.4 to 21); $p = 0.007$, Table 3 and Figures 2A, B].

In male animals, WT genotype significantly positively influenced respiratory rate [0.08 (0.01 to 0.16); $p = 0.030$, Table 4].

3.3 Body temperature

The median body temperature in all animals was 36.8 (36.5–37.6)°C (Table 2) with a significant difference in genotype [Tg2576 36.7 (36.3–37.2)°C, WT 37.2 (36.8–38.1)°C; $p = 0.022$] in univariate comparisons (Table 2).

TABLE 3 Multivariate linear mixed regression models with variables time, sex, genotype and combination of sex and genotype for heart rate, respiratory rate and body temperature.

	Heart rate		Respiratory rate		Body temperature	
	Beta (95% CI)	*p*-value	Beta (95% CI)	*p*-value	Beta (95% CI)	*p*-value
Sex						
Anesthesia time	−0.26 (−0.38 to −0.13)	<**0.001**	−0.14 (−0.18 to −0.10)	<**0.001**	0.01 (0.01 to 0.01)	<**0.001**
Sex		**0.020**		0.97		0.25
Male	–		–		–	
Female	−35 (−65 to −5.6)		0.21 (−9.4 to 9.9)		−0.29 (−0.79 to 0.21)	
Anesthesia time × Sex		<**0.001**		0.62		0.074
Anesthesia time × Female	0.42 (0.25 to 0.59)		0.01 (−0.04 to 0.07)		0.00 (0.00 to 0.00)	
Genotype						
Anesthesia time	−0.06 (−0.18 to 0.06)	0.31	−0.14 (−0.18 to −0.10)	<**0.001**	0.01 (0.01 to 0.01)	<**0.001**
Genotype		0.47		**0.007**		0.10
Tg2576	–		–		–	
WT	−11 (−41 to 19)		12 (3.4 to 21)		0.41 (−0.08 to 0.89)	
Anesthesia time × Genotype		0.37		0.74		0.99
Anesthesia time × WT	0.08 (−0.09 to 0.25)		0.01 (−0.05 to 0.07)		0.00 (0.00 to 0.00)	
Combination of sex and genotype						
Anesthesia time	−0.40 (−0.57 to −0.22)	<**0.001**	−0.18 (−0.24 to −0.12)	<**0.001**	0.01 (0.01 to 0.01)	<**0.001**
Combination of sex and genotype		**0.025**		0.059		0.23
Male Tg2576	–		–		–	
Male WT	−42 (−86 to 2.1)	0.063	8.5 (−4.9 to 22)		0.27 (−0.45 to 1.0)	
Female Tg2576	−63 (−106 to −21)	**0.003**	−3.6 (−17 to 9.3)		−0.43 (−1.1 to 0.26)	
Female WT	−48 (−90 to −6.2)	**0.025**	12 (−1.1 to 24)		0.10 (−0.59 to 0.78)	
Anesthesia time × Combination of sex and genotype		<**0.001**		0.14		0.33
Anesthesia time × Male WT	0.28 (0.03 to 0.53)	**0.026**	0.08 (0.00 to 0.17)		0.00 (0.00 to 0.00)	
Anesthesia time × Female Tg2576	0.61 (0.37 to 0.84)	<**0.001**	0.08 (0.00 to 0.16)		0.00 (0.00 to 0.01)	
Anesthesia time × Female WT	0.52 (0.28 to 0.76)	<**0.001**	0.03 (−0.05 to 0.11)		0.00 (0.00 to 0.01)	

Significance level was set at $p < 0.05$.

During anesthesia body temperature increased over time [0.001 (0.01 to 0.01); $p < 0.001$] without significant differences in regression models (Tables 3, 4 and Figures 3A–D).

Over the time of anesthesia, all vital parameters changed significantly, except for the model of heart rate and genotype [−0.06 (−0.18 to 0.06), $p = 0.31$, Table 3].

4 Discussion

This study is a secondary analysis of data collected during general anesthesia in a mouse model of AD. Heart rate, respiratory rate and body temperature of both male and female 10–12 months old Tg2576 and wild type mice under isoflurane

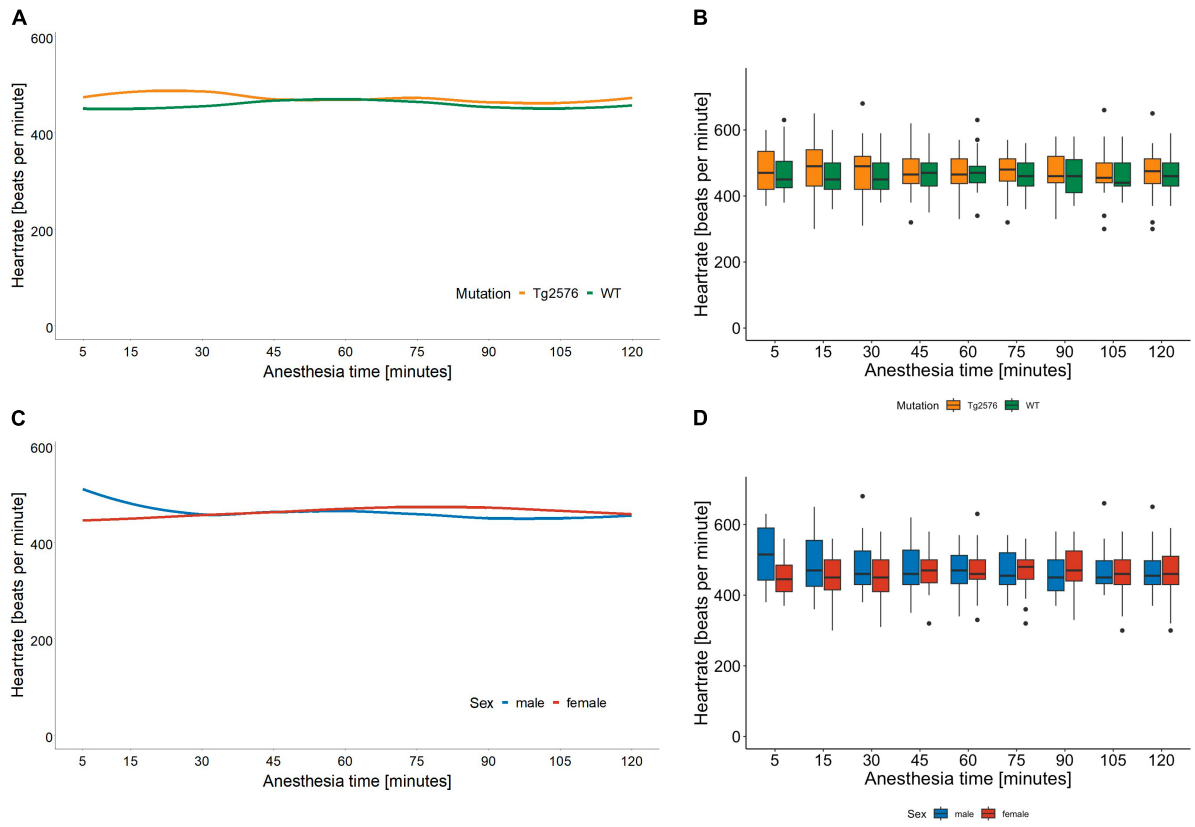

FIGURE 1
Heart rate in beats per minute and anesthesia time in minutes sorted by genotype **(A)** and corresponding boxplots over a 15 min interval **(B)**; median (horizontal lines), interquartile range (box) and range (whiskers), dots represent outliers at least 1.5 times of the interquartile range (IQR). The heart rate of Tg2576 mice and WT mice did not show significant differences. Heart rate in beats per minute and anesthesia time in minutes sorted by sex **(C)** and corresponding boxplots over a 15 min interval **(D)**; median (horizontal lines), interquartile range (box) and range (whiskers), dots represent outliers at least 1.5 times of the interquartile range (IQR). The heart rate of female animals was lower at the beginning of anesthesia and increased over the course of anesthesia. In male animals, the heart rate was higher at the beginning and decreased over time, with a tendency toward approximation in both sexes.

anesthesia were analyzed. We found time dependent as well as sex- and genotype-specific differences in vital parameters. After general anesthesia, mice underwent neurocognitive testing for 8 consecutive days. Results from the post-anesthesia part of the study have already been published (18). Data on anesthesia in Tg2576 mice over a period of 120 min are not very frequently encountered in the literature, as general anesthesia in animal experiments is often maintained for a shorter time period and published data on vital parameters is limited (13, 15, 17, 21). In view of this, these results can be considered a valuable contribution to the field of experimental AD research and provide a unique insight into the physiology of Tg2576 during general anesthesia.

Since its first description in 1996 (9), the Tg2576 animal model has been widely used in AD research to elucidate AD pathophysiology (10, 22–25), symptomology (26–28) and possible therapeutic strategies for this to date incurable neurodegenerative disease (29–33). Also, studies on the effect of general anesthesia on AD pathology have been done using this AD mouse model (17, 18, 21). Tg2576 animals have been very well described (34, 35) and are known to exhibit sex-specific differences similar to human AD pathology (11). In order to translate experimental evidence into the human organism, valid animal models are warranted. Although the Tg2576 animal model has already been well characterized in different aspects of AD research, literature on vital parameters during general anesthesia is limited. We therefore undertook a secondary analysis of heart rate, respiratory rate and body temperature in the Tg2576 mouse model taken during general anesthesia.

We found that the median heart rate did not differ significantly between animals in univariate analyses. However, in multivariate analyses female mice had a lower heart rate which increased over the course of anesthesia while the heart rate in male mice decreased, with a tendency toward approximation (**Figures 1C, D**). Heart rates in male Tg2576 and female mice approximated toward the end of general anesthesia (**Figures 1A, B**). This finding is in line with other studies on general anesthesia in laboratory animals, where heart rates in female (36) and animals of both sex (37, 38) increased over the course of isoflurane anesthesia. In (37) sex was not a significant factor for heart rate in C57BL/6J mice whereas our data showed a significant difference between male and female Tg2576 and WT mice. There is emergent evidence of a heart-brain-interaction in AD in terms of increased heart rate variability in males associated with better cognitive resilience (39) and susceptibility to AD pathology (40), so a sex-dependent effect

TABLE 4 Multivariate linear mixed regression model with variables time, sex, genotype and further stratification by experimental group for heart rate, respiratory rate and body temperature.

			Heart rate		Respiratory rate		Body temperature	
			Beta (95% CI)	*p*-value	Beta (95% CI)	*p*-value	Beta (95% CI)	*p*-value
Genotype	Tg2576	Anesthesia time	−0.40 (−0.59 to −0.21)	<**0.001**	−0.18 (−0.25 to −0.12)	<**0.001**	0.01 (0.00 to 0.01)	<**0.001**
		Sex		**0.005**		0.59		0.23
		Male	–		–		–	
		Female	−63 (−108 to −19)		−3.7 (−17 to 9.8)		−0.43 (−1.1 to 0.27)	
		Anesthesia time × Sex		<**0.001**		0.051		0.13
		Anesthesia time × Female	0.61 (0.35 to 0.86)		0.08 (0.00 to 0.16)		0.00 (0.00 to 0.01)	
	WT	Anesthesia time	−0.11 (−0.27 to 0.05)	0.16	−0.10 (−0.16 to −0.04)	<**0.001**	0.01 (0.01 to 0.01)	<**0.001**
		Sex		0.76		0.62		0.61
		Male	–		–		–	
		Female	−6.2 (−46 to 34)		3.2 (−9.3 to 16)		−0.18 (−0.87 to 0.51)	
		Anesthesia time × Sex		**0.032**		0.21		0.31
		Anesthesia time × Female	0.24 (0.02 to 0.45)		−0.05 (−0.13 to 0.03)		0.00 (0.00 to 0.00)	
Sex	Male	Anesthesia time	−0.40 (−0.58 to −0.22)	<**0.001**	−0.18 (−0.24 to −0.13)	<**0.001**	0.01 (0.01 to 0.01)	<**0.001**
		Genotype		0.076		0.11		0.43
		Tg2576	–		–		–	
		WT	−42 (−88 to 4.3)		8.6 (−1.8 to 19)		0.27 (−0.41 to 0.96)	
		Anesthesia time × Genotype		**0.027**		**0.030**		0.66
		Anesthesia time × WT	0.29 (0.03 to 0.54)		0.08 (0.01 to 0.16)		0.00 (0.00 to 0.00)	
	Female	Anesthesia time	0.21 (0.05 to 0.36)	**0.009**	−0.10 (−0.16 to −0.04)	<**0.001**	0.01 (0.01 to 0.01)	<**0.001**
		Genotype		0.44		**0.037**		0.14
		Tg2576	–		–		–	
		WT	15 (−24 to 54)		15 (0.93 to 30)		0.53 (−0.16 to 1.2)	
		Anesthesia time × Genotype		0.45		0.25		0.77
		Anesthesia time × WT	−0.09 (−0.31 to 0.14)		−0.05 (−0.13 to 0.03)		0.00 (0.00 to 0.00)	

Significance level was set at $p < 0.05$.

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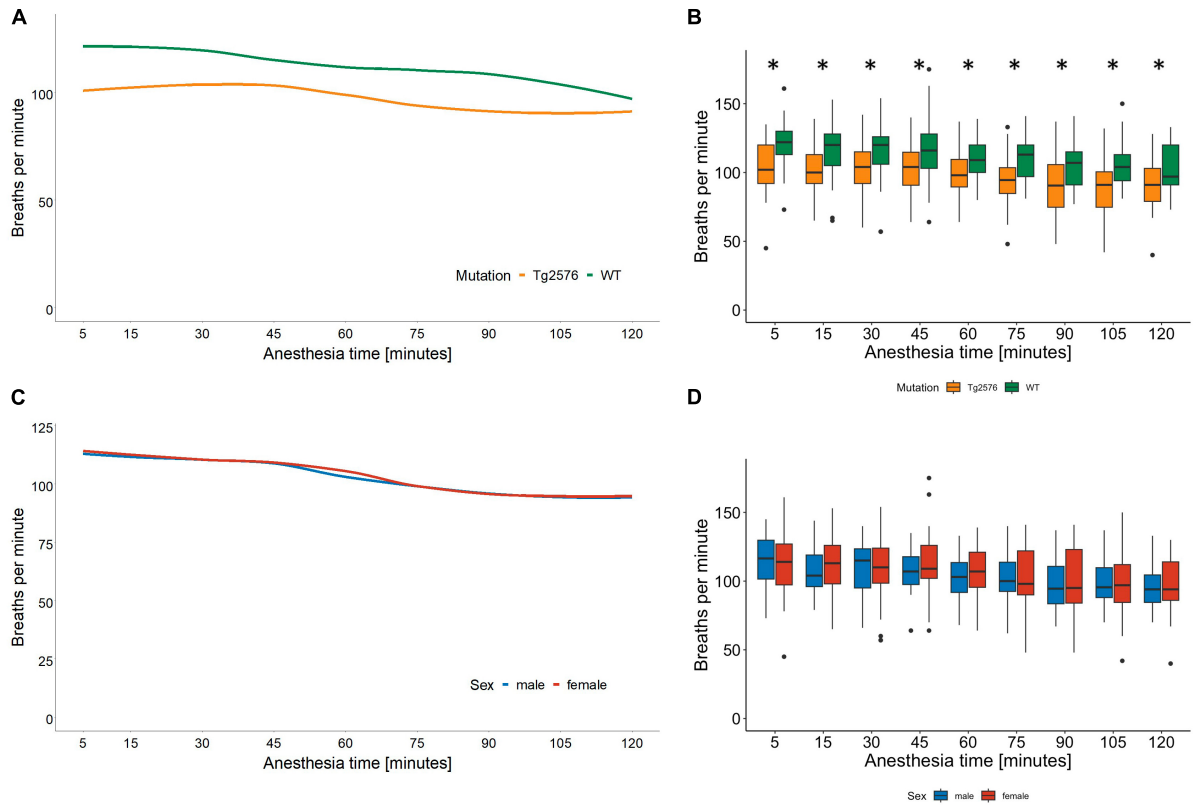

FIGURE 2
Respiratory rate in breaths per minute and anesthesia time in minutes sorted by genotype **(A)** and corresponding boxplots over a 15 min interval **(B)**; median (horizontal lines), interquartile range (box) and range (whiskers), dots represent outliers at least 1.5 times of the interquartile range (IQR), *p = 0.007. The respiratory rate in Tg2576 mice was significantly lower compared to WT mice. Respiratory rate in breaths per minute and anesthesia time in minutes sorted by sex **(C)** and corresponding boxplots over a 15 min interval **(D)**; median (horizontal lines), interquartile range (box) and range (whiskers), dots represent outliers at least 1.5 times of the interquartile range (IQR). The respiratory rate decreased in all animals over the course of isoflurane anesthesia, without a statistically significant difference between sex.

on the heart rate based on the respective genotype in this AD mouse model cannot be excluded. Also, isoflurane is known to induce hypotension (41) and an increase in heart rate could be a compensatory mechanism. We did not measure blood pressure during anesthesia, which on the one hand can be viewed as a limitation of our study. On the other hand, it must be noted that the American Heart Association recommended avoiding anesthesia during blood pressure measurement due to the effect of anesthetics on cardiovascular function (42). We aimed to avoid invasive blood pressure measurement techniques in order to minimize distress for the animals and decided against a tail-cuff method since mice have complex thermoregulating processes involving fluctuating vasomotor tone of the tail, especially under general anesthesia (43). For the same reason we refrained from taking blood samples.

The respiratory rate decreased in all animals during isoflurane anesthesia (**Figures 2C, D**). Tg2576 mice had a lower respiratory rate than WT littermates without significant sex-specific differences (**Figures 2A, B**). Again, these observations reflect the current literature on isoflurane anesthesia in mice (36–38) in terms of a decrease in absolute numbers during anesthesia. It has to be noted that respiratory rates in our study ranged between 94 and 111 breaths per minute, whereas other publications stated respiratory rates of <80 per minute (37), <60 per minute (36), and <100 per minute (38). These differences in respiratory rates might be due to different isoflurane concentrations and subsequently differing anesthetic depths. In our study, 4.5 Vol% of isoflurane was administered for induction of general anesthesia, followed by 1.6 Vol% for anesthesia maintenance. Isoflurane concentration was reduced to 1.6 Vol% immediately after loss of righting reflex. This concentration was found to be sufficient by tail clamp test assessment while other authors used isoflurane concentrations of 1.5–2.1% (37), 2.8% (36), and 2% (38). Several aspects have to be considered when putting these data into perspective. The cited studies used C57BL/6J mice (36, 37) or ddY mice (38) at a significantly younger age [6 weeks (36), 8–20 weeks (37), and 7 weeks (38)] and applied isoflurane anesthesia for a shorter time [40 min (38), 50 min (36) and 60 min (37)] compared to the 120 min of anesthesia in our experiments. It is known that genetic variability influences susceptibility to isoflurane in mouse strains (44) and humans (45) and that anesthetic requirement decreases with age (46), which might account for the differences observed in our data. SpO2 was not measured in our study which is a limitation. However, other animal studies found SpO_2 to be stable even with lower respiratory rates (37, 38), although it has to be noted that fractions of inspired oxygen as high as 100% were used.

Throughout the course of anesthesia body temperature increased in all animals while actively warmed using a warming pad (**Figures 3C, D**). Hypothermia is a known complication in general

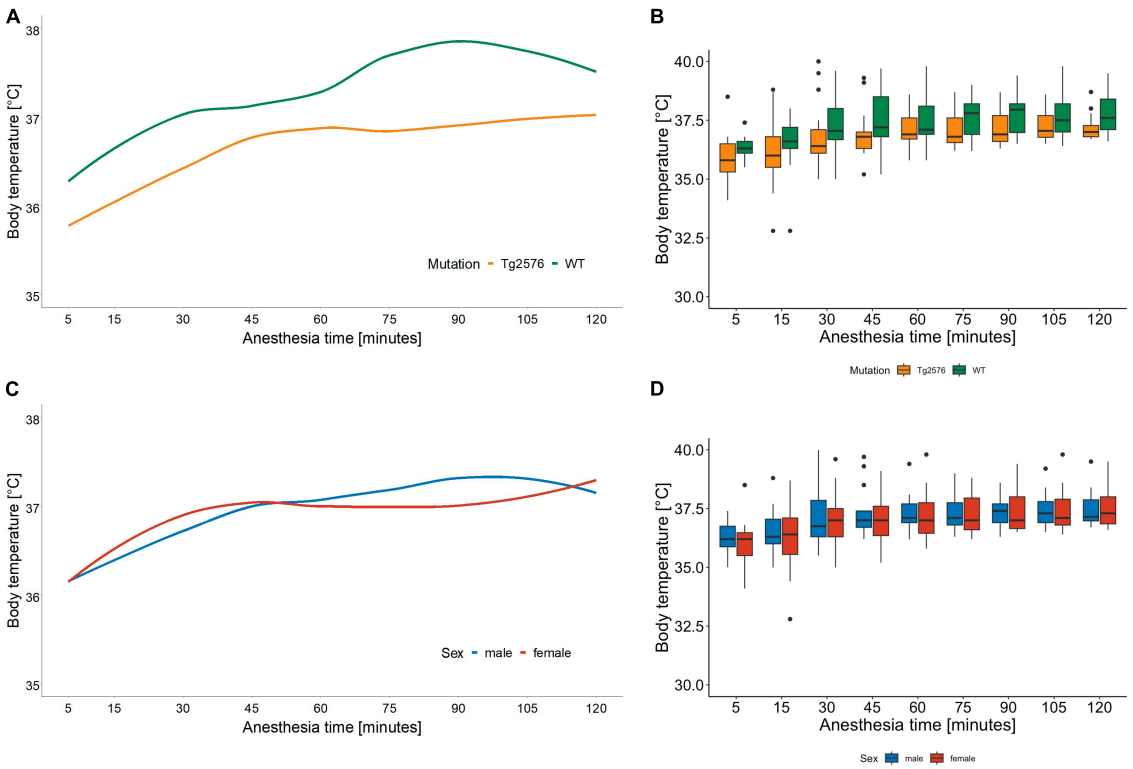

FIGURE 3
Body temperature in °C and anesthesia time in minutes sorted by genotype **(A)** and corresponding boxplots over a 15 min interval **(B)**; median (horizontal lines), interquartile range (box) and range (whiskers), dots represent outliers at least 1.5 times of the interquartile range (IQR). Body temperature of Tg2576 and WT mice differ over the course of anesthesia. Throughout anesthesia body temperature increased in all animals, without a statistically significant difference between genotype. Body temperature in °C and anesthesia time in minutes sorted by sex **(C)** and corresponding boxplots over a 15 min interval **(D)**; median (horizontal lines), interquartile range (box) and range (whiskers), dots represent outliers at least 1.5 times of the interquartile range (IQR). Body temperature increased in all animals over the course of anesthesia, without a statistically significant difference between sex.

anesthesia with numerous deleterious effects on both human (47) and laboratory animal (48) physiology. Body temperature correlated positively with heart rate and respiratory rate in female C57BL/6J mice (48) during 30 min of isoflurane anesthesia which is again an anesthesia time shorter than in our study. Although animals were handled identically, we found that body temperature differed significantly between genotypes in univariate but not in multivariate analyses. Tg2576 had a median body temperature of 36.7°C compared to 37.2°C in WT (**Figures 3A, B**). This is reflective of AD pathology in humans where old age, disruption in thermoregulation and neurodegeneration seem to be interconnected (49).

5 Conclusion

In this secondary analysis of vital parameters collected during general anesthesia of Tg2576 mice and WT littermates we found marginal, yet significant differences in heart rate, respiratory rate and body temperature. Despite these differences, all vital parameters remained within physiological limits. Our findings indicate that isoflurane anesthesia in this AD mouse model is safe and does not seem to influence experimental results by interacting with vital parameters. The present study provides information on appropriate anesthesia in order to advance research on anesthesia and AD and could contribute to improving laboratory animal welfare.

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 animal study was approved by the Regierung von Oberbayern, Maximilianstr. 39, 80538 Munich, Germany, Chair: Dr. B. Wirrer, Registration number: 55.2-1-54-2532-67-2016, July 28th, 2016. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

SB: Formal analysis, Investigation, Validation, Writing – review and editing. SS: Conceptualization, Methodology,

Supervision, Writing – review and editing. BU: Formal analysis, Methodology, Validation, Writing – review and editing, BJ: Conceptualization, Supervision, Writing – review and editing. MB: Methodology, Resources, Supervision, Writing – review and editing. LB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study received Institutional funding. We acknowledge support from Alzheimer Forschung Initiative e.V. for Open Access Publishing.

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

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TYPE Original Research
PUBLISHED 08 April 2024
DOI 10.3389/fmed.2024.1369967

OPEN ACCESS

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RECEIVED 13 January 2024
ACCEPTED 28 March 2024
PUBLISHED 08 April 2024

CITATION
Yang D, He Y, Wang Q and Yu Y (2024) Association between statin use and acute pulmonary embolism in intensive care unit patients with sepsis: a retrospective cohort study.
Front. Med. 11:1369967.
doi: 10.3389/fmed.2024.1369967

Association between statin use and acute pulmonary embolism in intensive care unit patients with sepsis: a retrospective cohort study

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Introduction: Acute pulmonary embolism (APE) is a life-threatening medical condition that is frequently encountered and associated with significant incidence and mortality rates, posing a substantial threat to patients' well-being and quality of life. Sepsis is prominent independent risk factor for the development of APE. Despite recent investigations indicating a reduced APE risk through statin therapy, its impact on patients with sepsis and APE remains unresolved.

Methods: The Medical Information Mart for Intensive Care (MIMIC)-IV database was utilized to identify patients diagnosed with sepsis and APE, irrespective of statin treatment status, as part of this study. The primary study aim was to assess the risk of APE, which was analyzed using multivariate logistic regression models.

Results: The study encompassed a total of 16,633 participants, with an average age of 64.8 ± 16.2 years. Multivariate logistic regression revealed that septic patients receiving statin therapy in the intensive care unit (ICU) exhibited a 33% reduction in the risk of developing APE (OR = 0.67, 95% CI: 0.52–0.86, $p < 0.001$). The findings of further analyses, including stratification based on statin usage, dosage, and propensity score matching, consistently reinforced the hypothesis that administering statins to patients with sepsis effectively mitigates their potential APE risk.

Discussion: The results of the study provide compelling evidence in favor of administering statins to septic patients as a prophylactic measure against APE, given that statins may reduce the risk of developing APE, and their anti-APE effect appears to be dose-dependent. Nonetheless, future randomized controlled trials are needed to validate these results.

KEYWORDS

statins, acute pulmonary embolism, ICU, medical information mart for intensive care, cohort study

Introduction

Acute pulmonary embolism (APE), which is classified as venous thromboembolism (VTE), is a cardiovascular disorder characterized by its high rates of occurrence and mortality, ranking closely behind myocardial infarction and stroke. Despite its notable prevalence and fatality, APE continues to be under-diagnosed, which poses a substantial risk to patients' overall well-being and quality of life (1, 2).

The increased incidence of APE observed in critically ill patients is attributed to various factors, including complete immobilization, reluctance to administer anticoagulant prophylaxis due to a heightened risk of bleeding, and impaired peripheral circulation in patients receiving vasopressor drugs to sustain central blood pressure, thereby leading to reduced subcutaneous heparin bioavailability (3, 4). Furthermore, sepsis is a notable stand alone risk factor for the development of APE (5–7). The initial phases of sepsis involve a multitude of concurrent pathophysiological mechanisms, encompassing inflammation and activation of coagulation pathways (8). The coagulation cascade is an intricately regulated process, and changes in patients' coagulation profile during sepsis are indicative of an adverse prognostic outcome (9). Additionally, individuals with sepsis display decreased concentrations of antifactor Xa, due to inflammation, tissue permeability, and pronounced subcutaneous edema, compared to a control group without edema (10, 11). Although long-term use of vitamin K antagonists effectively reduces the risk of VTE in high-risk individuals, it is associated with an increased likelihood of experiencing major hemorrhagic events (12, 13). In light of these factors, critically ill patients, especially those diagnosed with sepsis, are confronted with the pivotal issue of identifying secure alternatives to effectively manage the risk of APE, when conventional anticoagulation therapies and oral anticoagulants are either ineffective or contraindicated.

Statins are widely employed for the prophylaxis and management of atherosclerotic ailments both in primary and secondary settings (14). Current evidence suggests there is a common mechanism that underlies both VTE and atherosclerotic disease (15–17); e.g., cytokines released by inflammatory cells, which have been detected in atherosclerotic plaques, have also been identified in individuals suffering from venous thrombosis (18). Aside from their lipid-lowering properties, statins exhibit a spectrum of vasoprotective actions that could bolster the possible utility of statin therapy in the treatment of VTE (19, 20). Violi et al. published a review paper summarizing the positive impact of statins on the vascular wall, inflammation, and thrombotic factors, which collectively demonstrated a vasoprotective effect (21).

Given the existing evidence, our hypothesis was that statins have a role in preventing APE in high-risk patients admitted to the intensive care unit (ICU). Therefore, we conducted a retrospective study of a cohort of 16,633 critically ill patients. The data used for this study were obtained from the Medical Information Mart for Intensive Care (MIMIC-IV) dataset covering the period from 2001 to 2019. Our objective was to investigate the association between the use of statins and the risk of APE in ICU sepsis patients.

Materials and methods

This study used data from patients diagnosed with sepsis and APE (regardless of their prior use of statins) that were retrieved from the MIMIC-IV (version 2.2) database, which is a comprehensive and longitudinal collection of patients' information from a single healthcare center. The database encompasses data recorded between 2008 and 2019 (22); prior authorization to use the database was obtained from Yi Yu, who is one of the authors (certificate ID number 6477678). This study complies with the Guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (23).

Study sample and data extraction

The study enrolled individuals with a confirmed diagnosis of APE with sepsis based on their discharge diagnosis. The diagnosis of sepsis is based on the Sepsis 3.0 criteria. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. For clinical operationalization, organ dysfunction was represented by an increase in the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score of 2 points or more (24). The inclusion criteria were: (1) APE had to be listed among the top five discharge diagnoses and had to be explicitly mentioned in the discharge diagnosis; and (2) the patients had to be 18 years of age or older. In cases where patients had multiple ICU admissions, only data from the initial admission were used. A comprehensive set of patients' data was collected, including demographic details, vital signs, underlying conditions, laboratory results, clinical severity scores, and additional admission information. The diagnosis of APE was determined using the International Classification of Diseases, 9th and 10th editions.

Statin use

The presence of statin medications in the "prescriptions" data from the MIMIC-IV database was used to assess the administration of statins. The statins included in the analyses were atorvastatin, simvastatin, rosuvastatin, lovastatin, pravastatin, and fluvastatin. The average daily dose was calculated to determine the dosage of statins. The classification of statin dosages was based on the potency of each statin, as indicated on a standard conversion chart (25).

Covariates

The database contained variables previously reported to be cardiovascular risk factors and potential triggers for APE, as well as other variables (26–29). Personal demographic variables included age, sex, race, and body mass index (BMI). Health related variables included: respiratory rate, body temperature, the Saturation of Peripheral Oxygen ratio (SPO2), Sequential Organ Failure Assessment (SOFA) score, White Blood Cell (WBC) count, hemoglobin level, hematocrit, platelet count, and glucose level, and preexisting medical conditions (e.g., cardiovascular disease, kidney disease, rheumatic disease, liver disease, cancer, neurological disease, and chronic pulmonary disease).

Outcome

The outcome variable was the probability of developing APE.

Statistical analysis

The study initially analyzed the baseline characteristics of the total sample and compared the characteristics of the two cohorts (Statin use and No statin use). Categorical data are summarized as frequency counts and percentages, whereas continuous data are presented as mean ± standard deviation or median (interquartile range), where appropriate. Analysis of variance or rank sum tests were performed to analyze differences in cohort outcomes for continuous variables. The Chi-square or Fisher's exact tests were performed to analyze group (i.e., cohort) differences in outcomes for categorical variables.

We used a median replacement strategy to impute missing data on vital signs and laboratory parameters, as these variables contained missing data in 5% of the sample. Since the percentage of missing data for height and weight was low (ranging from 0.3–4%), no imputation was performed. We initially tested five multivariate logistic regression models to analyze the unique association between statins and APE, adjusting for different covariates. We performed some different statistical models to verify the results' stability. In the final model, we adjusted the factors basing the following three rules (1 or 2 or 3). (1) We adjusted for variables, if it was added to this model, the matched odds ratio would change at least 10%. (2) For univariate analysis, we adjusted for variables, of which the p values were <0.1. (3) For multivariable analysis, variables were chosen on the basis of previous findings and clinical constraints. Supplementary analyses were conducted to examine subgroup and interaction analyses, controlling for relevant covariates. Propensity score matching (PSM) was conducted to improve the rigor of the study, using a 1:1 nearest neighbor matching algorithm with a caliper width of 0.1. Multivariate logistic regression models with robust variance estimators were employed to estimate the odds ratio (OR) for APE.

The statistical analyses were performed with STATA software (version 17.0), R packages (The R Foundation),[1] and Free Statistics software version 1.8 (30). Statistical significance was set to $p < 0.05$ (two-tailed).

Results

Participants

Among the eligible patients, a total of 33,177 individuals met the sepsis criteria. After excluding cases of repeated ICU admissions and patients with an ICU stay of less than 24 h, the final cohort included 16,633 patients. Figure 1 presents a flowchart that illustrates the process of selecting study participants.

Baseline characteristics

A total of 16,633 patients (57.3% male, mean age = 64.8 ± 16.2 years) were selected for inclusion in the study. The baseline characteristics of the study sample are presented in Table 1. Comparisons between the two groups indicated that the non-statin group was younger and had (a) a higher proportion of females, (b) higher SOFA scores, (c) a lower Charlson comorbidity index, (d) higher liver disorders rates and (e) significantly higher rates of APE, deep vein thrombosis (DVT), 30- and 90-day mortality. Longer ICU stays also were observed in the non-statin group. In the statins group, there were no significant liver or muscle-related side effects.

Relationship between statin use and APE and DVT

The univariate analyses found that the use of statins significantly reduced the rates of APE compared to no statin use (OR = 0.67, 95% confidence interval = 0.53–0.83, $p < 0.001$; Table 2).

The multivariate logistic regression analyses (Table 2) found the ORs for the benefit of using statins remained consistently significant across all five models (ORs ranged from 0.65 to 0.76, $p < 0.05$ for all models). Model 5, which controlled for all the covariates, found the use of statins had a significant 33% reduction in APE risk (OR = 0.67, $p < 0.001$), and these results were robust.

The multivariate logistic regression analyses for DVT of using statins remained consistently significant across all five models (ORs ranged from 0.36 to 0.53, $p < 0.05$ for all models). Model 5, which controlled for all the covariates, found the use of statins had a significant 47% reduction in DVT risk (OR = 0.53, $p < 0.001$; Supplementary Table S2).

Subgroup analysis and sensitivity analysis

The results remained consistent across the logistic regression models. After PSM was conducted on both groups, the sample consisted of 4,437 well-matched pairs, and there were no significant differences in key variables between the two matched groups (Supplementary Table S1). Among the 4,437 pairs in the propensity-matched pool, the risk of APE was significantly lower in patients who were prescribed statins [97 (2.2%) versus 141 (3.2%), $p = 0.004$]. The multivariate logistic regression model that was adjusted for all the covariates yielded an OR = 0.68 ($p < 0.007$) for APE (Table 2). Furthermore, when analyzing the net effect of the dosage of statins, both the standard dose of statin (OR = 0.72) and the high dose of statin (OR = 0.65) were associated with a reduced risk of APE (Table 3). Similarly, when analyzing the classification of statins, atorvastatin (OR = 0.62) had a protective effect, while simvastatin (OR = 0.87) and other statins (OR = 0.54) did not show a significant association with APE (Table 4). Subgroup analysis further supported the robustness and reliability of the observed statin-APE relationship. The protective effects of statins in these subgroup analyses were more pronounced in patients who also used oral anticoagulants than in patients who used non-oral anticoagulants. No other significant interaction was observed in the subgroup analyses (p for interaction >0.05) (Figure 2).

Discussion

The main result

This current study builds upon previous promising findings about the use of statins for patients with sepsis. By utilizing a

1 http://www.R-project.org

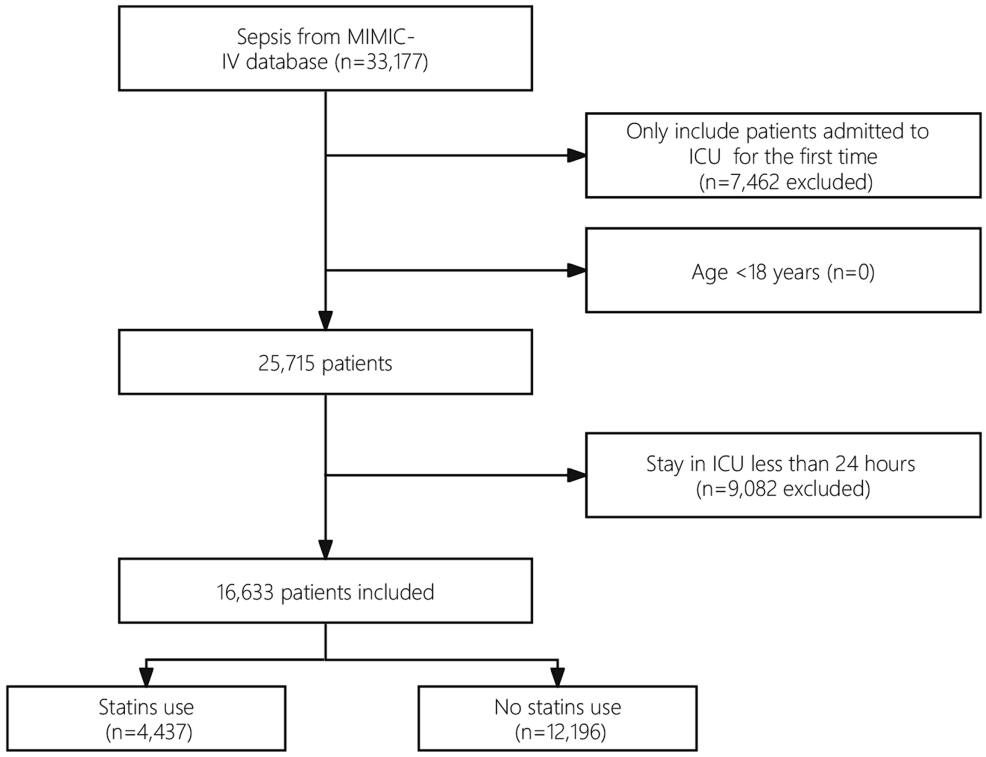

FIGURE 1
Study flowchart.

large-scale database, this study provides robust evidence supporting the favorable effects of statins in reducing the occurrence of APE in sepsis patients. The results of this study validate that administering statins is significantly associated with a substantial reduction in the likelihood of APE in sepsis patients. In addition, the subcategorization of statin usage, analysis of statin dosage, and PSM further strengthen the validity of these findings, by consistently demonstrating the protective effect of statins in reducing the risk of APE in patients with sepsis.

Effects of statins use on the APE risk of sepsis patients

Extensive research has examined the impact of statins on APE (31–34), and the findings consistently demonstrate that statins effectively mitigate the occurrence of APE in populations at high risk, while also reducing mortality rates associated with APE. Consistent findings were observed in our study, revealing a significant association between the use of statins and a decreased risk of APE in sepsis patients (OR = 0.67). However, it is crucial to note that some studies have not replicated our findings. One study of the administration of statins within the initial year following a successful kidney transplant reported that statins did not reduce the likelihood of PE (35), and a study by Huerta et al. found no substantial protective effect of statins on APE or deep vein thrombosis in the context of current or past statin use (36). While a randomized clinical trial reported that the use of rosuvastatin substantially reduced the occurrence of symptomatic venous thromboembolism, its use did not result in a decline in the frequency of APE (37). However, that study had some limitations, including its sole focus on individuals without existing health issues, and its limited duration of observation. Furthermore, it did not examine the link between statin dosage and the probability of VTE. Another study demonstrated that the efficacy of statin therapy in preventing thrombus formation in cancer patients remains unclear (38). But, it is worth noting that the study only included participants with progressive tumor growth. Additionally, its small sample size and short duration of monitoring were study limitations. Therefore, additional clinical studies are needed to assess the efficacy of statins in the prevention and treatment of APE.

The precise mechanism through which statin use is associated with a reduced risk of APE in patients with sepsis remains unclear. However, apart from their lipid-lowering effect, statins also possess anti-inflammatory properties, leading to decreased levels of inflammatory markers in the blood and improved endothelial function. Moreover, statins exert antithrombotic effects and can regulate coagulation cascades through various mechanisms that are independent of alterations in cholesterol levels (39, 40). The protective effect of simvastatin on APE-induced pulmonary arterial pressure, hypoxemia, and inflammatory changes may be attributed to its modulation of the signaling pathway involving silent information regulator 2 (SIRT2) and nuclear factor-kappa B (NF-κB). Additionally, pretreatment with atorvastatin has been

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TABLE 1 Baseline characteristics of the participants.

Variables	Total (N = 16,633)	No statin use (n = 12,196)	Statin use (n = 4,437)	p value
Age, years	64.8 ± 16.2	62.7 ± 17.0	70.6 ± 12.1	<0.001
Sex, Male, *n* (%)	9,539 (57.3)	6,864 (56.3)	2,675 (60.3)	<0.001
BMI, kg/m^2	29.1 ± 7.4	29.1 ± 7.6	29.4 ± 6.9	0.027
Race, *n* (%)				<0.001
White	11,116 (66.8)	8,098 (66.4)	3,018 (68)	
Black	1,503 (9.0)	1,264 (10.4)	239 (5.4)	
Others	4,014 (24.1)	2,834 (23.2)	1,180 (26.6)	
Hematocrit (%)	32.0 ± 6.1	31.8 ± 6.2	32.3 ± 5.8	<0.001
Hb (g/L)	10.5 ± 2.1	10.4 ± 2.1	10.7 ± 2.0	<0.001
PLT (×10^9)	207.5 ± 114.5	208.9 ± 120.4	203.7 ± 96.6	0.009
WBC (×10^9)	13.5 ± 9.5	13.6 ± 10.2	13.5 ± 7.1	0.642
Respiration rate (bpm)	20.0 ± 4.1	20.1 ± 4.2	19.4 ± 3.7	<0.001
Temperature (°C)	36.9 ± 0.7	36.9 ± 0.7	36.8 ± 0.7	<0.001
SPO_2 (%)	97.1 ± 2.2	97.1 ± 2.2	97.1 ± 2.0	0.238
Glucose (mmol/L)	144.7 ± 46.0	143.8 ± 46.6	146.9 ± 43.9	<0.001
Charlson comorbidity index	6.6 ± 3.2	6.6 ± 3.4	6.8 ± 2.6	<0.001
SOFA score	6.2 ± 3.4	6.4 ± 3.6	5.9 ± 3.0	<0.001
Myocardial infarct, *n* (%)	3,422 (20.6)	1909 (15.7)	1,513 (34.1)	<0.001
Congestive heart failure, *n* (%)	6,060 (36.4)	4,124 (33.8)	1936 (43.6)	<0.001
Peripheral vascular disease, *n* (%)	2,576 (15.5)	1731 (14.2)	845 (19)	<0.001
Cerebrovascular disease, *n* (%)	3,230 (19.4)	2,196 (18)	1,034 (23.3)	<0.001
Chronic pulmonary disease, *n* (%)	5,149 (31.0)	3,743 (30.7)	1,406 (31.7)	0.218
Rheumatic disease, *n* (%)	664 (4.0)	512 (4.2)	152 (3.4)	0.024
Malignant cancer, *n* (%)	2,770 (16.7)	2,283 (18.7)	487 (11)	<0.001
Severe liver disease, *n* (%)	1,437 (8.6)	1,344 (11)	93 (2.1)	<0.001
hypertension, *n* (%)	4,551 (27.4)	3,014 (24.7)	1,537 (34.6)	<0.001
Diabetes, *n* (%)				<0.001
None	11,103 (66.8)	8,411 (69)	2,692 (60.7)	
Without complications	3,307 (19.9)	2,148 (17.6)	1,159 (26.1)	
With complications	2,223 (13.4)	1,637 (13.4)	586 (13.2)	
ALT (U/L)*	50.0 (27.0, 125.0)	52.0 (29.0, 143.0)	39.0 (22.0, 82.0)	<0.001
AST (U/L)*	67.0 (35.0, 173.0)	69.0 (38.0, 198.0)	53.0 (29.0, 114.0)	<0.001
CK (U/L)*	198.0 (114.0, 367.0)	198.0 (110.0, 374.0)	198.0 (127.0, 350.0)	0.023
ICU stay, days	4.5 (2.9 ± 8.5)	4.6 (2.9 ± 8.7)	4.4 (2.9 ± 8.1)	0.01
30-Day mortality, *n* (%)	2,901 (17.4)	2,361 (19.4)	540 (12.2)	<0.001
90-Day mortality, *n* (%)	3,153 (19.0)	2,578 (21.1)	575 (13)	<0.001
DVT, *n* (%)	299 (1.8)	264 (2.2)	35 (0.8)	<0.001
Acute pulmonary embolism, *n* (%)	493 (3.0)	396 (3.2)	97 (2.2)	<0.001

Mean ± standard deviation, median (interquartile range), or number (percentage) is reported for each variable, as appropriate. BMI, body mass index; HB, hemoglobin; Plt, platelets; WBC, white blood cells; SPO_2, pulse oxygen saturation; SOFA, Sequential Organ Failure Assessment; ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; ICU, intensive care unit; DVT, deep vein thrombosis. *The maximum levels during the patient's stay in the ICU.

found to improve APE-induced pulmonary hypertension and increase 24-h survival rates by reducing the elevation of lung-activated matrix metalloprotein-9 following APE (41). The promising protective effects of simvastatin in patients with APE are linked to its modulation of the SIRT2/NF-κB signaling pathway. This is supported by its capacity to alleviate APE-induced

pulmonary artery pressure, hypoxemia, and inflammatory changes, highlighting its potential therapeutic benefits (42).

Strengths and limitations

Our study possesses several noteworthy strengths. First, it is worth noting, for example, though the effects of statin administration on APE have been extensively explored, there is a lack of conclusive evidence, specifically, patients with sepsis. Our findings shed light on the substantial reduction in APE risk associated with statin usage in sepsis patients. Second, the rationale for selecting statins lies in their widespread acceptance and ease of use within the medical community. Prior research has demonstrated the broad applicability of statins in the management and prevention of diverse conditions, including tumors, cardiovascular disease, and cerebrovascular disease (43–46). Third, we conducted several sensitivity analyses to ensure the robustness of our results.

These analyses are important for at least four reasons: (1) logistic regression analyses were adjusted using multiple models to control for potential confounding variables, and the stability of the results was confirmed using thorough model adjustments; (2) the analysis of the net effects of standard and high doses of statin, produced reliable findings, with the trend test indicating a more pronounced effect for high-dose administration; (3) the categorization of statin usage into non-use, atorvastatin, simvastatin, and others, revealed the protective effects of various statins against APE; and (4) the employment of PMS analysis yielded results consistent with those of the initial analyses.

We acknowledge several limitations of our study in line with previous observational studies. First, large amounts of missing data prevented us from conducting statistical analyses on lipid levels; therefore the optimal lipid value for APE in sepsis remains unknown. Second, the retrospective nature of our study and unmeasured confounders may have affected our findings. Furthermore, our analysis of serum markers of inflammation was limited to WBC. Interleukin-6, C-reactive protein, and procalcitonin were not measured due to a large proportion of missing values. A significant amount of data is also missing for risk stratification factors related to APE (echocardiography, electrocardiogram, CT - scan, BNP, and TNT). Third, our study may not be generalizable as it was conducted in a single institution in the United States. However, our substantial sample size and representative cohort lend support to our findings. Future prospective studies across multiple centers should help validate our findings. Fourth, we were not able to control for

TABLE 2 Statin use for APE.

	OR of statin use	95% CI	*p* value
Model 1	0.67	0.53–0.83	<0.001
Model 2	0.75	0.6–0.95	<0.001
Model 3	0.76	0.6–0.96	<0.001
Model 4	0.65	0.51–0.82	<0.001
Model 5	0.67	0.52–0.86	<0.001
PSM	0.68	0.52–0.9	0.007

OR, odds ratio; CI, confidence interval; PSM, propensity score matching. Model 1: not adjusted. Model 2: age, sex, BMI. Model 3: Model 2, race, glucose, WBC, PLT, hematocrit. Model 4: Model 3, SOFA score, deep venous thrombosis, ICU stay, aspirin use, oral anticoagulant. Model 5: Model 4, DM, hypertension, malignant cancer, peripheral vascular disease, chronic pulmonary disease, severe liver disease, renal disease, cerebrovascular disease, congestive heart failure.

TABLE 3 Dosage of statin use for APE.

		Model 1		Model 2		PSM		
Variable	N	OR (95%CI)	*p* value	OR (95%CI)	*p* value	N	OR (95%CI)	*p* value
No use	12,196	1 (Ref)		1 (Ref)		4,435	1 (Ref)	
Standard dose	1,866	0.69 (0.5–0.95)	0.022	0.7 (0.5–0.98)	0.038	1,865	0.72 (0.5–1.03)	0.076
High dose	2,571	0.65 (0.49–0.87)	0.003	0.65 (0.48–0.88)	0.005	2,570	0.65 (0.46–0.91)	0.012
Trend test			<0.001		0.002			0.008

APE, acute pulmonary embolism; OR, odds ratio; Ref, Reference; PSM, propensity score matching; CI, confidence interval. Model 1: not adjusted. Model 2: adjusted for age, sex, BMI, race, glucose, WBC, PLT, hematocrit, SOFA score, deep venous thrombosis, ICU stay, aspirin use, oral anticoagulant, DM, hypertension, malignant cancer, peripheral vascular disease, chronic pulmonary disease, severe liver disease, renal disease, cerebrovascular disease and congestive heart failure.

TABLE 4 Statin classifications for APE.

		Model 1		Model 2		PSM		
Variable	N	OR (95%CI)	*p* value	OR (95%CI)	*p* value	N	OR (95%CI)	*p* value
None	12,196	1 (Ref)		1 (Ref)		4,435	1 (Ref)	
Atorvastatin	2,584	0.62 (0.47 ~ 0.83)	0.001	0.62 (0.45 ~ 0.84)	0.002	2,583	0.62 (0.44–0.87)	0.006
Simvastatin	1,220	0.85 (0.6 ~ 1.22)	0.385	0.85 (0.59 ~ 1.23)	0.95	1,220	0.87 (0.59–1.29)	0.488
Others	633	0.48 (0.25 ~ 0.9)	0.022	0.52 (0.27 ~ 1)	0.048	632	0.54 (0.28–1.03)	0.062

APE, acute pulmonary embolism; OR, odds ratio; Ref, Reference; PSM, propensity score matching; CI, confidence interval. Model 1: not adjusted. Model 2: adjusted for age, sex, BMI, race, glucose, WBC, PLT, hematocrit, SOFA score, deep venous thrombosis, ICU stay, aspirin use, oral anticoagulant, DM, hypertension, malignant cancer, peripheral vascular disease, chronic pulmonary disease, severe liver disease, renal disease, cerebrovascular disease and congestive heart failure.

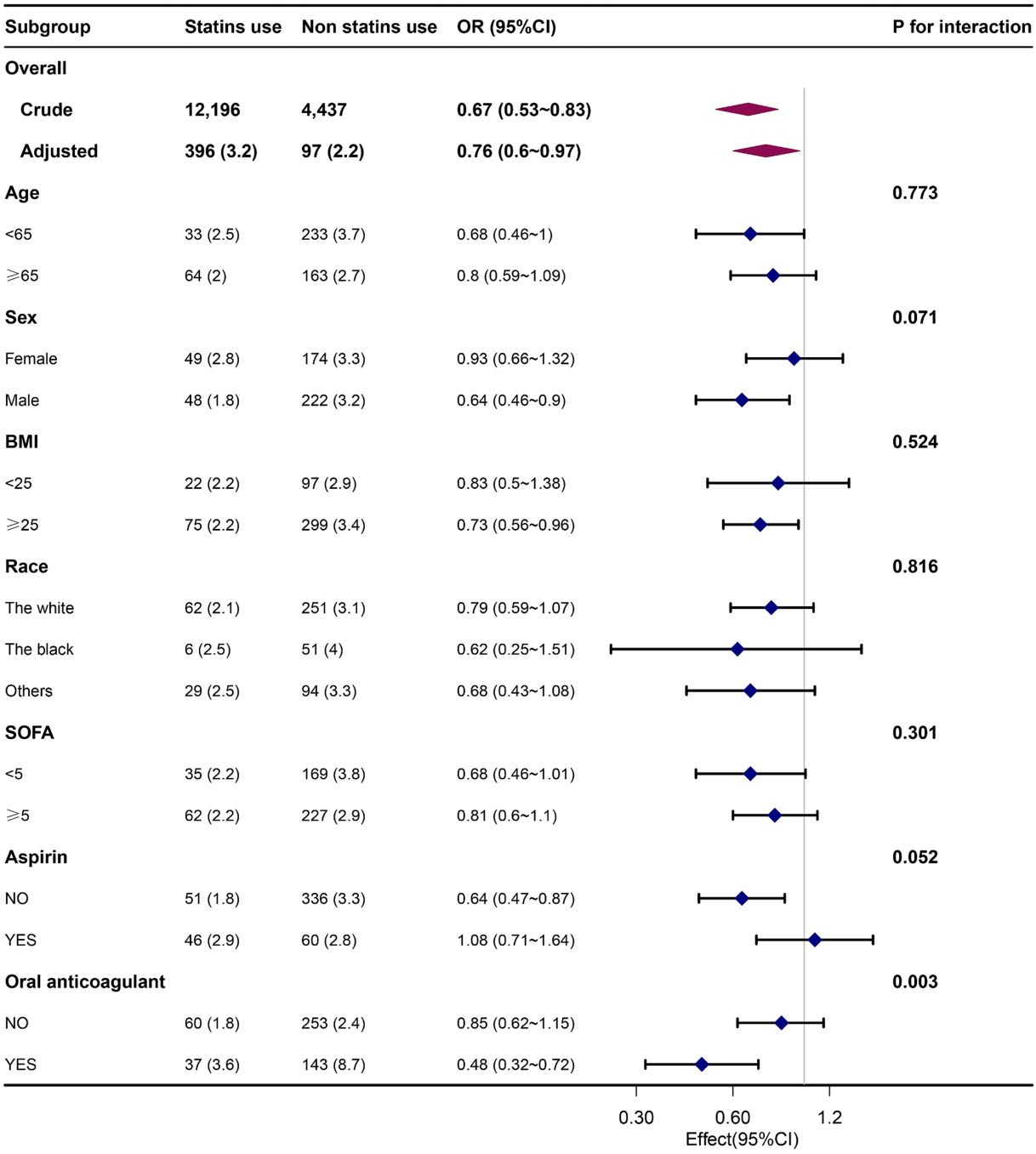

FIGURE 2
Association between statin use and APE by patients' characteristics at baseline. Each stratification was adjusted for all the covariates except the stratification variable itself. OR, odds ratio; BMI, body mass index; SOFA, Sequential Organ Failure Assessment.

several potential confounding variables, such as smoking history, drinking history, hormone use, and other medical histories, which may have influenced the risk of APE in patients with sepsis. Additionally, the retrospective nature of our study prevents us from providing detailed information on the impact of statins on individual patients' lipid levels, such as dosage and duration of use.

Conclusion

The current evidence on the use of statins in sepsis patients shows that statins may reduce the incidence of APE and that they may also have a dose-related anti-APE effect. Nonetheless, there is a need for future randomized controlled trials to validate the claims made in this manuscript.

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 Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

DY: Formal analysis, Investigation, Software, Writing – original draft. YH: Conceptualization, Data curation, Methodology, Supervision, Writing – original draft. QW: Conceptualization, Formal analysis, Investigation, Project administration, Validation, Visualization, Writing – original draft. YY: Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was funded by The National Natural Science Foundation of China (no. 82104989).

Acknowledgments

We thank the Free Statistics team for providing technical assistance and valuable tools for data analysis and visualization. In addition, S-lY especially wishes to thank all members of the team of Clinical Scientists, who have given her powerful spiritual support and encouragement.

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.2024.1369967/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 09 April 2024
DOI 10.3389/fmed.2024.1338061

OPEN ACCESS

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RECEIVED 14 November 2023
ACCEPTED 28 March 2024
PUBLISHED 09 April 2024

CITATION
Cui X, Shi Y, He X, Zhang M, Zhang H, Yang J and Leng Y (2024) Abdominal physical examinations in early stages benefit critically ill patients without primary gastrointestinal diseases: a retrospective cohort study. *Front. Med.* 11:1338061. doi: 10.3389/fmed.2024.1338061

Abdominal physical examinations in early stages benefit critically ill patients without primary gastrointestinal diseases: a retrospective cohort study

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Background: Gastrointestinal (GI) function is critical for patients in intensive care units (ICUs). Whether and how much critically ill patients without GI primary diseases benefit from abdominal physical examinations remains unknown. No evidence from big data supports its possible additive value in outcome prediction.

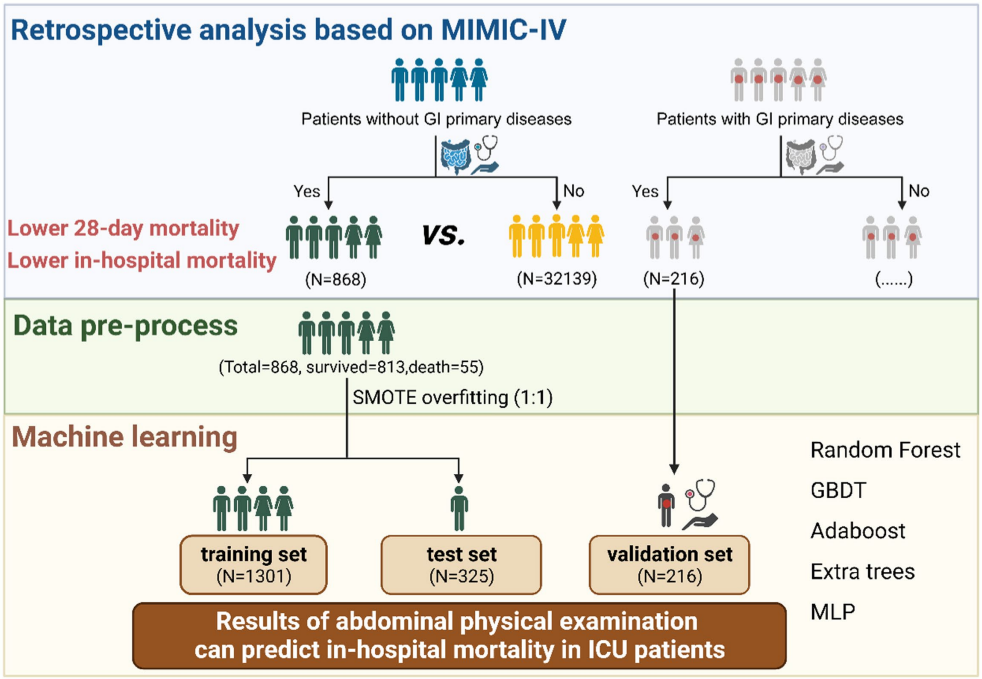
Methods: We performed a big data analysis to confirm the value of abdominal physical examinations in ICU patients without GI primary diseases. Patients were selected from the Medical Information Mart for Intensive Care (MIMIC)-IV database and classified into two groups depending on whether they received abdominal palpation and auscultation. The primary outcome was the 28-day mortality. Statistical approaches included Cox regression, propensity score matching, and inverse probability of treatment weighting. Then, the abdominal physical examination group was randomly divided into the training and testing cohorts in an 8:2 ratio. And patients with GI primary diseases were selected as the validation group. Several machine learning algorithms, including Random Forest, Gradient Boosting Decision Tree, Adaboost, Extra Trees, Bagging, and Multi-Layer Perceptron, were used to develop in-hospital mortality predictive models.

Results: Abdominal physical examinations were performed in 868 (2.63%) of 33,007 patients without primary GI diseases. A significant benefit in terms of 28-day mortality was observed among the abdominal physical examination group (HR 0.75, 95% CI 0.56–0.99; $p = 0.043$), and a higher examination frequency was associated with improved outcomes (HR 0.62, 95%CI 0.40–0.98; $p = 0.042$). Machine learning studies further revealed that abdominal physical examinations were valuable in predicting in-hospital mortality. Considering both model performance and storage space, the Multi-Layer Perceptron model performed the best in predicting mortality (AUC = 0.9548 in the testing set and AUC = 0.9833 in the validation set).

Conclusion: Conducting abdominal physical examinations improves outcomes in critically ill patients without GI primary diseases. The results can be used to predict in-hospital mortality using machine learning algorithms.

KEYWORDS

abdominal physical examination, mortality, machine learning, predictive model, intensive care units



GRAPHICAL ABSTRACT

Introduction

Gastrointestinal (GI) problems are common in intensive care units (ICUs) and are usually associated with poor outcomes in critically care patients (1–3). The GI tract acts as the "motor" of gut-derived sepsis and plays an important role in promoting the progression of multiple organ dysfunctions (MODS) (4–6). Nevertheless, GI dysfunction has not gained considerable attention compared with other organ dysfunctions. Widely used score systems describing patients' conditions in intensive care units (ICUs) have not considered the GI system, such as Sequential Organ Failure Assessment (SOFA) scores and Acute Physiology and Chronic Health Evaluation (APACHE) scores (7, 8).

To emphasize GI dysfunction as a part of MODS and offer a better-scaled system, the Working Group on Abdominal Problems (WGAP) of the European Society of Intensive Care Medicine (ESICM) first proposed a grading system for GI dysfunction in critical illnesses named Acute Gastrointestinal Injury (AGI) (9). The introduction of standardized descriptions of AGI and GI symptoms has markedly promoted the development of related clinical research. The AGI grading system can effectively assess the severity of GI dysfunction and its grade is closely related to clinical outcomes (10–12). The sum of GI symptoms, including vomiting, diarrhea, and GI bleeding, etc., can independently predict all-cause mortality in ICU patients (10, 13). These findings provide clinical evidence for the importance of performing AGI evaluations in the ICU.

For mechanically ventilated and/or sedated patients, it is more difficult to obtain feedback regarding abdominal discomfort. Conducting objective parameter monitoring and abdominal physical examinations are the two options for identifying AGI in the early stages. Intra-abdominal pressure (IAP) is a unique objective indicator for AGI assessment but is not compulsory for all patients in the ICU (14). Intra-abdominal hypertension (IAH) is correlated with poor outcomes, but mild and transient elevation of IAP is "permissible" in certain cases (15). Because of the different perspectives, IAP is mainly measured in patients with GI primary pathology, such as those undergoing abdominal surgery and with GI primary diseases, and relevant data are limited (9, 16). However, evidence has shown that the outcome of patients with secondary AGI is worse than that of patients with primary GI disease (17). This phenomenon indicates that early assessment of GI function should be performed in all patients in the ICU, especially in those without obvious abnormalities at admission.

Abdominal physical examination provides quick information regarding the GI tract and offers assistance for further clinical management in the ICU. Compared with IAP measurements, abdominal physical examinations are simple, economical, and more easily performed by clinicians and nurses. For mechanically ventilated and/or sedated patients, abdominal physical examinations can provide information on GI function and are feasible. A study revealed that clinicians paid the most attention to complaints of bowel distension and bowel sounds in conscious and unconscious patients, respectively (18). Alteration of bowel sounds as a classic abnormal GI sign was reported to be significantly associated with mortality (19). Taken together, the abdominal physical examinations may benefit from following the progression of illness at the bedside, but there is no conclusive evidence to prove its benefit on ICU patient outcomes.

As abdominal physical examinations can reflect illness progression, it is worthy to consider abdominal physical examinations results as a predictor of the model. To date, there's no literature supporting its additive value in outcome prediction. The logistic regression algorithm was the traditional model used in previous clinical research, but underfitting was performed because of the limited sample size and limited variables. In recent decades, machine learning methods, such as Random Forest, Gradient Boosting

Decision Tree, Adaboost, Extra Trees, Bagging, and Multilayer Perceptron algorithms, have been developed and applied successfully in many types of areas (20–24). Machine learning can easily incorporate a large number of variables and improve model accuracy through feature selection, data preprocessing, etc. and has great potential in clinical research and practice.

Therefore, to identify the beneficial effect of abdominal physical examinations for all ICU patients, we first designed a retrospective study of ICU patients without primary GI diseases to clarify the benefit of abdominal physical examinations in patients without GI diseases. Second, to further study its possible additive value for mortality prediction, we tried to develop a prediction model using machine learning in patients without GI diseases, which could be extended to all patients with or without indications for early GI monitoring in the ICU.

Methods

Data source

The data involved in this study were obtained from a large publicly available dataset called the Medical Information Mart for Intensive Care (MIMIC) -IV database, which was developed by the Laboratory for Computational Physiology at MIT. MIMIC-IV (Version 1.0) contains comprehensive data on patients admitted to the critical care units of the Beth Israel Deaconess Medical Center between 2008 and 2019 (25). The study was conducted according to the Reporting of Studies Conducted using Observational Routinely Collected Health Data (RECORD) statement, and was reported in line with the STROCSS criteria (26, 27). One of our authors obtained access to and was responsible for data extraction (certification number 53051604).

Participants

All the patients in MIMIC-IV aged ≥18 years without primary GI diseases (without direct insult to the GI tract and previous history of GI diseases) were enrolled for retrospective analysis and the development of predictive models (9). Among the patients, those who underwent abdominal palpation and auscultation within 48 h after ICU admission were allocated to the abdominal physical examination group, whereas the others were allocated to the no abdominal physical examination group. Adult patients with primary GI diseases who underwent physical examination were also included in the validation of the predictive models. Primary GI diseases were identified according to the International Classification of Diseases 9th Edition (ICD-9) code and the International Classification of Diseases 10th Edition (ICD-10) codes from MIMIC-IV. Patients who spent less than 48 h in the ICU or had missing outcome values were excluded. For those who had multiple admissions to the ICU, only the data from the first ICU admission were included in the analysis.

Variable extraction

Baseline characteristics and abdominal physical examinations within 48 h of ICU admission were extracted using a structured query language (SQL), as shown in Table 1; Supplementary Table S1. Baseline characteristics included age, sex, weight, ICU type, Sequential Organ Failure Assessment (SOFA) score, and Simplified Acute Physiology Score II (SAPS II) score. The SOFA score was calculated as the sum of the maximum values for each sub-score within 24 h of admission. Not only vital signs, including the mean arterial pressure (MAP), heart rate, temperature (°C), and respiratory rate, but also laboratory variables, including white blood cell (WBC) count, hemoglobin, platelet counts, and the content of various elements, including sodium, potassium, chloride, creatinine, and urea nitrogen, which were measured during the first 24 h in the ICU, were selected from the dataset. Moreover, the Charlson comorbidity index and comorbidities including congestive heart failure, cerebrovascular disease, chronic pulmonary disease, liver-related comorbidity, kidney-related comorbidity, and malignancy were extracted. In addition, we extracted the counts of abdominal physical examinations during ICU stay and calculated the average frequency of abdominal physical examinations (ratio of abdominal physical examination counts to the length of ICU stay).

Primary and secondary outcomes

The primary outcome was the 28-day mortality. Secondary outcomes included 60-day and 90-day in-hospital mortality and length of ICU stay (LOS).

Statistical analysis

Continuous variables are presented as means (standard deviations) or medians [interquartile ranges (IQRs)], and categorical variables were presented as total numbers and percentages. Comparisons between groups were made using the Chi-squared test for categorical variables and the t-test or Mann–Whitney *U* test for continuous variables, as appropriate.

The Cox proportional hazards model was used to characterize the relationship between abdominal physical examinations and outcomes. To determine the potential covariates, we first performed a univariate Cox analysis of the baseline data (Table 1). The parameters correlated with 28-day mortality ($p < 0.10$) and clinically judged significant by experts were finally included in the multi-Cox analysis. The covariables were age, gender, ICU admission types of ICU, baseline SAPS II score, SOFA score, Charlson comorbidity index, comorbidities, vital signs (heart rate, mean arterial pressure, respiratory rate, and temperature), and initial laboratory tests (hemoglobin, sodium, potassium, creatinine, and blood urea nitrogen). In addition, given that the effect of GI physical examinations may vary according to the inspection frequency during hospitalization, we also performed an additional analysis to show the association between the average frequency of abdominal physical examinations and mortality outcome.

We conducted propensity score matching (PSM) and inverse probability of treatment weighting (IPTW) analysis to adjust the covariates to reduce the influence of data biases and confounding variables to obtain more reasonable comparisons between the experimental and control groups (28, 29). Thus, a 1:1 nearest neighbor matching with a caliper width of 0.05 was applied in our study.

TABLE 1 Baseline characteristics.

Variables	Original cohort			
	Abdominal physical examination	No abdominal physical examination	*p*	SMD
N	868	32,139		
Age	57.27 (17.92)	65.35 (16.81)	<0.001	0.465
Gender, male (%)	545 (62.80)	18,307 (56.96)	<0.001	0.119
Weight (kg)	81.59 (20.85)	81.68 (25.00)	0.918	0.004
Types of ICU (%)			<0.001	0.585
SICU	212 (24.42)	4,713 (14.66)		
CVICU	209 (24.08)	7,824 (24.34)		
TSICU	200 (23.04)	3,911 (12.17)		
MICU	129 (14.86)	4,850 (15.10)		
MICU/SICU	67 (7.72)	4,303 (13.39)		
CCU	29 (3.34)	3,912 (12.17)		
NICU	22 (2.53)	2,626 (8.17)		
Severity of illness				
SOFA score	3.41 (2.20)	3.56 (2.43)	0.074	0.064
SAPS II score	32.31 (13.43)	35.35 (13.39)	<0.001	0.227
Charlson comorbidity index	4.17 (2.96)	5.47 (2.93)	<0.001	0.439
Comorbidities, n (%)				
Congestive heart failure	129 (14.86)	8,535 (26.56)	<0.001	0.292
Chronic pulmonary disease	172 (19.81)	7,560 (23.52)	0.012	0.090
Cerebrovascular disease	180 (20.74)	5,976 (18.59)	0.012	0.054
Renal disease	92 (10.60)	5,949 (18.51)	<0.001	0.226
Mild liver disease	72 (8.29)	1,834 (5.71)	0.002	0.102
Severe liver disease	21 (2.42)	870 (2.71)	<0.001	0.018
Malignant cancer	62 (7.14)	3,742 (11.64)	<0.001	0.155
Vital signs				
Heart rate (bpm)	84.99 (15.50)	83.81 (15.29)	0.025	0.077
MAP (mmHg)	79.78 (10.28)	78.68 (10.48)	0.002	0.106
Respiratory rate (bpm)	18.92 (3.56)	18.99 (3.63)	0.542	0.021
Temperature (°C)	36.98 (0.47)	36.86 (0.50)	<0.001	0.264
Laboratory tests				
WBC ($\times 10^9$/L)	12.75 (11.55)	12.46 (9.00)	0.352	0.028
Hemoglobin ($\times 10^{12}$/L)	11.35 (2.07)	11.00 (2.08)	<0.001	0.172
Platelets ($\times 10^9$/L)	207.77 (91.82)	203.48 (95.95)	0.194	0.046
Sodium (mmol/L)	138.03 (3.82)	138.38 (4.61)	0.028	0.082
Potassium (mmol/L)	4.13 (0.57)	4.26 (0.59)	<0.001	0.211
Creatinine (mg/dL)	1.17 (1.41)	1.32 (1.41)	0.003	0.104
BUN (mg/dL)	19.25 (16.30)	23.64 (19.13)	<0.001	0.247

SICU, surgical intensive care unit; CVICU, cardiac vascular intensive care unit; TSICU, trauma surgical intensive care unit; MICU, medical intensive care unit; MICU/SICU, medical/surgical intensive care unit; CCU, coronary care unit; NICU, neuro surgical intensive care unit; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; MAP, mean arterial pressure; WBC, white blood cell; BUN, blood urea nitrogen.

Standardized mean differences (SMDs) and *p*-values were calculated to evaluate the effectiveness of PSM and IPTW (30). The baseline characteristics and SMDs of the two groups after PSM and IPTW were shown in Supplementary Tables S2, S3. Moreover, for the matched cohort, we analyzed the long-term prognosis by plotting survival curves and testing the significance of mortality in the sample by Log Rank (Mantel–Cox) methods. After PSM and IPTW, we performed the Cox regression for further analysis.

All statistical analyses were performed with the Jupyter Notebook (Anaconda 3) and RStudio (version 4.2.0). A p-value was taken as statistically significant at $p < 0.05$ (two-sided).

Machine learning methods

To provide specific evidence on the value of abdominal physical examinations in predicting in-hospital mortality in critically ill patients, we performed machine learning studies. The above-mentioned baseline variables, together with the results of abdominal palpation and auscultation were included as predictors. Specifically, the baseline variables included age, gender, ICU admission types of ICU, baseline SAPS II score, SOFA score, Charlson comorbidity index, comorbidities, vital signs (heart rate, mean arterial pressure, respiratory rate, and temperature), and initial laboratory tests (hemoglobin, sodium, potassium, and blood urea nitrogen). Namely, according to whether the examinations were normal (Supplementary Table S1), as long as one of the four items had an abnormal result, it was defined as physically abnormal. Since the data set was imbalanced, where the ratio of surviving patients to deceased patients in the patient data of the abdominal physical examination group was approximately 15, the synthetic minority oversampling technique (SMOTE) algorithm (31), which is an oversampling method, was used to pre-process the data. To validate the model overfitting problem, the data of the validation group were left unprocessed to retain their imbalance characteristics, and the performance of the trained machine learning model on the imbalanced data set was observed and evaluated. The patient data of the abdominal physical examination group was randomly divided, of which 80% was used as the training set and 20% as the testing set. In addition, to verify the models' accuracy, robustness, and generalizability, excluded patients with primary GI diseases were selected to test the models as a validation group. For the machine learning classification algorithms, Random Forest, Gradient Boosting Decision Tree (GBDT), Adaboost, Extra Trees, Bagging, and Multilayer Perceptron (MLP) were applied. During training, the model was first optimized for a single parameter. According to the change trend results of each parameter and model performance, the grid optimization search algorithm was used to optimize the multi-parameter overall model, and the final predictive model was obtained. Accuracy, precision, recall, F1-score, and area-under-curve (AUC) were selected to evaluate the performance of algorithms.

Results

Study population and the baseline characteristics

According to the exclusion and inclusion criteria, 33,007 patients without primary GI diseases were enrolled. The study population was shown in Figure 1. Among them, 868 patients (2.63%) underwent bedside abdominal physical examinations in the first 48 h after ICU admission, while the remaining 32,139 patients did not. A retrospective analysis was performed for both groups. Multivariate Cox regression, PSM, IPTW were used to demonstrate the benefit of performing abdominal physical examinations for patients without indications by balancing the confounding factors. To further investigate the potential additive value of abdominal examinations in predicting mortality for all ICU patients, we tried to develop a prediction model using machine learning in patients without GI diseases. The abdominal physical examination group ($N = 868$) was used for model development, and 216 patients with GI primary diseases were used for model validation.

Table 1 showed the baseline characteristics between the groups with and without abdominal physical examination groups. Patients in the SICU (24.42% vs. 14.66%) and TSICU (23.04% vs. 12.17%) received more attention on GI function. The abdominal physical examination group had lower SAPS II scores on admission [32.31(±13.43) vs. 35.35(±13.39); $p < 0.001$] and had a lower Charlson comorbidity index [4.17 (2.96) vs. 5.47 (2.93)] and fewer comorbidities overall.

Application of abdominal physical examinations improved the primary outcome

To clarify the association between the application of abdominal physical examinations and the 28-day mortality, we used the multivariate Cox proportional hazard model. The results demonstrated a significant beneficial effect of bedside abdominal physical examinations on 28-day mortality (Table 2), with a hazard ratio (HR) of 0.75 (95%CI 0.56–0.99; $p = 0.043$). The PSM analysis generated 813 pairs. The imbalance in covariates between the two groups was significantly reduced after PSM (Supplementary Table S2), and the

TABLE 2 Primary and secondary outcomes analysis with three different statistical methods.

Outcomes	HR	CI of HR		p
		2.5%	97.5%	
*Cox regression**				
28-day mortality	0.75	0.56	0.99	0.043
60-day mortality	0.74	0.57	0.97	0.032
90-day mortality	0.74	0.56	0.96	0.025
In-hospital mortality	0.75	0.56	0.99	0.034
PSM + Cox regression				
28-day mortality	0.62	0.42	0.92	0.017
60-day mortality	0.59	0.40	0.85	0.005
90-day mortality	0.59	0.41	0.85	0.005
In-hospital mortality	0.62	0.42	0.92	0.017
IPTW + Cox regression				
28-day mortality	0.65	0.43	0.98	0.042
60-day mortality	0.65	0.43	0.98	0.042
90-day mortality	0.65	0.44	0.96	0.031
In-hospital mortality	0.65	0.43	0.98	0.005

*Covariables included age, gender, ICU admission types of ICU, baseline SAPS II score, SOFA score, Charlson comorbidity index, vital signs (heart rate, mean arterial pressure, respiratory rate, and temperature), and initial laboratory tests (hemoglobin, sodium, potassium, creatinine, and blood urea nitrogen). PSM, propensity score matching; IPTW, inverse probability of treatment weight; HR, hazard ratio; CI: confidence interval.

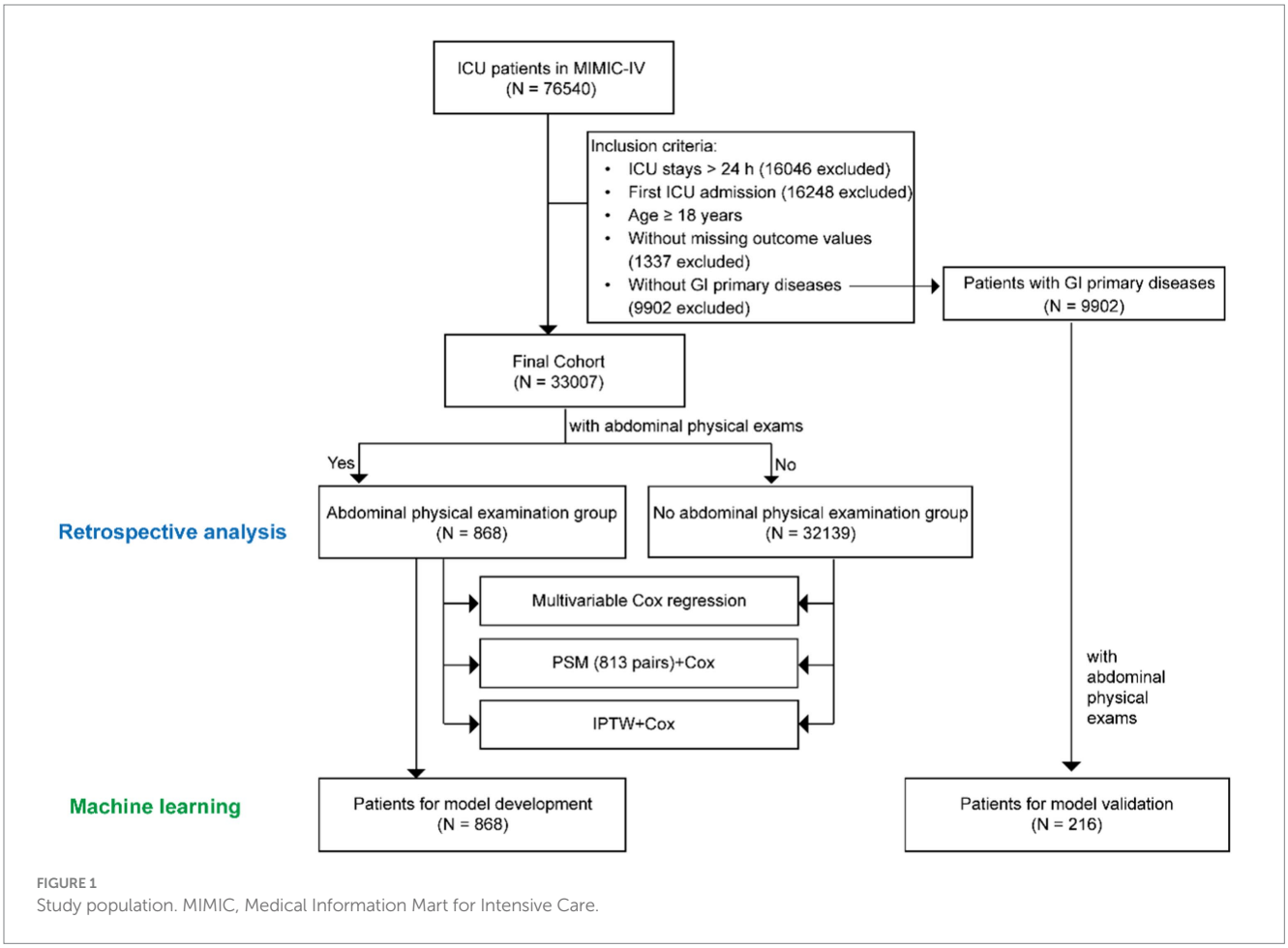


FIGURE 1
Study population. MIMIC, Medical Information Mart for Intensive Care.

TABLE 3 Association of average frequency of abdominal physical examinations during ICU and outcomes.

Outcomes	HR	CI of HR		*p*
		2.5%	97.5%	
Primary outcomes				
28-day mortality	0.62	0.40	0.98	0.042
Secondary outcomes				
60-day mortality	0.61	0.39	0.94	0.025
90-day mortality	0.60	0.39	0.92	0.020
In-hospital mortality	0.63	0.41	0.99	0.044

Average frequency of abdominal physical examinations = counts of abdominal physical examinations during ICU stays/length of ICU stays. Covariables included age, gender, ICU admission types of ICU, baseline SAPS II score, SOFA score, Charlson comorbidity index, vital signs (heart rate, mean arterial pressure, respiratory rate, and temperature), and initial laboratory tests (hemoglobin, sodium, potassium, creatinine, and blood urea nitrogen).

association remained robust (Table 2). The application of abdominal physical examinations was associated with improved 28-day mortality after PSM (HR 0.62, 95% CI 0.62–0.92; $p = 0.017$) and IPTW (HR 0.65, 95% CI 0.43–0.98; $p = 0.042$).

We also conducted an additional study to evaluate the association between the average frequency of abdominal physical examinations and outcomes (Table 3). In the abdominal physical examination group, the average frequency of abdominal physical examinations was 0.89 counts/day (IQR 0.49–1.61 counts/day). And the multivariate Cox model showed a significant beneficial effect of more abdominal physical examinations on 28-day mortality (HR 0.62, 95% CI 0.40–0.98; $p = 0.042$).

Analyses showed a beneficial effect of the application of bedside abdominal physical examination in terms of 28-day mortality, and the higher average frequency of examinations was associated with lower 28-day mortality.

Application of abdominal physical examinations to improved secondary outcomes

The application of abdominal physical examinations was also investigated for 60-day, 90-day, and in-hospital mortality (Table 2). The results showed that performing bedside abdominal physical examinations associated with improved 60-day mortality (HR 0.74, 95% CI 0.57–0.97; $p = 0.032$), 90-day mortality (HR 0.74, 95% CI 0.57–0.96; $p = 0.025$), and in-hospital mortality (HR 0.75, 95% CI 0.56–0.99; $p = 0.034$). The PSM model and IPTW model led to the same conclusion. Furthermore, the more average frequency was associated with lower 60-day (HR 0.61, 95% CI 0.39–0.94; $p = 0.025$), 90-day (HR 0.60, 95% CI 0.39–0.92; $p = 0.020$), and in-hospital mortality (HR 0.63, 95% CI 0.41–0.99; $p = 0.44$) (Table 3). After PSM, the Kaplan–Meier (KM) survival curve indicated the abdominal

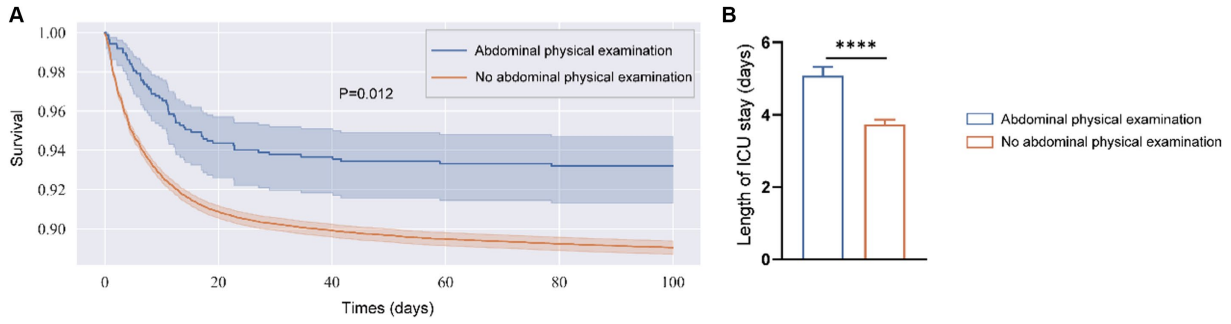


FIGURE 2
Kaplan–Meier survival curve **(A)** and length of stay in ICU **(B)** for two groups after PSM. **(A)** Shaded regions are 95% confidence intervals. **(B)** Was determined by unpaired *t*-test and data were shown in mean + SEM. ****$p < 0.001$.

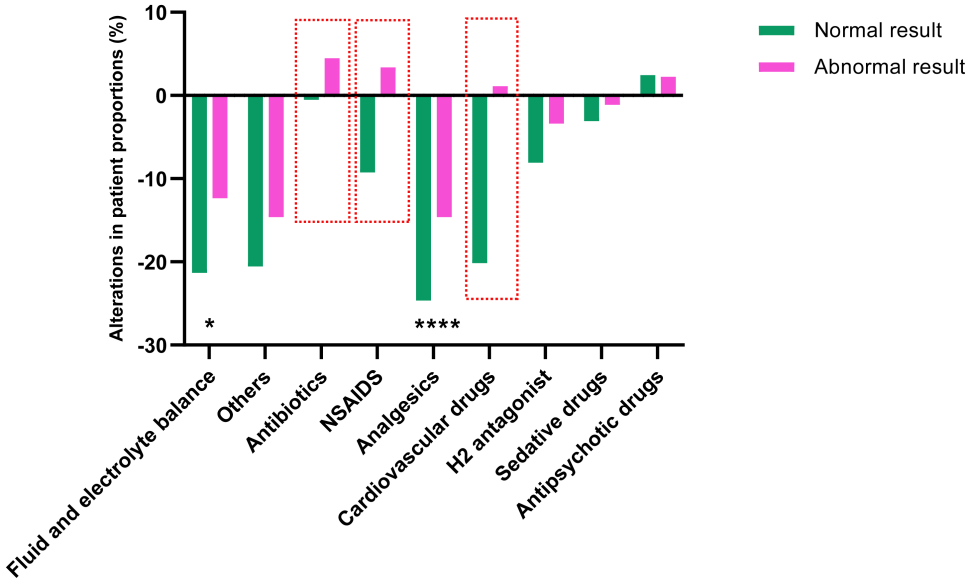


FIGURE 3
The alteration of following interventions after abdominal physical examinations. The height and the direction of the bars represent the differences of the proportion of patients taking representative drugs. Comparisons between groups were made using the chi-squared test. The red boxes indicate the drug with the most significant differences between the two groups. *$p < 0.05$ and ****$p < 0.001$.

physical examinations had a beneficial effect on the increased survival time (Figure 2). In addition, although the abdominal physical examination group had lower severity scores (Table 1), patients had longer lengths of stay in the ICU (Figure 2), which might be attributed to more care/treatment from clinicians.

The alterations of the following interventions based on the abdominal physical examinations results

To investigate how abdominal physical examinations affected subsequent therapeutic strategies, we compared the alteration of interventions after performing examinations (within 48 h), which might be directly related with the results of examination. We found that among the 868 detected patients, the examination results of 89 patients were abnormal, and the examination results of 779 patients were normal. Patients (%) with antibiotics, NSAIDs, and cardiovascular drugs were increased in the Abnormal result group, while decreased in the Normal result group after examination. This could be due to the abnormal results indicating the occurrence of abdominal infection or GI dysfunction. Clinicians attempt to control abdominal infection, relief pain and improve GI blood perfusion by antibiotics, NSAIDs and cardiovascular drugs. In addition, although all the patients (%) receiving fluid and electrolyte management and analgesics decreased, the proportion of patients in the Normal result group decreased significantly compared to that in the Abnormal result group. This suggests that when the results indicate abnormality, the clinicians should pay more attention on the fluids and electrolytes management and pain management (see Figure 3).

TABLE 4 Evaluation of machine learning algorithms.

Model	Test set					Validation set				
	Accuracy	Precision	Recall	F1-Score	AUC	Accuracy	Precision	Recall	F1-Score	AUC
Random Forest	0.95	0.99 (0) 0.90 (1)	0.91 (0) 0.99 (1)	0.95 (0) 0.94 (1)	0.9514	0.95	1.00 (0) 0.90 (1)	0.91 (0) 1.00 (1)	0.95 (0) 0.95 (1)	0.9901
GBDT	0.92	0.97 (0) 0.87 (1)	0.88 (0) 0.97 (1)	0.93 (0) 0.92 (1)	0.9270	0.95	0.99 (0) 0.91 (1)	0.92 (0) 0.99 (1)	0.96 (0) 0.95 (1)	0.9913
Adaboost	0.93	0.98 (0) 0.87 (1)	0.88 (0) 0.98 (1)	0.93 (0) 0.92 (1)	0.9304	0.93	0.98 (0) 0.87 (1)	0.88 (0) 0.98 (1)	0.93 (0) 0.92 (1)	0.9079
Extra Trees	0.92	0.96 (0) 0.88 (1)	0.89 (0) 0.96 (1)	0.93 (0) 0.92 (1)	0.9258	0.92	0.96 (0) 0.88 (1)	0.89 (0) 0.96 (1)	0.93 (0) 0.92 (1)	0.9517
Bagging	0.92	0.99 (0) 0.85 (1)	0.86 (0) 0.99 (1)	0.92 (0) 0.91 (1)	0.9225	0.92	0.99 (0) 0.85 (1)	0.86 (0) 0.99 (1)	0.92 (0) 0.91 (1)	0.9752
MLP	0.95	1.00 (0) 0.90 (1)	0.91 (0) 1.00 (1)	0.95 (0) 0.95 (1)	0.9548	0.95	1.00 (0) 0.90 (1)	0.91 (0) 1.00 (1)	0.95 (0) 0.95 (1)	0.9833

*GBDT, gradient boosting decision tree; MLP, multilayer perceptron.

Development and validation of in-hospital mortality predictive models based on the results of abdominal physical examinations

Data from the abdominal physical examination group was used to develop in-hospital mortality prediction models. The data was highly imbalanced in terms of mortality (survived = 813, death = 55). To achieve better prediction accuracy on such a data set, we used SMOTE overfitting (1:1) to pre-process the patient data in the abdominal physical examination group, while leaving the validation set data unprocessed. Ultimately, data from a total of 1,626 patients without GI primary diseases (survived = 813) were randomly divided into the training set for modeling and the testing set for validation in the ratio of 8:2. Then, the performance of the model was evaluated with the validation set data ($n = 216$, survived = 181). The final results of the testing set and the validation set attained with these models (Random Forest, XGBoost, Adaboost, Extra Trees, Bagging, MLP) an illustrated in Table 4. Supplementary Figures S1, S2 showed the receiver operating characteristic (ROC) curves of the models in the testing cohort and the validation cohort. The random forest model and the MLP model performed well in predicting in-hospital mortality, with AUC values of 0.9514 and 0.9548 in the testing set, and 0.9901 and 0.9833 in the validation set, respectively. But the MLP model had less storage space than the random forest, with only 151 kB (Supplementary Table S4). Taking model performance and storage space, the MLP model performed best.

Discussion

In our study, we demonstrated that the application of bedside abdominal physical examinations in patients without original GI causes was associated with significantly lower 28-day, 60-day, 90-day and in-hospital mortality. And this beneficial effect was associated with a higher frequency of examination. After the adjustment of confounding factors, the results were found to be robust. Therefore, we used machine learning methods to develop a model for the abdominal physical examination group without GI primary diseases to predict mortality and validated the robustness and extensibility of the model in patients with GI primary disease. Analysis results show that performing abdominal physical examinations within 48 h is valuable in improving patient outcomes, especially for those without GI primary diseases. Machine learning using physically examined results can be used to predict in-hospital mortality in critically ill patients.

Gut protection in ICUs has recently gained considerable attention. Whether GI evaluation should be added to the scoring system, such as the SOFA, has been widely discussed (13, 19). In 2013, Reintam Blaser et al. (19) showed that the appearance of GI symptoms during the first week in the ICU was associated with poor outcomes in patients requiring mechanical ventilation, among which absent bowel sounds and GI bleeding showed the most significant association with the 28-day mortality. But due to missing data and unclear definitions, they could not develop a more accurate scoring system with GI symptoms on the admission day compared with the SOFA score (AUROC: 0.706 vs. 0.703). In 2019, Padar et al. (13) conducted a retrospective study to describe the incidence and outcome of GI failure and tried to evaluate the feasibility of adding GI-variable to the SOFA score. They found that approximately 10% of ICU patients (413/3,959) had GI failure on the first day, which was accompanied by longer ICU stays and higher mortality. The number of GI symptoms on ICU admission can independently predict mortality, similar to other SOFA sub-scores. When combined with the SOFA score, a higher number of GI symptoms increased the accuracy of the former as a predictor. These findings reveal that GI evaluation is important for patients in the ICU. The present study further strengthens the credibility of the evidence through big data analysis and machine learning-based modeling.

To objectively evaluate GI function is difficult in ICU, although the concept of AGI has been defined (16). As Deane et al. (32)

discussed in their review, classic bedside examinations of bowel sounds and abdominal distension were important for initiating enteral nutrition in critically ill patients. In our study, we further extended their findings and found that early assessment of GI function through abdominal palpation and auscultation is helpful in achieving excellent performance in mortality prediction.

It should be noted that, new non-invasive, objective, sensitive, and explainable technologies can be anticipated. Although abdominal physical examinations were considered in the proposed predictive models, more objective, reproducible, non-invasive, and sensitive examinations for GI function are needed in the ICU. The assessment of GI symptoms and signs can be made more precise with artificial intelligence. For example, bowel sounds were considered in our study, but analysis of bowel sounds is subjective. Combined with acoustic signal processing techniques and machine learning methods, bowel sound detection and analysis will be more automatic and objective (33, 34). We developed equipment that can detect bowel sounds and intra-abdominal pressure in a sensitive, real-time, and non-invasive manner (35). It is believed that more intelligent, real-time, and non-invasive methods have promising demands for GI function examinations in the ICU. On the other hand, the underlying pathophysiology of GI failure is complicated, and the relevant monitoring technologies are limited (36, 37). Magnetoenterography is a non-invasive technique that detects gastrointestinal magnetic signals. It has high sensitivity, and a high signal-to-noise ratio compared with electrogastrography and electrointestinography, and has been used for mesenteric ischemia and damage to the intestinal microstructure (38–40).

Several limitations in this study should be noted. First, the examinations may affect the subsequent interventions and further influence the outcome. We did not make a robust causal inference between abdominal physical exams and prognosis. Advanced statistical approaches like marginal structural models may be useful for revealing causal relationships (41). Future studies need to take this into account. Second, our research is an observational study. More relevant and persuasive clinical trials are the gold standard for causal inference and required to confirm our findings and conclusions. Third, our study is a retrospective cohort study based on electronic health records (EHRs). Manually error records are unavoidable. Fourth, the items about abdominal physical examinations chosen from the MIMIC database were not based on objective observation, and the involved symptoms and signs are subjective. Fifth, given that application of abdominal physical examinations can improve outcomes, future studies are still needed to prove whether IAP measurement is necessary to become routine. Besides, our results were merely based on the MIMIC-IV database, and we did not perform external validation of our predictive model. It should be pointed out that if an external validation is carried out, the results will be more solid. In the future, it is necessary to conduct multi-center clinical studies to demonstrate the reliability of our conclusions and predictive models.

Despite these limitations, it can be observed that performing abdominal physical examinations can improve outcomes and results can predict mortality as part of predictors in ICU patients. The use of physical exams is better than abandoning routine assessment for GI function. Since the assessment of GI function remains indispensable to evaluating patients' outcomes, future assessment score systems should include the GI system.

In conclusion, big data analysis on the MIMIC-IV database shows that patients without GI primary diseases could benefit from abdominal physical examinations, which highlights the essential role of the GI system in MODS. The predictive model with machine learning algorithms based on the results of abdominal physical examinations can effectively predict the mortality and be extended to all ICU patients, which has important and practical meaning in ICU. More objective, non-invasive, and sensitive tools for GI standardized assessment are expected to be developed.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

XC: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft. YS: Data curation, Investigation, Methodology, Software, Validation, Visualization, Writing – original draft. XH: Data curation, Visualization, Writing – original draft. MZ: Data curation, Methodology, Resources, Software, Writing – original draft. HZ: Methodology, Writing – review & editing. JY: Conceptualization, Methodology, Resources, Supervision, Writing – review & editing. YL: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The protocol was financially supported by the National Natural Science Foundation of China (Grant nos. 82172126 and 82372219), Natural Science Foundation of Beijing Municipality (Grant no. 7232215), the special fund of the Beijing Clinical Key Specialty Construction Program, P. R. China (2021) and Peking University Third Hospital (Grant no. BYSYZD2022010).

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.2024.1338061/full#supplementary-material

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Glossary

GI	Gastrointestinal
MODS	Multiple organ dysfunctions
ICU	Intensive care units
SOFA	Sequential Organ Failure Assessment
APACHE	Acute Physiology and Chronic Health Evaluation
WGAP	Working Group on Abdominal Problems
ESICM	European Society of Intensive Care Medicine
AGI	Acute gastrointestinal injury
MIMIC	Medical Information Mart for Intensive Care
ICD-9	International Classification of Diseases 9th Edition
ICD-10	International Classification of Diseases 10th Edition
SQL	Structured query language
SAPS II	The Simplified Acute Physiology Score II
MAP	Mean arterial pressure
WBC	White blood cells
LOS	Length of ICU stay
IQRs	Interquartile ranges
PSM	Propensity score matching
IPTW	Inverse probability of treatment weighting
SMDs	Standardized mean differences
GBDT	Gradient Boosting Decision Tree
MLP	Multilayer Perceptron
ROC	Receiver operating characteristic curve
AUC	Area-under-curve
SICU	Surgical intensive care unit
CVICU	Cardiac vascular intensive care unit
TSICU	Trauma surgical intensive care unit
MICU	Medical intensive care unit
MICU/SICU	Medical/surgical intensive care unit
CCU	Coronary care unit
NICU	Neuro surgical intensive care unit
BUN	Blood urea nitrogen
HR	Hazard ratio
CI	Confidence interval
PPI	Proton pump inhibitors
NSAIDS	Nonsteroidal anti-inflammatory drugs
CRRT	Continuous renal replacement therapy

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 09 April 2024
DOI 10.3389/fmed.2024.1344160

OPEN ACCESS

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RECEIVED 25 November 2023
ACCEPTED 26 March 2024
PUBLISHED 09 April 2024

CITATION
Xu J, Jian J, Zhang Y, Wu J and Qiu Y (2024) The efficacy of nasal administration of esketamine in patients having moderate-to-severe pain after preoperative CT-guided needle localization: a randomized, double-blind, placebo-controlled trial.
Front. Med. 11:1344160.
doi: 10.3389/fmed.2024.1344160

The efficacy of nasal administration of esketamine in patients having moderate-to-severe pain after preoperative CT-guided needle localization: a randomized, double-blind, placebo-controlled trial

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Background: Whether nasal administration of esketamine can provide effective analgesia is unclear in patients with acute pain after preoperative CT-guided needle localization.

Methods: In this double-blind, randomized, placebo-controlled trial, patients were assigned to receive either nasal administration of esketamine (0.3mg/kg or 0.5mg/kg) or saline (identical in appearance to esketamine) when they had visual analog scale (VAS) pain scores >3/10 during deep breathing after preoperative CT-guided needle localization. The primary outcome was the percentage of patients with satisfactory pain relief, which was defined as VAS pain scores ≤3/10 measured 15min after intranasal of esketamine or saline. Secondary outcomes included VAS measured following esketamine or saline, the incidence and cumulative dose of rescue hydromorphone use, and related adverse events.

Results: A total of 90 patients were included in the final analysis. Following intranasal treatment, the percentage of patients with satisfactory pain relief was 16.7% (5/30) in the saline group, 56.7% (17/30) in the 0.3 mg/kg esketamine group, and 53.3% (16/30) in the 0.5 mg/kg esketamine group ($p = 0.002$). The median VAS during deep breathing was less after the intranasal administration of esketamine {median (IQR), 3 (3, 5) in 0.3 mg/kg or 0.5 mg/kg esketamine compared to the saline group [5 (4, 6)], $p = 0.009$}. The incidence of rescue hydromorphone use was detected less in the esketamine group compared to the saline group (43.3% in the 0.3 mg/kg esketamine group, 36.7% in the 0.5 mg/kg esketamine group, and 73.3% in the saline group, $p = 0.010$). The adverse events were similar among the three groups ($p > 0.05$).

Conclusion: Intranasal administration of esketamine is easier and more effective in alleviating acute pain in patients after preoperative CT-guided needle localization without significant adverse effects.

KEYWORDS

pain, analgesia, pulmonary nodules, localization, video-assisted thoracoscopic surgery

1 Introduction

Low-dose computed tomography has detected millions of small pulmonary nodules (SPNs) and a substantial number of SPNs require resection by video-assisted thoracic surgery (VATS) (1). SPNs are difficult to palpate and finding a SPN during VATS without guidance can be fraught (2). Preoperative CT-guided needle localization can accurately localize SPNs prior to VATS, but needle localization may lead to substantial acute pain (3, 4). Our prospective observational study found that 50.8% of the patients had a visual analog scale (VAS) pain score ≥ 4 during deep breathing after preoperative needle localization (3). Consistently, another study showed that the localization-related pain score could reach 4.7 ± 1.6 (4). The substantial pain due to the rigid wire remaining in place would persist until surgical resection and it might greatly aggravate patients' anxiety or fear prior to VATS (4, 5). Implementation of effective therapies is vital to solving this pain and enhancing patients' satisfaction.

Several analgesic medications or regional blocks may alleviate the pain severity but they may also increase the burden of medical personnel resources, especially in developing countries. Finding a resource-less, relatively safe, and pain-sparing method is challenging for thoracic anesthesiologists. Ketamine, the N-methyl-D-aspartate receptor antagonist, is a potent analgesic without significant respiratory depression. Esketamine, the S-(+)-isomer of ketamine [S-(+)-K], has twice the analgesic potency compared to ketamine but with less psychomimetic side effects (6–8). The intranasal spray of esketamine has been approved by FDA in treatment-resistant depression (9, 10), but the analgesic feature of the intranasal spray of esketamine on acute pain has yet to be clarified. A previous study found that the intranasal spray of esketamine with midazolam was similar in effectiveness compared to standard morphine patient-controlled analgesia in the postoperative setting (11). Nonetheless, whether intranasal spray of esketamine alone could produce analgesic efficacy remains to be illustrated in patients after CT-guided needle localization.

Esketamine for intranasal delivery may provide more favorable mucosal absorption because of its relatively low molecular weight (12). The increased bioavailability of intranasal delivery may also lower the doses administered and thereby limit the adverse psychomimetic effects (13). Moreover, intranasal delivery of esketamine would circumvent the limitations associated with intravenous routes. Previous studies showed that esketamine's effect was driven by its pharmacokinetics (14) and intranasal esketamine in patients with treatment-resistant depression existed in a dose-dependent manner (15). Whether intranasal administration of esketamine may have an ascending dose-dependent effect on acute pain remains controversial (15, 16).

In this study, we aimed to investigate whether intranasal administration of esketamine provides analgesia in patients receiving CT-guided needle localization. Specifically, we tested the primary hypothesis that the intranasal administration of esketamine increases the percentage of patients with satisfactory pain relief after CT-guided needle localization; Second, we tested the hypothesis that the intranasal administration of esketamine reduces the pain score, decreases the use of rescue analgesics, and does not increase adverse effects.

2 Materials and methods

2.1 Ethics and registration

This study protocol was approved by the Shanghai Chest Hospital Institutional Review Board (IRB IS22033), and written informed consent was obtained from each patient. This trial was registered before subject enrolment began at the Chinese Clinical Trial Registry (ChiCTR2200061734; principal investigator, Yuwei Qiu; date of registration, 1 July 2022).

2.2 Study design and participants

We conducted this randomized, controlled, and double-blinded clinical trial at Shanghai Chest Hospital. Eligible patients were between 18 and 75 years old, had an American Society of Anesthesiologists (ASA) physical status of I–III and body mass index between 18 and 30 kg/m^2, diagnosed with SPNs requiring preoperative CT-guided needle localization, and had VAS pain score exceeding 3/10 during deep breathing after needle localization. Patients were excluded if they had clinically significant cardiovascular diseases, were unable to perform VAS, had chronic pain, including herpes zoster around chest regions and complex regional pain syndrome, or took opioids in the last month. Patients who had undergone previous thoracic surgeries were also excluded in case they might have neuropathic pain or intercostal nerve damage.

2.3 Randomization and masking

On the surgical day, the patients were admitted to the CT room for needle localization. After sterile prep and drape of the patient, 1% lidocaine was injected at the site of needle insertion by the radiologists. A Hawkins III Hardwire breast localization needle (20-gage, 12.5 cm in length) was then inserted through the chest wall and advanced to approach the small nodules.

Ten minutes after CT-guided needle localization, an investigating researcher assessed pain intensity using a 10 cm VAS (0 cm = no pain and 10 cm = worst imaginable pain) in the pre-anesthesia room. When VAS exceeded 3/10 cm during deep breathing, patients were randomized into one of the three groups using a set of computer-generated random numbers kept in sealed envelopes by an investigator not involved in clinical care. Envelopes were opened shortly before the medications were given to keep allocation concealed as long as practical. The three groups were: (1) intranasal spray of saline placebo; (2) intranasal spray of 0.3 mg/kg esketamine (Esketamine, Hengrui Medicine Co., Ltd., Jiangsu, China). 50 mg/2 mL; and (3) intranasal spray of 0.5 mg/kg esketamine. The pain assessors on site and patients were not informed of their group assignments.

2.4 Study drug and administration

An independent investigator was in charge of the medication preparation according to the random sequence. Study medication was provided in a disposable nasal spray device containing 1–2 mL of

either esketamine or placebo (i.e., 10–15 sprays, 100 μL/per spray, Figure 1). To maintain blinding, the placebo (intranasal solution of saline) was prepared identical in appearance to esketamine. After the patients signed the written informed consent, they were given esketamine or saline placebo into each nostril at different points, each separated by 10 s.

2.5 Outcome assessments

Analgesic efficacy was assessed at 5 min, 10 min, and 15 min after esketamine or saline was given, using VAS, by the pain assessors who were blinded to group assignments. The primary outcome was the percentage of patients with satisfactory pain relief, which was defined as VAS pain scores ≤3/10 during deep breathing measured 15 min after intranasal of esketamine or saline. If VAS pain scores still exceeded 3/10 at 15 min after nasal spray, the nurses started to establish intravenous access, and rescue hydromorphone was given from 0.5 mg to 2 mg at intervals until VAS ≤ 3. Then, adverse effects were assessed at 5 min after hydromorphone use.

Secondary outcomes included the VAS pain score, incidence and cumulative dose of hydromorphone use, and adverse events. Adverse events included dizziness, over-sedation, hallucinations, nausea, vomiting, confusion and disorientation, and rashes during the 15-min period after study medication was given. Sedation is assessed by the Richmond Agitation Sedation Scale (RASS) (17), which is a 10-point scale from −5 to +4, with −5 denoting not responding to voice or physical stimulation and + 4 denoting combative or violent. We also assessed the pain intensity in the post-anesthesia care unit (PACU).

FIGURE 1
Nasal spray device. Study medication was provided in a disposable nasal spray device containing 1–2 mL of solution.

2.6 Statistical analysis

2.6.1 Sample size estimation

We conducted a pilot study and found the percentage of patients having VAS pain score ≥ 3/10 was 60% in 0.3 mg/kg esketamine nasal administration (6/10) and 80% in saline placebo (8/10), respectively. Accounting for the potential dose-dependent profile, we assumed that increasing the dose to 0.5 mg/kg may further reduce the percentage of moderate-to-severe pain to 30%. The effect size was then calculated as 0.41 by PASS 15.0, and a sample size of 75 patients had 90% power to detect a 5% two-sided significance. To account for 10% of dropouts, we increased the sample size to 90 (30 subjects per group).

2.6.2 Data analysis

Continuous or discrete data were described using mean and standard deviation (SD) or median and 25th and 75th quartiles. Categorical data were described using numbers and percentages.

Kolmogorov–Smirnov test was used to test whether the continuous variables met the normal distribution. F-test was used to compare the effects on normally distributed continuous outcomes. Otherwise, the Mann–Whitney U-test was used when continuous outcomes or data were skewed or met the non-normal distribution.

Primary efficacy analyses were performed in the intention-to-treat population of all randomized patients. The percentage of moderate-to-severe pain, adverse events, and hydromorphone use was compared between the three groups using $\chi 2$ test or Fisher's exact test. Each median score of VAS before the nasal administration and 5 min, 10 min, and 15 min after the nasal administration was compared using the Mann–Whitney U-test.

Statistical analyses were performed with SPSS (version 25, IBM Statistics, United States). All reported p-values were two-sided, and a p-value under 0.05 was considered statistically significant.

3 Results

3.1 Patients

From 5 May 2022 to 20 December 2022, we screened a total of 211 patients diagnosed with SPNs requiring preoperative CT-guided needle localization. Finally, 90 patients with VAS exceeding 3/10 during deep breathing after needle localization were randomly assigned to receive either of the intended interventions. All 90 patients were included in the final analysis (Figure 2). Patient characteristics are summarized in Table 1. The mean age was 54 (SD = 12) years and 71.1% were female. Baseline characteristics and needle-location data were comparable between groups (Table 1).

3.2 Primary outcome

Before the nasal administration of study drugs, VAS during deep breathing was 5 [5,7] in the saline group, 5.5 [5,7] in the 0.3 mg/kg esketamine group, and 5 [4,7] in the 0.5 mg/kg esketamine group, respectively ($p > 0.05$, Table 1). After nasal administration of 0.3 mg/kg or 0.5 mg/kg esketamine, pain intensity reduced in a time-dependent manner ($p = 0.05$, Table 2). At 15 min after the nasal administration of study drugs, the percentage of patients having VAS

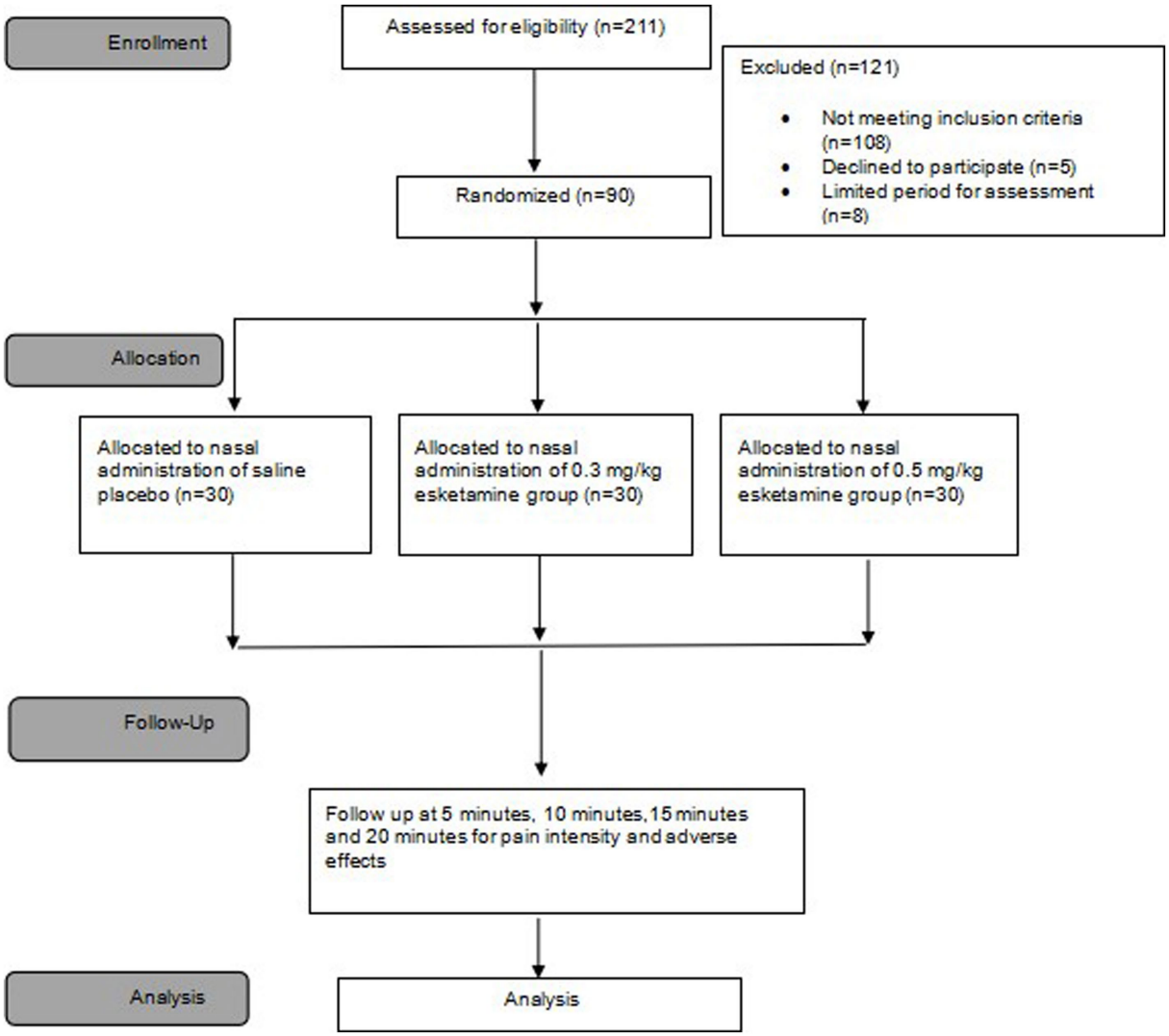

FIGURE 2
Flow diagram of subjects' recruitment and treatment.

exceeding 3/10 during deep breathing was 83.3% in the saline group, 43.3% in the 0.3 mg/kg esketamine group, and 46.7% in the 0.5 mg/kg esketamine group, respectively ($p = 0.002$, Table 2).

3.3 Secondary outcomes

Both doses of nasal esketamine reduced the pain intensity compared to saline placebo (Table 2). The median VAS during deep breathing was significantly less in nasal esketamine groups than in saline placebo at 15 min after administration ($p = 0.009$, Table 2), but the pain scores did not differ between the two doses of esketamine ($p > 0.05$, Table 2).

Patients given either nasal esketamine or rescue hydromorphone had less use of rescue hydromorphone than the saline group, with 73.3% (22/30) in the saline group compared to 43.3% (13/30) in 0.3 mg/kg esketamine and 36.7% (11/30) in 0.5 mg/kg esketamine ($p = 0.01$, Table 2). The cumulative dose of hydromorphone decreased from the median dose of 1 mg in the saline group to 0 mg in both esketamine groups ($p = 0.012$, Table 2). After rescue hydromorphone use, more patients experienced dizziness in the saline group than in both esketamine groups ($p = 0.015$, Table 3).

3.4 Adverse effects

The incidence of nausea, vomiting, rash, dizziness, and desaturation was not statistically different among the three groups ($p > 0.05$, Table 3). Nonetheless, we found the incidence of dizziness increased after esketamine administration, from 0 in the saline group to 13.3% in 0.3 mg/kg esketamine and 16.7% in 0.5 mg/kg esketamine, even without reaching a statistical difference ($p > 0.05$, Table 3). None of the patients experienced confusion, disorientation or hallucinations. The pain intensity in PACU was similar among the three groups ($p > 0.05$, Table 2).

4 Discussion

In patients after preoperative CT-guided needle localization, intranasal administration of either 0.3 mg/kg or 0.5 mg/kg esketamine

TABLE 1 Baseline, demographics, and needle location-related factors.

Variables	Nasal saline placebo $n = 30$	Nasal 0.3 mg/kg esketamine $n = 30$	Nasal 0.5 mg/kg esketamine $n = 30$	p-value
Age, year	53 ± 12	55 ± 13	53 ± 10	0.696
Gender Female, *n* (%)	21 (70)	21 (70)	22 (73.3)	0.947
Height, cm	164.80 ± 8.03	164.27 ± 6.53	162.70 ± 7.13	0.510
Weight, kg	61.17 ± 11.87	59.43 ± 9.39	60.63 ± 9.19	0.798
BMI, kg/m^2	22.39 ± 3.15	21.97 ± 2.78	22.87 ± 2.98	0.499
ASA status, %				0.517
I	2 (6.7)	4 (13.3)	2 (6.7)	
II	16 (53.3)	18 (60)	21 (70)	
III	12 (40)	8 (26.7)	7 (23.3)	
Education level				0.551
Middle school	13 (43.3)	14 (46.7)	10 (33.3)	
High school and above	17 (56.7)	16 (53.3)	20 (66.7)	
Number of Needles	1 [1–2]	1.5 [1–2]	1 [1–2]	0.261

Data are presented as means ± SDs, median (inter-quartile range, 25th percentile–75th percentile) or number (%). F-test was used for normally distributed continuous outcomes, Mann–Whitney U-test for non-normally distributed outcomes, and chi-square or Fisher's exact tests for category outcomes. BMI, body mass index; ASA, American Society of Anesthesiologists; VAS, visual analog pain scores. Moderate-to-severe pain is defined when VAS pain scores exceeded 3/10.

reduced the incidence of moderate-to-severe pain by half compared with nasal saline. In parallel, the VAS pain score was also reduced from the median VAS at 5 in the saline group to 3 in both nasal esketamine groups. Due to the alleviation of moderate-to-severe pain after nasal esketamine, rescue hydromorphone use and related adverse effects were greatly reduced. Therefore, intranasal esketamine provided a feasible and resource-sparing route of analgesic delivery in the preoperative acute pain setting.

The localization needle passed through the skin, penetrated the lung parietal and visceral parenchyma, anchored the pulmonary nodules, and then kept the rigid wire in place until resection (18, 19). Hence, the needle localization-related pain may be sustained until surgical resection. Timely analgesia is critical for those patients with moderate-to-severe pain before VATS. The substantial reduction in the incidence of moderate-to-severe pain (approximately one-half) and pain intensity after the nasal spray of esketamine is clinically meaningful in the preoperative pain setting. Nasal administration of esketamine may thus serve as a possible therapeutic measure for acute pain after CT-guided needle localization. Although intranasal esketamine was approved by the FDA for treatment-resistant depression (9, 20, 21), the evidence testing intranasal esketamine for acute pain was scarce (11, 22, 23). A pilot study including 22 patients found that intranasal spray of esketamine combined with midazolam was similar in analgesic effectiveness compared to standard morphine patient-controlled analgesia in patients after spine surgery (11). Intranasal spray of esketamine could thus be considered a non-invasive analgesic alternative in patients with challenging IV access. A recent trial showed esketamine nasal drops in children after tonsillectomy could reduce pain and shorten the recovery time (23). Our hypothesis was inherited from the pilot study (11), and our data were similar to the two above studies (11, 23) that the intranasal spray of esketamine could be used as a non-invasive analgesic to alleviate acute pain in the pre-anesthesia setting.

There is no evidence supporting which single intranasal dose should be chosen for acute pain related to needle localization in adult patients. We selected 0.3 mg/kg or 0.5 mg/kg doses according to existing literature and our assumptions. Recently, several studies showed that small doses of esketamine might be enough to reduce pain scores (24). A dose of 0.2 mg/kg IV esketamine before the induction of anesthesia was recommended to reduce the pain of propofol injection (6, 24). Another trial showed that intravenous injection of 0.25 mg/kg esketamine improved pain during exercise at 24 h post-operatively in patients receiving elective cesarean delivery (25). Subanesthetic doses of esketamine reduced postoperative pain in patients scheduled for laparoscopic cholecystectomy in the PACU (26). The analgesic effects of intranasal esketamine were supposed to be mediated by being absorbed through the nasal cavity, and a previous study showed that the dose of esketamine absorbed through the nasal cavity was reduced by 38% after 28-mg dose (13), which meant 60% of esketamine or higher dose might be intravenously absorbed. According to the quantified absolute nasal bioavailability of esketamine, we chose 0.3 mg/kg intranasal esketamine (approximately 0.2 mg/kg intravenously) as the potential effective dose. We also wanted to test whether there was a dose-dependent manner of nasal esketamine, so we selected a 0.5 mg/kg nasal dose (approximately 0.3 mg/kg intravenous dose). Our result demonstrated that 0.3 mg/kg intranasal esketamine was clinically effective in reducing moderate-to-severe pain during breathing. Nonetheless, our data did not support the dose-dependent manner of intranasal esketamine. Consistent with Brinck's findings (16), we did not detect a difference in pain relief between 0.3 mg/kg and 0.5 mg/kg nasal esketamine. Higher nasal esketamine could not improve pain alleviation further but might increase the risk of dizziness.

There are several ways to treat localization-related pain. Lidocaine topical infiltration around the insertion site yielded optimal pain control, as we found previously (3). We assumed that the parietal pleura-induced pain is perhaps dominant and may hardly be relieved by non-steroidal anti-inflammatory drugs (27, 28). The parietal pain is mainly supplied by the intercostal nerves on its lateral aspects, by the T1 spinal nerve on its apex, and by the phrenic nerves on the

TABLE 2 Efficacy outcomes of nasal administration of saline, 0.3 mg/kg esketamine, and 0.5 mg/kg esketamine on acute pain after CT-guided needle localization.

Pain parameters	Nasal saline placebo *n* = 30	Nasal 0.3 mg/kg esketamine *n* = 30	Nasal 0.5 mg/kg esketamine *n* = 30	*p*-value
Incidence of moderate-to-severe pain after treatment during deep breathing, *n* (%)	25 (83.3)	13 (43.3)	14 (46.7)	0.002**
Absolute median VAS reduction (15 min minus before treatment)	1 [0–2]	2 [1–2]	2 [1–3]	0.024*
VAS at rest before treatment	3.5 [2–5.25]	4.5 [3–6]	4 [3–5]	0.411
VAS during deep breathing before treatment	5 [5–7]	5.5 [5–7]	5 [4–7]	1.000
VAS at 5 min after treatment during deep breathing	5.5 [4.75–6.0]	4.5 [3–7]	5 [4–6.0]	0.480
VAS at 10 min after treatment during deep breathing	5 [4–6.25]	4 [3–5.25]	4 [3–6.0]	0.148
VAS at 15 min after treatment during deep breathing	5 [4–6]	3 [3–5]	3 [3–5]	0.009**
VAS at 15 min after treatment at rest	3 [2–4]	2 [1–3.25]	2.5 [2–3]	0.875
Incidence of rescue hydromorphone use, *n* (%)	22 (73.3)	13 (43.3)	11 (36.7)	0.010*
Cumulative dose of hydromorphone use, mg	1 [0–1]	0 [0–1]	0 [0–1]	0.012*
VAS at rest in PACU	2 [0–2]	2 [1–2]	1 [0–2]	0.328
VAS during breathing in PACU	3 [2–4]	3 [2–4]	3 [2–4]	0.669

Data are presented as median (inter-quartile range, 25th percentile–75th percentile), or number (%). Chi-square or Fisher's exact tests for binary outcomes. Mann–Whitney U-test for non-normally distributed outcomes. Denotes statistically significant (*$p < 0.05$; **$p < 0.01$) differences among groups.

TABLE 3 Adverse events in the study participants.

Adverse effects	Nasal saline placebo *n* = 30	Nasal 0.3 mg/kg esketamine *n* = 30	Nasal 0.5 mg/kg esketamine *n* = 30	*p*-value
After nasal administration				
Nausea, *n* (%)	0 (0)	0 (0)	2 (6.7)	0.326
Vomiting, *n* (%)	0 (0)	0 (0)	1 (3.3)	1.000
Rash, *n* (%)	0 (0)	0 (0)	1 (3.3)	1.000
Dizziness, *n* (%)	0 (0)	4 (13.3)	5 (16.7)	0.071
Confusion and disorientation, *n* (%)	0 (0)	0 (0)	0 (0)	Not applicable
Hallucinations, *n* (%)	0 (0)	0 (0)	0 (0)	Not applicable
Desaturation, *n* (%)	1 (3.3)	0 (0)	1 (3.3)	1.000
RASS	0 [0–0]	0 [0–0]	0 [0–0]	Not applicable
After rescue hydromorphone use, *n* (%)				
Dizziness, *n* (%)	13 (43.3)	8 (26.7)	3 (10)	0.015*
Drowsiness, *n* (%)	5 (16.7)	1 (3.3)	5 (16.7)	0.215

Data are presented as numbers (%). Abbreviations: RASS, Richmond Agitation Sedation. Scale. Denotes statistically significant (*$p < 0.05$; **$p < 0.01$) differences among groups.

diaphragm (29). Intercostal, interpleural, epidural, and paravertebral blocks have all been proven useful in controlling pleuritic pain (29, 30), but all blocks will consume medical resources and perhaps lead to some complications. Potent opioids are historically effective in relieving significant pain but may have adverse effects. As we found in our study, rescue hydromorphone use led to more than 40% of patients experiencing dizziness in the saline group. We proved that 0.3 mg/kg nasal esketamine could serve as a resource-sparing and non-invasive method to treat needle-location pain without opioid-related side effects.

We also wanted to verify the analgesic effectiveness of nasal esketamine was timely, so we designed 15 min as the therapeutic window. A previous study showed the fraction of the esketamine dose absorbed through the nasal cavity was complete and fast, and the mean absorption time was 0.341 h, as previously reported (16). We observed the analgesic effect of esketamine from the start of nasal administration until 15 min at 5-min intervals. The nasal esketamine showed a time-dependent manner of analgesia, and 0.3 mg/kg or 0.5 mg/kg of nasal esketamine demonstrated effectiveness in pain relief after 15 min.

This trial has several limitations. We conducted the trial in a single tertiary center, and the results needed to be verified in more generalized institutions. Second, we set two fixed doses to investigate in a dose-dependent manner. Although the chosen doses depended on the population pharmacokinetics of esketamine nasal spray in healthy subjects and previous pain studies, the linear or proportional dose-effect manner should be investigated further. Third, we set a saline nasal group to mask the positive drug and mimic the placebo effect, but we did not add the bittering agent to the intranasal placebo

to simulate the taste of the esketamine solutions, which might affect patients' objective self-assessment. Fourth, our sample size was designed to test the analgesic effect of esketamine on moderate-to-severe pain, but the sample size was not enough to differentiate the effect on moderate pain or severe pain, respectively. Finally, we did not observe the effect of esketamine after 15 min, which would underestimate the analgesic effect of esketamine.

5 Conclusion

In patients after preoperative CT-guided needle localization, nasal administration of 0.3 mg/kg or 0.5 mg/kg esketamine could reduce the incidence of moderate-to-severe pain by half compared with saline. Nasal spray of esketamine could be used as a feasible and non-invasive method to alleviate acute thoracic pain in the pre-anesthesia setting.

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 humans were approved by Shanghai Chest Hospital Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

JX: Data curation, Formal analysis, Investigation, Writing – review & editing. JJ: Data curation, Formal analysis, Investigation, Writing – review & editing. YZ: Investigation, Resources, Writing – review & editing. JW: Conceptualization, Supervision, Methodology, Writing – review & editing. YQ: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing, Investigation.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was supported by the funding of the Shanghai Municipal Commission of Health grant 202040200. The funders had no role in the study design, data collection, data analysis, interpretation of the data, or preparation of the manuscript.

Acknowledgments

The authors thank all patients for participating in the study.

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

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frontiers | Frontiers in Medicine

TYPE Study Protocol
PUBLISHED 12 April 2024
DOI 10.3389/fmed.2024.1359878

OPEN ACCESS

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RECEIVED 22 December 2023
ACCEPTED 26 March 2024
PUBLISHED 12 April 2024

CITATION
Liao D, Peng K, Zhang Y, Liu H, Xia Z, Guo J, Wei F, Chen C, Lv X, Tong J, Li X, Qu X, Wang X, Wang Y, Ou S, Liu H, Shan X and Ji F (2024) Effect of liposomal bupivacaine for preoperative erector spinae plane block on postoperative pain following video-assisted thoracoscopic lung surgery: a protocol for a multicenter, randomized, double-blind, clinical trial.
Front. Med. 11:1359878.
doi: 10.3389/fmed.2024.1359878

Effect of liposomal bupivacaine for preoperative erector spinae plane block on postoperative pain following video-assisted thoracoscopic lung surgery: a protocol for a multicenter, randomized, double-blind, clinical trial

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Background: There is still a controversy about the superiority of liposomal bupivacaine (LB) over traditional local anesthetics in postoperative analgesia after thoracic surgery. This study aims to determine the effect of LB versus bupivacaine hydrochloride (HCl) for preoperative ultrasound-guided erector spinae plane block (ESPB) on postoperative acute and chronic pain in patients undergoing video-assisted thoracoscopic lung surgery.

Methods: This multicenter, randomized, double-blind, controlled trial will include 272 adult patients scheduled for elective video-assisted thoracoscopic lung surgery. Patients will be randomly assigned, 1:1 and stratified by site, to the liposomal bupivacaine (LB) group or the bupivacaine (BUPI) HCl group. All patients will receive ultrasound-guided ESPB with either LB or bupivacaine HCl before surgery and patient-controlled intravenous analgesia (PCIA) as rescue analgesia after surgery. The numeric rating scale (NRS) score will be assessed after surgery. The primary outcome is the area under the curve of pain scores at rest for 0–72 h postoperatively. The secondary outcomes include the total amount of opioid rescue analgesics through 0–72 h postoperatively, time to

the first press on the PCIA device as rescue analgesia, the area under the curve of pain scores on activity for 0–72 h postoperatively, NRS scores at rest and on activity at different time points during the 0–72 h postoperative period, Quality of Recovery 15 scores at 72 h after surgery, and NRS scores on activity on postsurgical day 14 and postsurgical 3 months. Adverse events after the surgery are followed up to the postsurgical day 7, including postoperative nausea and vomiting, fever, constipation, dizziness, headache, insomnia, itching, prolonged chest tube leakage, new-onset atrial fibrillation, severe ventricular arrhythmia, deep venous thrombosis, pulmonary embolism, pulmonary atelectasis, cardiac arrest, ileus, urinary retention, chylothorax, pneumothorax, and organ failure. Analyzes will be performed first according to the intention to treat principle and second with the per-protocol analysis.

Discussion: We hypothesize that LB for preoperative ultrasound-guided ESPB would be more effective than bupivacaine HCl in reducing postoperative pain in video-assisted thoracoscopic lung surgery. Our results will contribute to the optimization of postoperative analgesia regimens for patients undergoing video-assisted thoracoscopic lung surgery.

Clinical trial registration: http://www.chictr.org.cn, identifier ChiCTR2300074852.

KEYWORDS

liposomal bupivacaine, erector spinae plane block, thoracoscopic, postoperative pain, area under the curve

Introduction

Thoracoscopic surgery has emerged as the backbone of surgical procedures for lung resection in recent years, but these procedures still cause moderate-to-severe postoperative acute and chronic pain (1–4). Preemptive analgesia is regarded as a proven approach to minimize postsurgical pain (5). Several preemptive analgesia approaches have been employed in thoracoscopic surgery, including paravertebral block, intercostal nerve block, and thoracic epidural block (6). The erector spinae plane block (ESPB), a new inter-fascial plane block technique first described in 2016 for thoracic pain treatment (7), has the advantages of easy handling, high safety, and a good analgesic effect (8, 9). However, ESPB with a single dosage of currently available local anesthetics is limited by the short duration of analgesia (typically 24 h or less). The duration of analgesia can be prolonged by continuous peripheral nerve blocks using a perineural catheter; however, this may result in a variety of inconveniences and side effects, such as management complexity, catheter-related infections, leakage, and accidental dislocation (10, 11).

Liposome bupivacaine (LB) is a novel local anesthetic with water-soluble bupivacaine wrapped in a liposome, allowing for a steady, continuous release of the drug for up to 72 to 96 h (12, 13). In 2011, liposomal bupivacaine was approved by the U.S. Food and Drug Administration to be used in single-dose wound infiltration for postsurgical analgesia in adults, and then the indication was expanded to transverse abdominis plane blocks and interscalene brachial plexus blocks (14, 15). Liposome bupivacaine appears safe when used in fascial plane blocks and peripheral nerve blocks (16–20). Whether LB is superior to traditional local anesthetics in postoperative analgesia after thoracic surgery remains controversial. Several retrospective studies have suggested that LB applied in minimally thoracic surgery improved postoperative pain, decreased opioid use, and shortened hospital stay in comparison with bupivacaine hydrochloride (HCl) (21–23). A recent randomized controlled trial including 50 patients undergoing minimally invasive lung surgery indicated that LB for intercostal nerve block provided no benefit in mitigating postoperative pain compared with bupivacaine plus epinephrine (18). However, that study had a smaller sample size and did not exclude the patients with more complex pain problems. To date, the analgesic efficacy of LB used in ESPB procedures on acute or chronic postsurgical pain remains unknown.

In this context, we designed this multicenter randomized controlled trial to determine the effect of LB versus bupivacaine HCl for preoperative ultrasound-guided ESPB on postoperative acute and chronic pain in patients undergoing video-assisted thoracoscopic lung surgery. In addition, we will also evaluate its safety profile when used in the ESPB procedures.

Methods

Ethics and registration

The study protocol was approved by the ethics committees of the leading center (the First Affiliated Hospital of Soochow University, Suzhou; Approval No. 2023–207) and each participating center. This trial was registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn, identifier: ChiCTR2300074852) before the enrollment of the first subject. This protocol adheres to the guidelines of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (24).

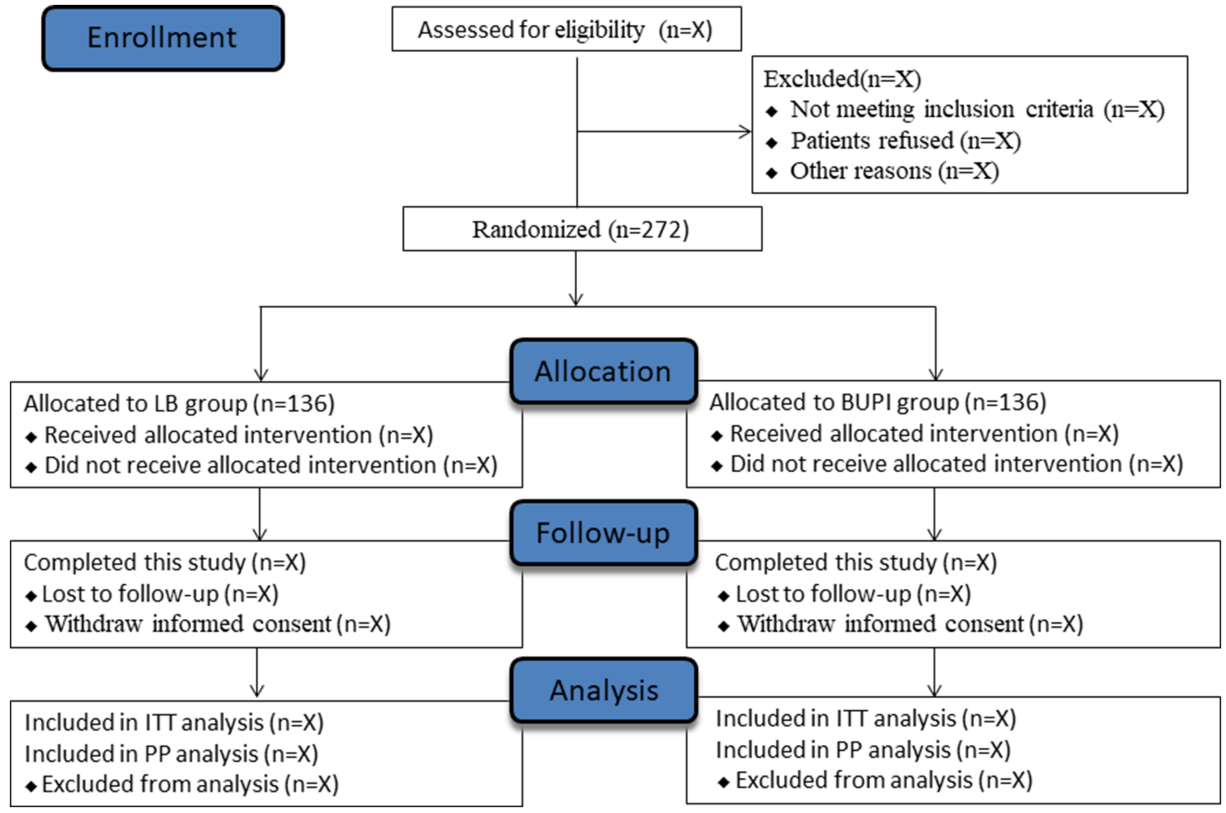

FIGURE 1
Study flow diagram.

Study design and status

This investigator-initiated, multicenter, randomized, double-blind, parallel-controlled trial will be conducted at 12 tertiary hospitals in China. Subjects will be randomized to receive either liposomal bupivacaine or bupivacaine HCl for ultrasound-guided ESPB after induction of anesthesia. Group allocation is performed by the online central randomization system.

This trial start date is 1 September 2023, and the anticipated end date is 31 March 2025. By the time of this manuscript submission, the recruitment of participants has started, but all follow-up data will be stored in the electronic data capture (EDC) system, which will be locked until the final analysis. Figure 1 shows the study flow diagram. Table 1 presents the schedule of subject enrollment, study intervention, and outcome evaluation following the SPIRIT statement.

Participants and enrollment

We plan to recruit eligible subjects who meet the following inclusion criteria: (1) American Society of Anesthesiologists (ASA) class I-III, (2) adult subjects who are 18–75 years of age, and (3) subjects scheduled for elective video-assisted thoracoscopic single or multi-port lung surgery under general anesthesia with bronchial intubation.

The exclusion criteria are as follows: (1) trauma and emergency subjects, (2) subjects with New York Heart Function Scale (NYHA) levels of 3–4, (3) patients with heart conduction block (sinus block or atrioventricular block), (4) patients with unstable coronary artery disease, (5) patients with gastric ulcer or gastric bleeding, (6) patients with body mass index (BMI) of $<18\ kg/m^2$ or $>37\ kg/m^2$, (7) patients with diabetes and are being treated with insulin, (8) patients with renal dysfunction (serum creatinine values exceed normal thresholds), (9) patients with liver dysfunction (Alanine aminotransferase or Aspartate aminotransferase is more than twice the normal value), (10) subjects with coagulation dysfunction (prothrombin time or activated partial thromboplastin time is higher than the normal threshold) or patients who are taking oral anticoagulants for other medical reasons and have not stopped it before surgery, such as warfarin or new anticoagulants rivaroxaban or dabigatran, (11) subjects with alcohol abuse or heavy dependence on narcotic drugs in the last 2 months, (12) subjects with uncontrolled anxiety, schizophrenia, or other mental illness, (13) subjects who are pregnant or preparing for pregnancy, and (14) subjects with a history of allergy to local anesthetic drugs or any of the experimental medications. Written informed consent will be signed by participants before enrollment.

Randomization and blindness

A research coordinator who would not participate in the subsequent study conducted the online randomization with a 1:1 ratio

TABLE 1 Diagrammatic representation of trial processes.

	Pre-Op (study days-6-0)	Allocation 2 h before surgery	Intra-Op (study day 1)	PACU (study day 1)	Post-Op (0–72 h) (study days 1–4)	Day of discharge	Post-Op (study days 5–8)	Post-Op (study day 15)	Post-Op 3 months
Enrollment									
Eligibility screening	×								
Informed Consent	×								
Demographics	×								
Randomization		×							
Allocation		×							
Vital signs			×						
Interventions									
ESPB procedure			×						
Measurements									
Intra-operative information			×						
NRS scoring at rest				×	×				
NRS scoring on activity				×	×			×	×
Opioid rescue medication					×	×			
Initiation of postoperative activities					×				
QoR-15 scores					×				
Chest tube evaluation					×	×	× (If applicable)		
Adverse events[a]			×	×	×	×	×		
Oral analgesic medication					×	×	× (If applicable)	× (If applicable)	× (If applicable)

According to the SPIRIT statement of defining a standard protocol for clinical trials. Op, Operation; ESPB, erector spinae plane block; NRS, numeric rating scale; QoR-15 scores, Quality of Recovery 15 scores.[a]including postoperative nausea and vomiting, fever, constipation, dizziness, headache, insomnia, itching, prolonged chest tube leakage, new-onset atrial fibrillation, severe ventricular arrhythmia, deep venous thrombosis, pulmonary embolism, pulmonary atelectasis, cardiac arrest, ileus, urinary retention, chylothorax, pneumothorax, and organ failure.

and permuted block size of 4.[1] According to the random sequence, subjects were randomly assigned to either the liposomal bupivacaine group (LB) or the bupivacaine HCl group (BUPI). The allocation concealment was guaranteed using identical opaque sealed envelopes. An independent anesthesia nurse at each study center prepared the study medications, either liposomal bupivacaine or bupivacaine HCl, according to the random results. As liposomal bupivacaine emulsions and bupivacaine HCl have different appearances, we ensure the blinding of surgeons and operating room staff by transferring the medication to an identical opaque syringe, which is labeled with the patient's number only. The ESPB procedures will be performed by a skilled anesthesiologist at each center who will not be involved in managing anesthesia and overseeing postoperative care. All other perioperative clinical care will be carried out following institutional standard practice. All relevant data will be recorded on the trial case report form (CRF) and entered into the EDC system within 1 week of completing the CRF forms.

Study interventions

The drugs are prepared as follows: liposomal bupivacaine (20 mL, 266 mg) is diluted to 30 mL with 10 mL of normal saline in the LB group, while bupivacaine HCl (100 mg) is diluted to 30 mL with 10 mL of normal saline in the BUPI group. After the induction of anesthesia, an independently trained anesthesiologist performs single-injection ESPB under ultrasound guidance in the lateral position. Initially, a high-frequency linear ultrasound probe is used in a vectorial position to locate the T4 spinous process longitudinally, and then the probe is moved outward to target the T5 transverse process. Guided by planar

1 http://random.91trial.com

ultrasound visualization, the nerve block operator carefully advances the needle until the top reaches the T5 transverse process bone, and then 30 mL of local anesthetic is injected slowly after the confirmation of no blood or cerebrospinal fluid with a syringe aspiration.

All subjects will receive patient-controlled intravenous analgesia (PCIA) as rescue analgesia after surgery using 100 μg of sufentanil diluted to 100 mL with normal saline (a final concentration of 1 μg/mL). The parameters for the PCIA device are as follows: no background infusion, a self-controlled bolus of 2 mL, a lockout time of 5 min, and a locking dose of 20 mL per hour. PCIA is started once the patients enter the recovery room. Patients are instructed to self-administer sufentanil using PCIA to treat pain on the numeric rating scale (NRS) score of ≥4. If the pain remains unrelieved, additional rescue medications with morphine of 2–5 mg or other opioid analgesics can be slowly injected intravenously. The PCIA is discontinued after 48 h postoperatively. Later, if subjects still experience pain (NRS scores ≥4), morphine of 5–10 mg or other opioid analgesics can be administered. Subjects in both groups receive oral celecoxib of 200 mg twice daily (at 08:00 and 16:00) as a component of the multimodal analgesic regimen from the first postsurgical day (day 2) until complete pain relief. Oral celecoxib can be used after hospital discharge if necessary.

Perioperative management

The flow of the participants through this trial is depicted in Figure 1. Subjects do not receive sedative or analgesic medications preoperatively. In the operating room, standard monitoring includes electrocardiography, non-invasive cuff blood pressure, pulse oximetry, and temperature. The left or right radial artery is cannulated following anesthesia induction, and continuous radial artery pressure is measured. General anesthesia is induced with propofol (2–2.5 mg/kg), sufentanil (0.3–0.5 μg/kg), and cisatracurium (0.2 mg/kg) in sequence. Following tracheal intubation with a double-lumen tube, unilateral bronchial ventilation is conducted with a tidal volume of 4–6 mL/kg and a respiratory rate of 12–16 times/min, aiming to maintain the end-tidal carbon dioxide at 35–45 mmHg and pulse oxygen saturation of ≥95%. The location of the bronchial tube is then confirmed using flexible fiberoptic bronchoscopy. Anesthesia is maintained with sevoflurane inhalation targeting a bispectral index value between 40 and 60. Intraoperative analgesia is provided with sufentanil and remifentanil: sufentanil 0.1–0.2 μg/kg is given before incision at the beginning of surgery, and remifentanil (0.05–0.2 μg/kg/min) is infused continuously for intra-operative analgesia. Additional doses of sufentanil can be given intraoperatively if necessary, and sufentanil is added 0.1–0.2 μg/kg when the remifentanil is discontinued at the end of the operation. The additional doses of cisatracurium can be incremented intraoperatively as needed. Intraoperative hypotension (defined as a decrease in mean blood pressure [MBP] of >20% of baseline or MBP of <65 mmHg) would be treated with intravenous ephedrine of 6–10 mg or phenylephrine of 50–100 μg, and bradycardia (defined as heart rate [HR] of <50 beats/min) would be treated with intravenous atropine of 0.3–0.5 mg.

At the end of the surgery, all subjects received ondansetron of 8 mg as an antiemetic after the last stitches. Subjects are transferred to a post-anesthesia care unit (PACU) and kept there for at least 1 h before returning to the thoracic ward. The surgical day is regarded as the study day 1, and the day following surgical day is the study day 2.

Postsurgical assessments

Pain intensity assessments are conducted at 0 h (~15 min after extubation), 1 h (± 10 min), 6 h (± 2 h), 12 h (± 2 h), 18 h (± 2 h), 24 h (± 2 h), 32 h (± 2 h), 40 h (± 2 h), 48 h (± 2 h), 60 h (± 2 h), and 72 h (± 2 h) postoperatively, and at patient's request for rescue medication, where the time of the completion of surgery is considered 0 of the postoperative time. Pain intensity is assessed using an 11-point NRS (0 = no pain; 10 = worst possible pain) at rest and on activity; the latter refers to the scoring when turning over on bed if the subjects are still not out of bed for activity, or the scoring on active movement if the subjects are already out of bed. Telephone follow-up is performed if the subjects are discharged from the hospital within 72 h. During the nighttime (23:00 to 06:00, the next day), the subject is not awakened for scoring. If the subject is awake during the time window, the NRS score is assessed based on the subject's own or companion's recollection in the following morning; if the patient is asleep during the time window, the NRS score is standardized to a uniform value of 2. Considering the potential impact of opioid rescue medications on pain measurements, the windowed worst observation carried forward (wWOCF) method is utilized to accurately document NRS pain scores in the initial 72 h following surgery. The wWOCF approach operates in the following manner: to obtain the wWOCF for subjects who receive rescue medication, any NRS scores noted within a 2-h "window" following the administration of opioid rescue medication are replaced by the highest ("worst") NRS scores recorded before the administration of their initial rescue medication. The time to the first rescue analgesia using PCIA was recorded, and the amount of medication used for rescue analgesia with the PCIA analgesic pump was also calculated. Quality of Recovery 15 (QoR-15) scores at 72 h after surgery are used to evaluate the subject's recovery. NRS scores are measured once daily after 72 h postoperatively until study day 15. The number of continued days and the dosage of the oral analgesic drug celecoxib after discharge are also recorded.

Data monitoring committee

An independent Data Monitoring Committee (DMC) comprising experienced anesthesiologists and statisticians has been established to resolve any uncertainties related to data collection and to determine whether postsurgical analgesic medications that have been administered are beyond the protocol. This DMC comprises a chair (an experienced anesthesiologist), an attending anesthesiologist, two statisticians, and an attending thoracic surgeon. When ambiguity occurs in data collection or in adherence to protocol medications, these issues are discussed at the DMC to reach a final conclusion.

Trial outcome definitions

Primary outcome

The primary outcome for the trial is the area under the curve of pain scores at rest for 0–72 h (AUC NRS-$R_{0\text{-}72}$) postoperatively.

Secondary outcomes

The secondary outcomes include (1) the total amount of opioid rescue analgesics through 0–72 h postoperatively, (2) the time to first press on the PCIA device as rescue analgesia, (3) the area under the curve of pain scores on activity for 0–72 h (AUC NRS-$A_{0\text{-}72}$) postoperatively, (4) NRS scores at rest and on the activity at different time points during the 0–72 h postoperative period, (5) Quality of Recovery 15 (QoR-15) scores at 72 h after surgery, (6) NRS scores on activity on postsurgical day 14 (study day 15), which will be followed up via telephone, with a permitted time window of 14 ± 3 days, and (7) NRS scores on the activity at postsurgical 3 months will be followed up via telephone, with a permitted time window of 3 months ±7 days. Opioids are first converted to intravenous morphine equivalents for each subject, and then the total amount will be naturally logarithmically converted before analysis. The time to first opioid rescue analgesia using PCIA was measured in hours, i.e., the date and time of the first opioid rescue minus the date and time of the end of surgery.

Tertiary outcomes

Tertiary outcomes include (1) the time to initiation of postoperative activities around the bed, (2) the total volume of chest tube drainage, (3) the time to chest tube removal, (4) the duration of oral analgesic medications taken by the subject postoperatively in the telephone follow-up, and (5) the total amount of oral analgesic medications taken postoperatively. The total volume of chest tube drainage is referred to as the total amount of chest tube drainage until the chest tube removal. The time to initiate postoperative activities around the bed and time to chest tube removal are measured in hours, i.e., the time of the event minus the time of the end of surgery.

Safety outcomes

Safety outcomes are assessed separately and then combined for all subjects, consisting of adverse events during and after surgery. The incidence of adverse events after the surgery is tracked up to the 7th postsurgical day (study day 8). Adverse events include postoperative nausea and vomiting (PONV), fever, constipation, dizziness, headache, insomnia, itching, prolonged chest tube leakage, new-onset atrial fibrillation, severe ventricular arrhythmia, deep venous thrombosis, pulmonary embolism, pulmonary atelectasis, cardiac arrest, ileus, urinary retention, chylothorax, pneumothorax, and organ failure. The definitions of adverse events are displayed in the Supplementary Table S1. Any adverse event in relation to the study interventions must be reported to DMC in the form of an "Adverse Event Form" within 24 h. In the event of a serious adverse event, such as an unexpected deterioration in the patient's clinical condition during the perioperative period, the attending anesthesiologist could require unblinding and adjustment or discontinuation of administration.

Sample size calculation

Between January 2023 and March 2023, we conducted a prospective study on two groups of 10 patients each. All participants underwent video-assisted thoracoscopic lung surgery and were administered a preoperative ultrasound-guided ESPB, with one group receiving liposome bupivacaine and the other bupivacaine HCl. The results showed that the postoperative AUC NRS-R0-72 was 247 ± 35 in the LB group versus 262 ± 43 in the BUPI group. Based on the preliminary study, the sample size was determined to ensure the ability to detect a mean difference of 15 in the primary efficacy outcome, and we suggest that this difference is clinically relevant. This calculation is performed with a two-group *t*-test, a standard deviation of 38.7, an 80% power, and a 0.05 level of significance. Considering a 20% dropout rate, this study will enroll a total of 272 patients, with 136 in each group. The sample size is calculated using the SAS software (version 9.4, SAS Institute Inc).

Statistical analysis

Baseline characteristics will be tabulated using applicable summary statistics. Outcome data will be analyzed according to the intention to treat (ITT) principle and secondarily with the per-protocol (PP) analysis.

The ITT population will comprise all randomized patients who receive ultrasound-guided ESPB procedures and complete the surgery with the primary outcome measurement available. These subjects will be analyzed according to the groups to which they are randomized, regardless of whether the surgical procedure is converted to an open thoracotomy or any other surgical procedure implemented within 3 months postoperatively. Subjects who are given non-protocol pain medication postoperatively will also be included in the ITT analysis. Subjects whose consent is withdrawn will have their data retained until the time of withdrawal. The PP population will comprise those patients who complete the study based on the original protocol. Subjects with modifications of the original surgical approach to open thoracotomy or who undergo any other surgical procedures within 3 months after surgery are specifically excluded from this analysis. Data from subjects whose consent is withdrawn will be used until the time of withdrawal of consent.

Demographic information and baseline characteristics will be described using descriptive statistics only, with no between-group comparisons. Continuous data will be displayed as means and standard deviations or medians and interquartile ranges, depending on data distribution. Categorical data will be summarized as counts and percentages. Between-group differences of continuous data will be analyzed using the independent t-test or Mann–Whitney rank sum test as appropriate, while categorical data will be analyzed using the Chi-squared test or Fisher's exact test as appropriate. To analyze the treatment effect, odds ratios are calculated for binary data and mean differences for continuous data, each together with their 95% confidence intervals. For the primary outcomes, the between-group difference of AUC NRS-$R_{0\text{-}72}$ is regarded as significant at the two-side *p*-value of 0.05. For the secondary and tertiary outcomes, multiple comparisons are adjusted for the significance level of probability values by computing the false discovery rate using the Benjamini-Hochberg method. To further understand the cumulative effect of study interventions on postsurgical pain, *post-hoc* analysis is conducted, including AUC NRS-$R_{0\text{-}24}$, AUC NRS-$R_{24\text{-}48}$, AUC NRS-$R_{48\text{-}72}$, AUC NRS-$A_{0\text{-}24}$, AUC NRS-$A_{24\text{-}48}$, and AUC NRS-$A_{48\text{-}72}$, the cumulative amount of opioid rescue analgesics during 0–24, 24–48, and 48––72 h, and the proportion of subjects who are pain-free (NRS-R score of 0 or 1) at 1, 6, 24, 48, and 72 h. To address the missing NRS pain intensity scores during the postoperative 0–72 h,

interpolation is performed using one of the following methods: (1) by last observation carried forward (LOCF) imputation method if missing data are located after the last non-missing score, (2) by linear interpolation if more than one missing data occur and are located between two non-missing scores (25). All data will be analyzed using the SAS software (version 9.4, SAS Institute Inc) by an independent statistician.

Discussion

This multicenter, randomized, double-blind, parallel-controlled trial will include 272 subjects who will undergo elective video-assisted thoracoscopic lung surgery. We will determine the effect of LB versus bupivacaine HCl for preoperative ultrasound-guided ESPB on AUC NRS-$R_{0\text{-}72}$, the amount of opioid rescue analgesics after surgery, time to the first rescue analgesia, AUC NRS-$A_{0\text{-}72}$, NRS scores at rest and on activity at different time points during the 0–72 h postoperative period, and NRS scores on activity on postsurgical day 14 and postsurgical 3 months. Our primary hypothesis is that the use of LB for ultrasound-guided ESPB preemptive analgesia provides a lower area under the curve of pain scores at rest 0–72 h postoperatively compared to bupivacaine HCl. Moreover, we will explore the adverse events associated with the application of LB for ultrasound-guided ESPB. The administration of this trial and the presentation of results will follow the Consolidated Standards of Reporting Trials guidelines.

Regional nerve block maneuvers before skin incisions are considered an optimal method of preemptive analgesia, which facilitates the reduction of postsurgical pain. ESPB is a novel interfascial regional anesthesia technique first introduced by Forero et al. in 2016 for thoracic neuropathic pain treatment and has rapidly gained prevalence in a diverse range of surgical procedures (7, 26). In particular, it is easy to implement owing to the simple identification of anatomic landmarks on ultrasound and the fact that no vital organs are nearby (27). Anatomical and radiological investigations in fresh cadavers have suggested that the clinical effects of ESPB are likely derived from the theoretical anterior distribution of the local anesthetics through the intertransverse connective tissue or the costotransverse foramen to infiltrate the ventral crus of the spinal nerves, the dorsal root ganglion, and the sympathetic chain, thereby resulting in an effect similar to epidural analgesia (7, 28).

Recent studies have demonstrated that ESPB is a simple, safe, wide-ranging, and efficacious alternative analgesic technique for postsurgical pain (7–9, 29). A recent meta-analysis including 14 studies indicated that ESPB significantly lowered pain scores at rest or on movement, decreased 24 h opioid consumption, and reduced the incidence of postoperative nausea and vomiting compared with the non-block care in breast and thoracic surgery (30). Another meta-analysis also suggested that ultrasound-guided ESPB could provide an opioid-sparing effect in subjects undergoing surgeries with general anesthesia, thereby reducing the adverse events related to opioid administration, such as nausea, vomiting, and delayed peristalsis (29, 31, 32). The currently prevalent regional nerve block maneuvers in thoracoscopic surgery involve paravertebral and intercostal nerve blocks. Each of these procedures has its unique strengths and inherent disadvantages. For instance, paravertebral block is performed close to the spinal canal and vascular plexus, with technical complexity and potential risk of serious complications, while the effectiveness of intercostal nerve block may be limited to a dermatomal extent (33). Given the combination of its efficacy and lower associated risks, ESPB has been preferred in our study.

Liposomal bupivacaine (Bupivacaine Liposome Injection; Jiangsu Hengrui Pharmaceuticals Co., Ltd.; China) is a novel liposome-encapsulated local anesthetic used for surgical site administration to yield postsurgical analgesia. The delivery of local anesthetics using encapsulating agents is a desirable alternative, as it provides a system for sustained release and subsequently enhances analgesia (34). Liposomal bupivacaine has been shown to provide postsurgical analgesia with a similar safety profile to bupivacaine HCl in a variety of surgical scenarios, such as hemorrhoidectomy, total knee arthroplasty, mammoplasty, and thoracic surgery (18, 35–37). Liposome bupivacaine appears safe when used in fascial plane blocks and peripheral nerve blocks, such as ESPB, paravertebral block, and intercostal nerve block (16–20, 23).

However, evidence of the clinical effectiveness of interfascially or perineurally applied liposomal bupivacaine in extending the duration of postoperative analgesia of nerve blocks is insufficient. Several retrospective studies have demonstrated the superiority of LB over bupivacaine HCl in controlling postsurgical pain when the paravertebral blocks or intercostal nerve blocks are applied in thoracic surgery (21–23). Another retrospective study included 387 patients receiving either liposomal bupivacaine for an intrathoracic intercostal nerve block or thoracic epidural bupivacaine HCl in video-assisted thoracoscopic surgery (38). Liposomal bupivacaine used for the regional block was comparable with bupivacaine HCl for epidural analgesia, taking into account healthcare costs and analgesia efficacy. A randomized controlled trial compared the analgesic efficiency and safety of single-dose transversus abdominis plane (TAP) blocks with liposomal bupivacaine and sustained epidural analgesia, with bupivacaine HCl in 498 subjects undergoing major abdominal surgery (39). The results showed that pain scores at rest during the initial postsurgical days were similar between groups. Compared to subjects receiving epidural analgesia with bupivacaine HCl, those who received TAP blocks with liposomal bupivacaine required more opioid medication but had fewer complications, such as hypotension. Another randomized controlled study with a non-inferiority design that enrolled 112 patients undergoing ambulatory shoulder surgery demonstrated that interscalene nerve blocks with perineural LB offered similarly effective analgesia as the perineural standard bupivacaine with dexamethasone (40). A recent meta-analysis also suggested that perineural liposomal bupivacaine provided a statistically significant but clinically unconsidered improvement in the area under the curve of postoperative pain scores compared to plain local anesthetic (41, 42).

The variations in study protocols and injection site locations could influence study results. The pharmacokinetics profile of liposomal bupivacaine is apparently related to the duration of regional blocks (43). Liposomal bupivacaine exhibits a biphasic model, dose-related release profile with an initial peak release within 1 h of execution related to extra liposomal bupivacaine included in every ampule, followed by a further peak 12 to 48 h later, associated with the release from the liposomes (13, 44). Hence, preemptive analgesia with liposomal bupivacaine has the potential to reduce postoperative pain intensity. Furthermore, the rate of bupivacaine release from liposomes is speculated to be related to the vascularity of the surrounding tissue at the injection site. For example, approximately 30% of bupivacaine

is released during the first 24 h when it infiltrates directly into tissues in knee replacement, and approximately 90% in more vascularly distributed hemorrhoidectomy (45). The erector spinae plane does not have a rich vascular plexus, and the rate of bupivacaine release from liposomes may be similar to other fascial plane blocks, allowing for prolonged anesthetic duration. More studies are warranted to determine the exact features and effectiveness of this block in various surgical procedures. To date, this is the first randomized controlled study to determine the efficiency of liposomal bupivacaine for ESPB on postoperative pain in thoracic surgery.

In this study, we formulate certain rules for NRS scoring to achieve multicenter consistency and eliminate the influence of external factors on pain outcomes. For instance, we have implemented the wWOCF protocol for recording NRS pain intensity scores in the first 72 h after surgery. This method is designed to reduce the influence of opioid rescue medications on the NRS evaluations. Specifically, if patients receive rescue medication within a 2 h "window" before an assessment, we will replace the score for that time point with the highest ("worst") NRS score recorded before the administration of the initial rescue medication. In addition, we employ a nocturnal recall score to minimize the disruption to the patient's nighttime rest. We do not take bedside face-to-face scoring at night (23:00 to 06:00, the following day). If the subject is awake within the time window, the subject or companion recollects the pain state the following morning, and if the subject is asleep during the time window, the NRS score is assigned a uniform value of 2.

Our study has several limitations. First, partial subjects were discharged within 72 h after surgery, and NRS scores for these subjects could only be followed up by telephone. Second, adverse events are only tracked up to the 7th postsurgical day without further follow-up. Finally, varying durations of oral analgesic medications or non-protocol analgesics may interfere with the NRS scoring for pain.

In conclusion, this randomized clinical trial was designed to determine the effect of liposomal bupivacaine versus bupivacaine HCl for preoperative ultrasound-guided ESPB on postoperative pain in video-assisted thoracoscopic lung surgery. We expected that liposomal bupivacaine could be safely employed in ESPB, and liposomal bupivacaine for preoperative ultrasound-guided ESPB would be more effective than bupivacaine HCl in reducing the area under the curve of pain scores at rest from 0 to 72 h postoperatively.

Ethics statement

The studies involving humans were approved by the Medical Ethics Committee of the First Affiliated Hospital of Soochow University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. 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

DL: Data curation, Project administration, Writing – original draft, Writing – review & editing. KP: Conceptualization, Investigation, Methodology, Supervision, Writing – review & editing. YZ: Data curation, Formal analysis, Methodology, Project administration, Writing – review & editing. HuL: Conceptualization, Data curation, Investigation, Software, Writing – review & editing. ZX: Conceptualization, Project administration, Writing – review & editing. JG: Conceptualization, Project administration, Writing – review & editing. FW: Conceptualization, Project administration, Writing – review & editing. CC: Conceptualization, Project administration, Writing – review & editing. XLv: Conceptualization, Project administration, Writing – review & editing. JT: Conceptualization, Project administration, Writing – review & editing. XLi: Conceptualization, Project administration, Writing – review & editing. XQ: Conceptualization, Project administration, Writing – review & editing. XW: Conceptualization, Project administration, Writing – review & editing. YW: Conceptualization, Project administration, Writing – review & editing. SO: Conceptualization, Project administration, Writing – review & editing. HoL: Supervision, Validation, Writing – review & editing. XS: Conceptualization, Project administration, Writing – original draft, Writing – review & editing. FJ: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. Research support was provided by the institutional and departmental sources at the First Affiliated Hospital of Soochow University and funding support was provided by the Jiangsu Province Medical Research Key Project (ZD2022021) and Suzhou Medical Innovation Applied Research (SKY2022138).

Conflict of interest

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

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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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.2024.1359878/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 25 April 2024
DOI 10.3389/fmed.2024.1361777

OPEN ACCESS

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RECEIVED 26 December 2023
ACCEPTED 08 April 2024
PUBLISHED 25 April 2024

CITATION
Wang P, Li K, Wu D, Cheng S, Zeng Y, Gao P, Wang Z and Liu S (2024) Pain control and neonatal outcomes in 211 women under epidural anesthesia during childbirth at high altitude in Qinghai, China.
Front. Med. 11:1361777.
doi: 10.3389/fmed.2024.1361777

Pain control and neonatal outcomes in 211 women under epidural anesthesia during childbirth at high altitude in Qinghai, China

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Background: High altitudes are characterized by low-pressure oxygen deprivation. This is further exacerbated with increasing altitude. High altitudes can be associated with reduced oxygenation, which in turn, can affect labor, as well as maternal and fetal outcomes. Epidural anesthesia can significantly relieve labor pain. This study aimed to assess the effects of elevation gradient changes at high altitude on the analgesic effect of epidural anesthesia, labor duration, and neonatal outcomes.

Methods: We divided 211 women who received epidural anesthesia into groups according to varying elevation of their residence (76 in Xining City, mean altitude 2,200 m; 63 in Haibei Prefecture, mean altitude 3,655 m; and 72 in Yushu Prefecture, mean altitude 4,493 m). The analgesic effect was assessed using a visual analog scale (VAS). Labor duration was objectively recorded. The neonatal outcome was assessed using Apgar scores and fetal umbilical artery blood pH.

Results: VAS scores among the three groups did not differ significantly ($p > 0.05$). The neonatal Apgar scores in descending order were: Xining group > Haibei group > Yushu group ($p < 0.05$). The stage of labor was similar among the three groups ($p > 0.05$). Fetal umbilical artery blood pH in descending order were: Xining group > Haibei group > Yushu group ($p < 0.05$).

Conclusion: Elevation gradient changes in highland areas did not affect the efficacy of epidural anesthesia or labor duration. However, neonatal outcomes were affected.

KEYWORDS

labor, epidural, analgesia, altitude, Apgar score

1 Introduction

High altitudes are characterized by low-pressure oxygen deprivation, which is further exacerbated with increasing altitude (1). Several recent studies have shown that a series of metabolic and physiological functional changes caused by exposure to high altitudes can negatively affect human organ systems, thus, affecting the health of people working and living in high-altitude areas (2, 3). Numerous studies have shown that prolonged exposure to low-pressure hypoxia causes increased respiratory rate and tidal volume. During acute

high-altitude exposures, hypocapnia is the main feature of the hypoxic ventilatory response, which increases blood pH. However, the effect of increased blood pH on pharmacokinetics is unknown and may depend on drug-specific properties (4). High altitude can adversely affect the cardiovascular system, leading to numerous unfavorable outcomes, including an increased risk of arrhythmias, systemic hypertension, high-altitude pulmonary hypertension, right ventricular hypertrophy, and right ventricular failure (5). In a low-oxygen plateau, the gray matter, white matter, arteries, and veins of the brain are altered, which in turn, affects brain functions, especially cognitive function, and induces the development of plateau diseases (6). People living at high altitudes for prolonged periods have poorer renal function and a reduced glomerular filtration rate (GFR) (7). Physiological changes due to altitude stress may affect drug absorption, distribution, metabolism, and excretion, as well as alter drug pharmacokinetics. As such, dose regimens to ensure drug efficacy and safety may need to be altered (7).

Qinghai Province is located in the northeastern part of the Tibetan Plateau, with an average elevation of more than 3,000 m above sea level. High altitude affects hemoglobin levels and is associated with reduced oxygenation, which can affect labor, as well as maternal and fetal outcomes. Labor pain is one of the most excruciating types of pain experienced by a woman (8). Only 9% of mothers can tolerate labor pain (9). Epidural anesthesia effectively relieves labor pain (10, 11). Most studies on epidural anesthesia for labor analgesia have been conducted in areas of normal altitude, e.g., plains. Few studies have been conducted in high-altitude areas, although higher altitudes are associated with greater adverse effects on the human body. Therefore, this study aimed to explore the differences in pain relief and neonatal prognosis after epidural anesthesia for labor analgesia in women who have been living at three different altitudes in the Qinghai region for prolonged periods.

2 Patients and methods

2.1 Ethics statement

This study was approved by the Ethics Committee of the local hospital (approval number: KY-2021-33). All women in labor signed an informed consent form for epidural anesthesia for labor analgesia. All procedures were conducted in line with the Declaration of Helsinki.

2.2 Participants

This observational cohort study was conducted at Qinghai Red Cross Hospital (Xining, Chengzhong, China) between October 2020 and October 2021. The study included 211 permanent residents of the Qinghai Province. A total of 408 women were screened for eligibility. Of these, 197 were excluded because they did not meet the inclusion criteria or refused to participate. Finally, 211 completed the study. The 211 women were divided into three groups according to varying altitudes (76 in the Xining group, mean altitude, 2200 m; 63 in the Haibei group, mean altitude, 3,655 m; and 72 in the Yushu group, mean altitude, 4,493 m). All 211 women voluntarily received epidural anesthesia for labor analgesia. This study followed strict inclusion and exclusion criteria. The inclusion criteria were as follows: 23–35 years of age, first vaginal delivery, singleton cephalic position, and 37–40 weeks of gestation. The exclusion criteria were serious medical or surgical illness, mental illness, infection at the puncture site, uncooperative labor, having already received other analgesics, and not a permanent resident of Xining City, Haibei Prefecture, or Yushu Prefecture. Figures 1, 2 show the study flowchart.

2.3 Anesthesia management

The mother and her family received epidural anesthesia for labor analgesia voluntarily. The anesthesiologist and obstetrician evaluated and confirmed that epidural anesthesia was not contraindicated. The family provided informed consent for the anesthesia, and the midwife provided intravenous access and connected all the monitoring equipment. The L3–4 space was selected and punctured using a 16-G Tuohy needle when the cervical opening was 0–3 cm. An epidural catheter was inserted 4 cm into the L3–4 space. A test dose of 4 mL of 2% lidocaine hydrochloride was injected into the epidural catheter. After confirming the absence of errors, a patient-controlled epidural analgesic pump was inserted. The formulation consisted of 0.67 mg/mL ropivacaine, 0.33 μg/mL sufentanil, and 138 mL physiological saline solution (total = 150 mL). The analgesic pump parameters were as follows: total volume, 150 mL; first dose, 10–15 mL/time; continuous infusion volume, 8–12 mL/h; self-controlled dosage, 0–12 mL/h; locking time, 40 min; and maximum limit, 30 mL/h.

2.4 Information recording

Maternal demographic information included age, ethnicity, gestational week, body mass index, educational background, place of residence (urban/rural), attendance at maternity school, signs of basal vitality (heart rate, blood pressure, and fetal heart rate), and the main indicator (visual analog scale (VAS) scores). The VAS is usually measured using a 10-cm straight line, ranging from 0 cm (no pain at all) to 10 cm (the worst pain imaginable). In this study, the following VAS cut-offs were used: 0–3 cm for mild pain, 4–6 cm for moderate pain, and 7–9 cm for severe pain. Maternal VAS scores were recorded at T0 (5 min before analgesia), T1 (10 min after labor analgesia), T2 (60 min after labor analgesia), T3 (at the opening of the uterus to 10 cm), and T4 (at delivery).

Asphyxia was assessed via five signs: heart rate, respiration, muscle tone, laryngeal reflexes, and skin color within 1 min, 5 min, and 10 min after birth. Each sign was scored between 0–2 points. Heart rate: heart rate greater than 100 beats per minute, 2 points; less than 100 beats per minute, 1 point; no heart rate, 0 points. Breathing: 2 points for even breathing and loud crying; 1 point for slow and irregular breathing or weak crying; and 0 points for no breathing. Muscle tone of limbs: 2 points if limbs are active, 1 point if limbs are slightly flexed, and 0 points if limbs are flaccid. Response to stimuli: After playing with the soles of the feet or inserting a nasal cannula, the baby cries, sneezes, or coughs for two points; only frowns and other slight reactions for one point; and no reaction for zero points. Skin

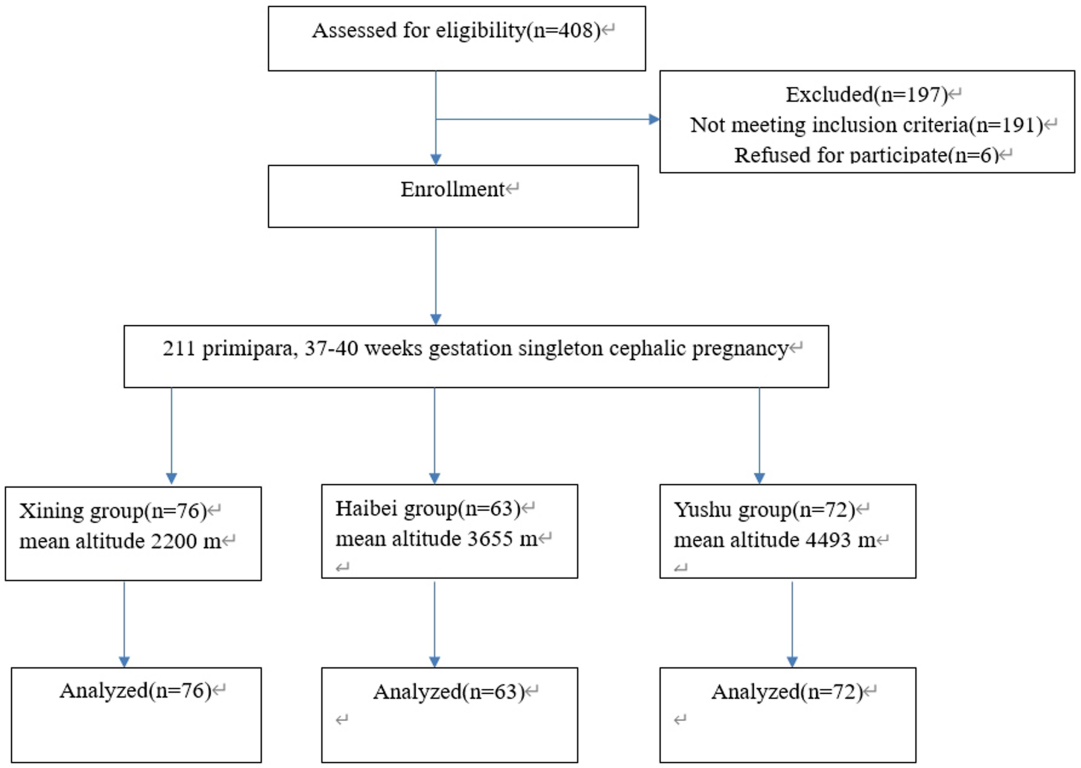

FIGURE 1
CONSORT flow diagram of study enrollment and analysis.

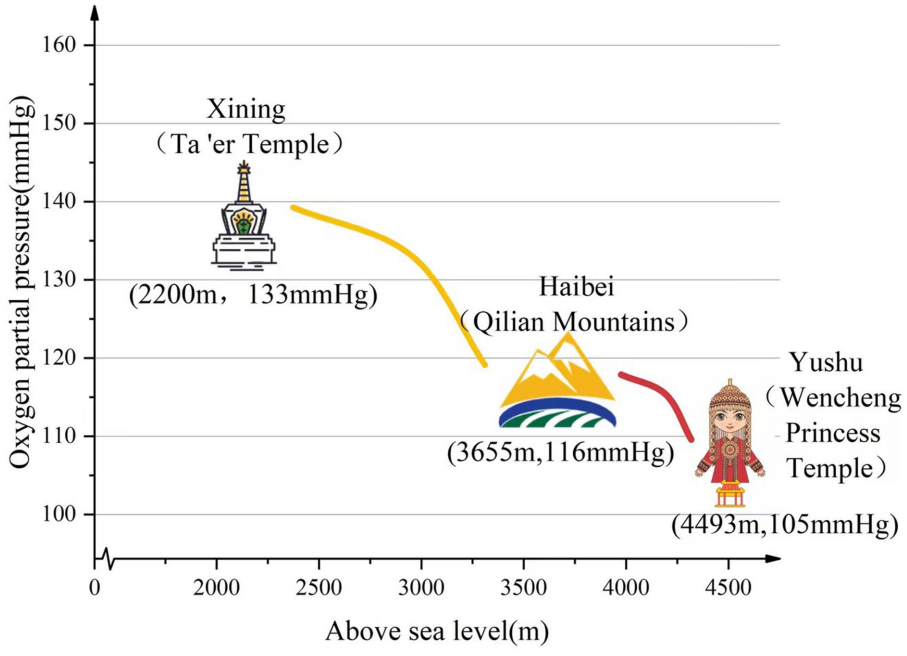

FIGURE 2
Oxygen partial pressure at different altitudes.

color: Pink skin on the whole body was scored 2 points, pink skin on the trunk, bruising on the limbs was scored 1 point, and bruising or pallor on the whole body was scored 0 points. The total score was calculated as the sum of the scores for the 5 signs (maximum = 10). Labor and neonatal umbilical artery blood pH, which was used to

assess for intrauterine hypoxia and neonatal prognosis, were considered as secondary indicators.

The maternal VAS scores, heart rate, blood pressure, and fetal heart rate, were recorded for analysis.

2.5 Sample size estimation and blinding

We calculated the sample size with consideration for the primary outcome (adequate analgesia). This estimation was based on an 80% power of the study and a 95% confidence interval. In total, 265 patients were considered adequate.

The nurse anesthesiologist who prepared the drug was aware of the grouping information. However, the anesthesiologist who administered the drug, the patients, and the data collector were blinded to the allocation.

2.6 Statistical analysis

The SPSS, version 22.0 (IBM, Chicago, IL, United States) was used for all data analyses. Numerical data are presented as ($x \pm s$). The differences among the three groups were assessed using the *t*-test. Comparisons between different time points within the same group were assessed using a paired *t*-test. Categorical data are presented as *n* (%). Comparisons between the groups were performed using the chi-square test. Factors of variables were controlled for with a skewed Analysis of covariance. $p < 0.05$ was considered statistically significant in this study.

3 Results

3.1 Patient demographics and clinical characteristics

The demographic characteristics of the three groups were comparable in terms of parturition age (years), ethnicity (Han Chinese/ethnic minority), gestational age (weeks), maternal body mass index (kg/m^2), maternal educational background (secondary/specialized/undergraduate and above), place of residence (urban/rural), participation in maternity schools (yes/no), and newborn weight (g). Table 1 presents the results of this study. Ethnic minorities accounted for a larger proportion of women who gave birth in the Yushu group. In contrast, the urban population predominated among women who gave birth in the Xining group and the number of participants who attended antenatal clinics was also higher ($p < 0.001$). The baseline characteristics of the mothers in the three groups are shown in Table 2. The three groups did not differ significantly in heart rate and blood pressure at each time point. At T1, the Yushu group had the lowest fetal heart rate values, the Haibei group had the second highest, and the Xining group had the highest ($p < 0.001$).

3.2 Main indicators

3.2.1 Assessment of analgesic efficacy

As shown in Table 3 and Figure 3, the VAS scores among the three groups were similar ($p > 0.05$).

TABLE 1 Demographics of the three groups.

	Xining (*n* = 76)	Haibei (*n* = 63)	Yushu (*n* = 72)	X^2/F	*p*
Age (years)	26.62 ± 3.04	26.97 ± 2.98	26.86 ± 3.11	0.245	0.783
Nationality (%)				74.753	<0.001
Han	54 (71.1)	21 (33.3)*	2 (2.8)*#		
Majority	22 (28.9)	42 (66.7)*	70 (97.2)*#		
Gestational age (weeks)	38.91 ± 1.21	38.87 ± 1.16	38.53 ± 1.37	2.014	0.136
Puerpera BMI (kg/m^2)	28.85 ± 2.53	28.68 ± 2.89	29.35 ± 2.96	1.070	0.345
Educational background (%)				12.516	0.014
Middle school	18 (23.7)	27 (42.9)	36 (50)*		
Three-year college	35 (46.1)	24 (38.1)	25 (34.7)*		
Bachelor and above	23 (30.3)	12 (19)	11 (15.3)*		
Residency (%)				76.651	<0.001
Cities and towns	63 (82.9)	23 (36.5)*	9 (12.5)*#		
Countryside	13 (17.1)	40 (63.5)*	63 (87.5)*#		
Participation in maternity schools (%)				50.339	<0.001
Yes	27 (35.5)	45 (71.4)*	65 (90.3)*#		
No	49 (64.5)	18 (28.6)*	7 (9.7)*#		
Newborn weight (g)	3209.58 ± 308.54	3162.83 ± 326.24	3134.69 ± 296.35	1.104	0.333

*p <0.05 vs Xining group; #p <0.05 vs Haibei group.

3.2.2 Neonatal outcomes

The 1-min Apgar score was the highest in the Xining group, followed by the Haibei group, and the lowest in the Yushu group ($p < 0.001$). The three groups did not differ significantly in the 5- and 10-min Apgar scores ($p > 0.05$). As shown in Table 4 and Figures 4, 5, fetal umbilical arterial blood pH was higher in the Xining group, followed by the Haibei group, and the lowest in the Yushu group ($p < 0.001$).

3.2.3 Labor stage assessment

Labor duration did not differ significantly among the three groups ($p > 0.05$, Table 5; Figure 6).

4 Discussion

This study compared the differences in analgesic effects among women who received epidural anesthesia at different altitudes in a high-altitude region and neonatal prognosis. The three groups of women resided in Qinghai at different altitudes and received the same epidural anesthesia for labor analgesia. Our results suggest that labor at locations of increasing altitude affects neonatal prognosis despite a painless labor. Importantly, a higher altitude resulted in lower 1-min Apgar scores among the neonates and lower neonatal umbilical arterial blood pH, which adversely affects neonatal outcome but demonstrated no effect on analgesic efficacy or labor duration.

The environmental characteristics of low-pressure hypoxia at high altitudes are great threats to human beings. The higher the altitude, the lower the atmospheric pressure and partial pressure of oxygen. At altitudes beyond 2,500 m, the partial pressure of oxygen declines even further, which in turn, leads to an exponential reduction in arterial oxygen saturation (SaO2) (4). In the 1960s, Grahn and Kratchmann reported that atmospheric pressure was significantly correlated to neonatal mortality (12). At high altitudes, pregnant women have less available iron and vitamins A and D, higher erythropoietic requirements, and lower arterial oxygen levels during the antenatal period (13). Adequate oxygen for fetal development depends not only on atmospheric oxygen levels, but also on the efficient transport of oxygenated blood via the uteroplacental circulation and the cardiac output in women also reduces during pregnancy (14–16). Therefore, the efficient transport of oxygenated blood into the uteroplacental circulation is further compromised, affecting fetal development. To quickly assess the clinical status of a newborn within 1 min and determine whether timely intervention is needed to restore respiration, Dr. Virginia Apgar devised a scoring system in 1952 to provide a standardized assessment of the infant after birth (the Apgar score) (17). The Apgar score consists of five indicators, including skin color, heart rate, reflex irritability, activity/flexion, and respiratory effort. Each indicator can be scored on a scale of 0–2 for a summed

TABLE 2 Comparison of baseline information between the three groups.

	Group	*n*	T0	T1	T2	T3	T4
Rate	Xining	76	81.37 ± 11.54	87.41 ± 8.98[a]	83.24 ± 8.01	80.62 ± 6.97	80.14 ± 8.63[a]
	Haibei	63	81.32 ± 10.5	88.98 ± 9.54[a]	83.30 ± 7.73	80.02 ± 8.23	80.65 ± 8.64[a]
	Yushu	72	81.01 ± 9.93	85.61 ± 9.95[a]	81.81 ± 8.35	80.14 ± 7.61	80.64 ± 8.32[a]
	F		0.062	2.399	0.719	0.681	0.306
	p		0.939	0.147	0.489	0.507	0.273
Systolic blood pressure	Xining	76	113.50 ± 8.43	103.54 ± 8.62[a]	110.46 ± 8.49[a]	113.42 ± 10.22	112.64 ± 9.54
	Haibei	63	114.06 ± 9.62	102.90 ± 8.77[a]	110.25 ± 10.19[a]	111.37 ± 8.87	113.71 ± 9.80
	Yushu	72	113.03 ± 8.97	103.44 ± 9.11[a]	110.22 ± 9.03[a]	112.72 ± 8.72	112.12 ± 10.04
	F		0.274	0.084	0.136	0.679	0.845
	p		0.761	0.919	0.873	0.508	0.431
Diastolic blood pressure	Xining	76	71.96 ± 6.55	71.50 ± 8.10	71.89 ± 8.21	71.80 ± 6.57	71.55 ± 6.38
	Haibei	63	71.62 ± 6.26	71.83 ± 5.93	71.08 ± 7.23	71.05 ± 7.01	71.60 ± 6.09
	Yushu	72	71.36 ± 7.60	71.17 ± 6.86	71.74 ± 6.49	71.89 ± 7.89	71.53 ± 6.61
	F		0.676	0.830	0.253	0.201	0.057
	p		0.510	0.438	0.777	0.818	0.945
Fetal heart	Xining	76	135.76 ± 4.38	127.14 ± 4.83[a]	133.26 ± 4.28[a]	136.45 ± 4.28	135.91 ± 4.55
	Haibei	63	136.46 ± 4.27	125.17 ± 3.90*[a]	133.27 ± 4.69[a]	136.68 ± 4.35	136.35 ± 4.48
	Yushu	72	136.89 ± 3.85	121.39 ± 4.25*#[a]	133.04 ± 4.58[a]	136.46 ± 4.33	135.81 ± 4.02
	F		0.002	10.479	0.025	0.800	0.609
	p		0.998	<0.001	0.976	0.451	0.545

*p <0.05 vs Xining group; #p <0.05 vs Haibei group; [a]p <0.05 vs T0.

TABLE 3 VAS score associated with Xining vs Haibei vs Yushu.

	Group	*n*	T0	T1	T2	T3	T4
VAS score	Xining	76	7.87 ± 1.01	3.64 ± 1.02[a]	2.82 ± 0.92[a]	4.97 ± 1.03[a]	5.47 ± 1.13[a]
	Haibei	63	7.87 ± 0.81	3.24 ± 1.04*[a]	2.48 ± 0.93*[a]	4.56 ± 1.33*[a]	5.08 ± 1.15*[a]
	Yushu	72	7.97 ± 1.02	2.82 ± 1.09*[#a]	2.13 ± 0.96*[#a]	3.82 ± 1.07*[#a]	4.50 ± 0.99*[#a]
	F		0.085	4.400	12.326	13.216	4.968
	p		0.919	0.015	<0.001	<0.001	0.008

*p <0.05 vs Xining group; #p <0.05 vs Haibei group; ap <0.05 vs T0.

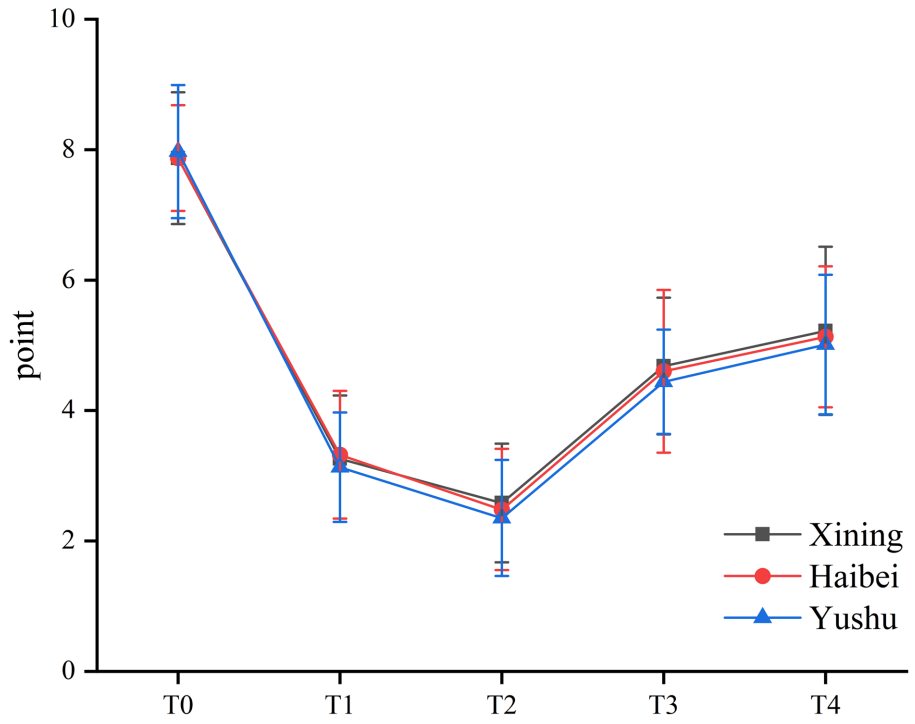

FIGURE 3
The VAS scores among the three groups.

TABLE 4 Comparison of neonatal Apgar scores between the three groups.

	Xining (*n* = 76)	Haibei (*n* = 63)	Yushu (*n* = 72)	X^2/F	*p*
1 min Apgar scale (points)	8.88 ± 0.56	8.51 ± 0.50*	8.28 ± 0.63*#	7.915	<0.001
5 min Apgar scale (points)	8.99 ± 0.42	8.86 ± 0.64	8.79 ± 0.79	5.287	0.506
10 min Apgar scale (points)	9.93 ± 0.41	9.79 ± 0.60	9.75 ± 0.78	0.649	0.524
Fetal cord blood PH	7.36 ± 0.09	7.31 ± 0.08*	7.26 ± 0.07*#	11.725	<0.001

*p <0.05 vs Xining group; #p <0.05 vs Haibei group.

total of 10 points. A score of 8–10 indicates good condition, 4–7 indicates fair condition, and 0–3 indicates poor condition (18). In a controlled study of newborns in Cerro de Pasco (4,340 m above sea level) and Lima (150 m above sea level), Peru, arterial oxygen saturation and 1-min Apgar scores were lower in newborns who were born at higher altitudes (19). In this study, the Yushu group demonstrated the lowest 1-min Apgar scores, while the Xining group showed the highest. The Haibei group demonstrated 1-min Apgar scores that were between the other two groups. These results demonstrated that the 1-min Apgar scores decreased with increasing altitude. Notably, the 1-min Apgar scores in all three groups were above 8, indicating good neonatal conditions.

In contrast, a study in Colorado, United States, identified lower neonatal birthweights at high altitudes as a potentially significant factor for reduced neonatal outcomes (20). The average weight of neonates in the Yushu group (highest altitude group) was 3 kg. Numerous factors can influence neonatal Apgar scores, including maternal sedation or anesthesia during labor, congenital malformations, gestational age, trauma, and inter-observer variability. The 1-min Apgar score assesses acute or transient neonatal problems.

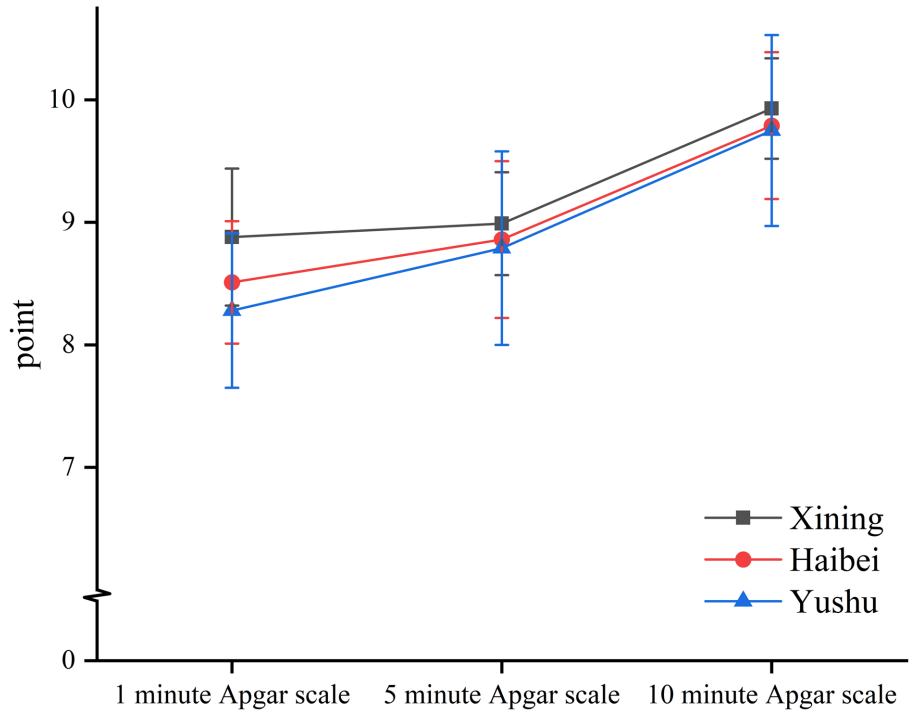

FIGURE 4
Apgar scores among the three groups.

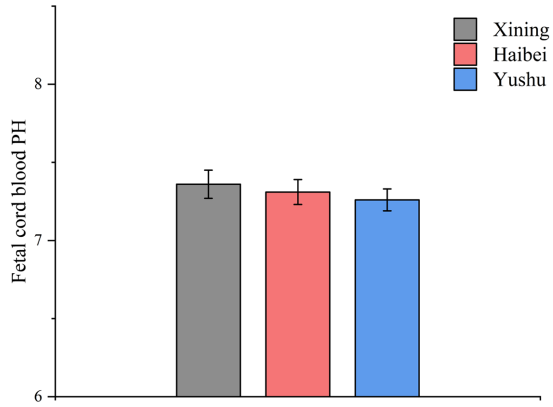

FIGURE 5
Fetal cord blood PH among the three groups.

Conversely, the 5-min Apgar score is more appropriate for assessing neonatal prognosis as it reflects measures, such as prior resuscitation, and the score is not related to birthweight (17). If the 5-min Apgar score was low, the score should be measured again at 10 min (21). In the present study, the 5- and 10-min Apgar scores between the three groups did not differ significantly. The lack of difference may be due to a high neonatal 1-min Apgar score in all three groups, and the neonates were provided with oxygen and warmth immediately after birth. Fetal heart decreased after 10 min of analgesia in all three groups of mothers in this study. The early decrease in fetal heart rate may be related to uterine contractions and vagal excitation due to fetal head compression (22).

Cord blood pH and lactate dehydrogenase levels are used to predict fetal hypoxia-related damage and metabolic acidosis (21). A recent study concluded that cord blood pH at birth, assessed in conjunction with Apgar scores, is a good predictor of asphyxia severity at birth and early neonatal prognosis (23). When the products of anaerobic metabolism exceed the buffering capacity of fetal arterial blood, the pH of the umbilical artery decreases because of decreased oxygen availability to body tissues and increased lactate content (24). Prolonged gestation, premature rupture of the membranes, low amniotic fluid, and/or fetal growth retardation can decrease the pH of umbilical cord arterial blood in newborns (25, 26). Transient fetal and placental hypoxia may result urteroplacental perfusion reduces by 60% or more due to uterine contractions during delivery (25). The greatest physiological challenge for women in late pregnancy is maintaining sufficient oxygenated blood to supply the uteroplacental circulation and ensure proper fetal development. Oxygen transport is made more difficult by living in high-altitude and hypoxic environments for prolonged periods. Although physiological adjustments can be made to counteract arterial hypoxemia to promote hemodynamic stability and increase uteroplacental blood flow, these adjustments can negatively affect newborns (27). In this study, the pH of the neonatal umbilical cord arterial blood in the Xining group was the highest, followed by that of the Haibei group. Conversely, the Yushu group had the lowest umbilical cord arterial blood pH. Despite the differences, the pH was above 7.2 in all three groups. Our results confirmed that an increase in altitude can affect the fetal umbilical artery blood.

Some studies have found that maternal hypotension caused by epidural anesthesia for labor analgesia decreases the fetal umbilical

TABLE 5 Stage of labor associated with Xining vs Haibei vs Yushu.

Group	*n*	First stage of labor (min)	Second stage of labor (min)	Third stage of labor (min)
Xining	76	456.34 ± 134.17	62.93 ± 15.36	5.54 ± 2.04
Haibei	63	473.76 ± 135.42	62.33 ± 17.77	5.60 ± 1.80
Yushu	72	465.26 ± 159.3	62.14 ± 15.73	5.83 ± 2.08
F		0.200	0.347	0.149
p		0.819	0.707	0.862

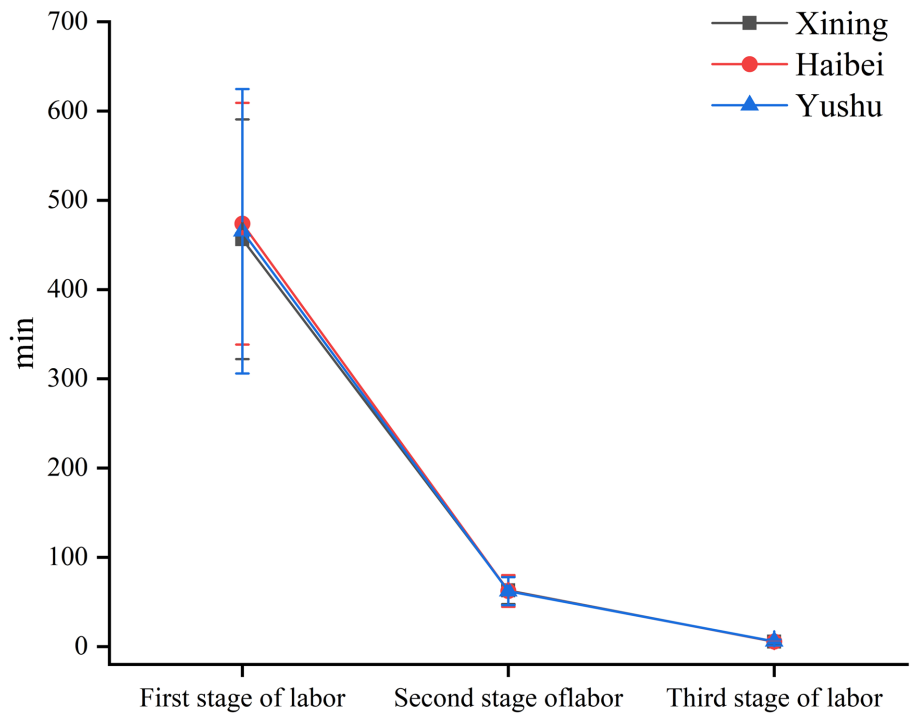

FIGURE 6
Labor duration among the three groups.

cord blood pH (28). In this study, all three groups received epidural anesthesia for labor analgesia. All of our mothers had a transient decrease in blood pressure 5 min after the onset of analgesia, but the maternal blood pressure gradually recovered soon after. Further studies are needed to confirm whether cord blood pH is affected by this phenomenon.

Pain during labor comes primarily from uterine contractions and cervical dilatation. These stimulations are transmitted to the spinal nerves at T10–L1, leading to visceral pain. Descent of the fetal head stretches the perineum and vagina, and pain fibers in the pudendal and spinal nerves in S2–4 are activated (29). Epidural analgesia, which involves injecting opioids and other adjuvants through an epidural catheter into the epidural space, blocks these pathways to achieve analgesia (30). The World Health Organization recognizes this as an effective analgesic strategy for relieving labor pain (31). Physiological changes induced by altitude stress may affect drug absorption, distribution, metabolism, and excretion and alter drug pharmacokinetics (32). However, the present study found no differences in maternal VAS scores among the three groups. Our results may be due to the mothers being adapted to high-altitude living over prolonged periods (6, 33). Genomical adaption may also contribute to this (34).

Some studies have shown that labor duration is related to the number of births, maternal age, newborn weight, medical interventions, and other factors (35). Greenberg et al. found that older maternal ages correlated with longer first stages of labor in both primiparous and transient labor (36). Similarly, Chen et al. reported that older women had prolonged first and second stages of labor (35). Moreover, medical interventions during labor can also prolong the first and second stages of labor (37). Furthermore, recent studies have shown that epidural labor analgesia prolongs the first and second stages of labor (38). On the contrary, Feng et al. found that epidural labor analgesia did not affect the labor duration (39). Our results also showed that epidural labor analgesia did not affect the course of labor, and the course of labor between the three groups did not differ significantly. In this study, the difference in altitude did not affect the labor duration in women who received epidural labor analgesia.

5 Limitation

This study has some limitations. We only included women who receive epidural labor analgesia at varying high altitudes and did not include data from the plains for comparison. This conclusion may not apply to other high-altitude regions because of variations in climate and human environment, economic base, racial differences, educational backgrounds, etc. in each region. In the future, studies should include a control group from the plains to enhance the study design. Future studies should also consider including a greater number of women in labor, focusing on the effects of differences in racial, economic, educational, and other indicators on the mothers and newborns living at high altitudes. Furthermore, the different effects between general anesthesia and nerve block anesthesia at high altitudes should also be further investigated.

6 Conclusion

Changes in elevation gradients in highland areas do not affect the efficacy of epidural labor analgesia or labor duration, but they do affect neonatal outcomes. Our findings provide a good guide for local physicians in the planning for birth deliveries and maternal and neonatal interventions, especially for expectant mothers living at high altitudes for a long time or when they travel to high altitudes to practice medicine. Doctors should also inform women of reproductive age who want to move to high altitudes about the need for health assessment for themselves and their children.

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 humans were approved by Ethics Committee of Qinghai Red Cross Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The 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

PW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Writing – original draft, Writing – review & editing. KL: Investigation, Methodology, Writing – review & editing. DW: Writing – review & editing. SC: Data curation, Writing – review & editing. YZ: Software, Writing – review & editing. PG: Supervision, Writing – review & editing. ZW: Data curation, Resources, Investigation, Project administration. SL: Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

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

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 07 May 2024
DOI 10.3389/fmed.2024.1377902

OPEN ACCESS

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RECEIVED 28 January 2024
ACCEPTED 26 March 2024
PUBLISHED 07 May 2024

CITATION
Hiller M, Burisch C, Wittmann M, Bracht H, Kaltwasser A and Bakker J (2024) The current state of intensive care unit discharge practices - Results of an international survey study. *Front. Med.* 11:1377902.
doi: 10.3389/fmed.2024.1377902

The current state of intensive care unit discharge practices - Results of an international survey study

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Background: Increasing pressure on limited intensive care capacities often requires a subjective assessment of a patient's discharge readiness in the absence of established Admission, Discharge, and Transfer (ADT) guidelines. To avoid suboptimal care transitions, it is important to define clear guidelines for the admission and discharge of intensive care patients and to optimize transfer processes between the intensive care unit (ICU) and lower care levels. To achieve these goals, structured insights into usual ICU discharge and transfer practices are essential. This study aimed to generate these insights by focusing on involved stakeholders, established processes, discharge criteria and tools, relevant performance metrics, and current barriers to a timely and safe discharge.

Method: In 2022, a structured, web-based, anonymous cross-sectional survey was conducted, aimed at practicing ICU physicians, nurses, and bed coordinators. The survey consisted of 29 questions (open, closed, multiple choice, and scales) that were divided into thematic blocks. The study was supported by several national and international societies for intensive care medicine and nursing.

Results: A total of 219 participants from 40 countries (105 from Germany) participated in the survey. An overload of acute care resources with ~90% capacity utilization in the ICU and the general ward (GW) leads to not only premature but also delayed patient transfers due to a lack of available ward and intermediate care (IMC) beds. After multidisciplinary rounds within the intensive care team, the ICU clinician on duty usually makes the final transfer decision, while one-third of the panel coordinates discharge decisions across departmental boundaries. By the end of the COVID-19 pandemic, half of the hospitals had implemented ADT policies. Among these hospitals, nearly one-third of the hospitals had specific transfer criteria established, consisting primarily of vital signs and laboratory data, patient status and autonomy, and organization-specific criteria. Liaison nurses were less common but were ranked right after the required IMC capacities to bridge the care gap between the ICU and normal wards. In this study, 80% of the participants suggested that transfer planning would be easier if there was good transparency regarding the capacity

utilization of lower care levels, a standardized transfer process, and improved interdisciplinary communication.

Conclusion: To improve care transitions, transfer processes should be managed proactively across departments, and efforts should be made to identify and address care gaps.

KEYWORDS

survey, intensive care unit discharge, discharge process, discharge criteria, discharge tools, discharge barriers, care transitions, patient transfer

1 Introduction

Discharge decisions for intensive care unit (ICU) patients are frequently taken under pressure to free up ICU beds. Without established guidelines or hospital Admission, Discharge, and Transfer (ADT) policies, evaluating the readiness to be discharged commonly relies on subjective judgments (1). In daily clinical practice, the challenge is to make the right decision at the right time for the right patient. A premature discharge to the ward can increase the risk for patients being readmitted to the ICU and may even elevate their risk of mortality (1). On the contrary, delayed discharge may waste resources and may result in the overtreatment of patients (2). In many countries, guidelines for patient discharge and transfers exist but are typically created locally. These guidelines often lack robust scientific foundations, fail to seamlessly integrate with hospital-wide patient flow procedures, and overlook relevant stakeholders' insights. Several studies have highlighted the need to define guidelines for ICU admission and discharge and to optimize the processes by involving the ICU and GW teams before and after discharge (3–5). Thus, structured insights into current clinical practices around patient transfers are needed to define the baseline and to implement any improvement measures. Therefore, the primary objective of this survey was to gain insights into the current status of ICU patient care transitions. We focused on transfer practices from the ICU, the involvement of stakeholders, transfer criteria, the established processes and tools used, the metrics related to ICU transfer processes, and current barriers to a timely and safe discharge. As a secondary objective, we intended to use the results to develop more specific guidelines for the standardization and optimization of care transition processes from the intensive care unit.

2 Methods

The study was conducted using a structured, web-based, anonymous, cross-sectional survey that is open to any participant from the target group, including practicing intensive care physicians, intensive care nurses, and bed coordinators in the acute care area. The participants' informed consent was obtained through dedicated questions before the start of the questionnaire. The survey was open for participation between 8 March 2022 and 19 September 2022. Participants could save their answered questions and continue later until the deadline of the survey. The survey was embedded in an online survey tool platform, adhering to the General Data Protection Regulation (welphi.com, Decision Eyes, Lisbon, Portugal). Ethical approval was obtained through a waiver by the Erasmus MC CRB (MEC-2022-0522). The survey was based on a systematic literature review (6) and the previous work of the research group (7–11).

The survey encompassed 29 questions, consisting of open, closed, and multiple-choice questions as well as five-point Likert scales (refer to Supplementary Datasheet 1). The questions were arranged in categorical blocks as follows: A. Demographics; B: Hospital size, type, and unit characteristics; C: Variables related to the current ICU discharge practice; D: Stakeholders and discharge decision-makers; E: Established discharge criteria; F: Discharge planning and discharge process; G: Occurrence of premature and delayed discharges; and H: Other reasons for suboptimal discharges that may relate to suboptimal care at the receiving unit, readmissions, or avoidable adverse events.

The survey was distributed in two languages: English and German. Both versions were pre-tested by eight test users per survey. Minor adjustments were made based on the feedback of pre-test users. No sample size calculation was performed, as the survey served as descriptive research. The survey was designed to maximize the completion rate and minimize dropout reasons. Therefore, only the minimum number of questions to generate the required insights were used. No iterative item reduction strategies were applied. The survey was endorsed by several intensive care societies [European Society of Intensive Care Medicine (ESICM), European Federation of Critical Care Nursing Associations (EfCCNa), Deutsche Gesellschaft für Fachkrankenpflege und Funktionsdienste e.V. (DGF), Deutsche interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI), and Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e. V. (DGAI)]. The link to the survey was distributed via the society's members lists. Data were summarized by a statistician using descriptive statistics. The absolute number and percentage of responses were calculated and used to interpret the opinion distribution for each question.

Abbreviations: ADT, admission, discharge, and transfer; ICU, intensive care unit; GW, general ward; IMC, intermediate care unit; OR, operating room; ESICM, European Society of Intensive Care Medicine; EfCCNa, European Federation of Critical Care Nursing Associations; DGF, Deutsche Gesellschaft für Fachkrankenpflege und Funktionsdienste e. V.; DIVI, Deutsche interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin; DGAI, Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin e.V.

10.3389/fmed.2024.1377902

TABLE 1 Survey panel demographics and hospital and unit characteristics.

Survey panel demographics					
Sex ($n = 199$ spec.)	Male 63%; $n = 125$	Female 37%; $n = 74$			
Professional group ($n = 200$ spec.)	ICU physicians 68%; $n = 136$	ICU nurses 24%; $n = 48$	ICU bed managers 1.5%; $n = 3$	Others 6.5%; $n = 13$	
Leadership positions ($n = 147$ spec.)	Senior physicians 48%; $n = 71$	Head of the department 38%; $n = 56$	Head of ICU nurses 14%; $n = 20$		
ICU work experience ($n = 194$ spec.)	>20 yrs. 41%; $n = 7$	16–20 yrs. 15%; $n = 29$	11–15 yrs. 20%; $n = 38$	5–10 yrs. 15%; $n = 29$	< 5 yrs. 10%; $n = 19$
Hospital and unit characteristics of panelists' workplace					
Hospital type ($n = 193$ spec.)	University hospital 38%; $n = 74$	Teaching hospital 30%; $n = 58$	Municipal hospital 14%; $n = 26$	Church hospital 9%; $n = 17$	Private hospital 7%; $n = 13$
Hospital size ($n = 188$ spec.)	>900 beds 25%; $n = 47$	600–900 beds 22%; $n = 41$	450–599 beds 15%; $n = 29$	250–449 beds 22%; $n = 42$	<250 beds 15%; $n = 29$
ICU size ($n = 176$ spec.)	>25 beds 19%; $n = 34$	21–25 beds 11%; $n = 19$	13–20 beds 29%; $n = 51$	6–12 beds 40%; $n = 70$	<6 beds 1%; $n = 2$
No. of patients treated in participant's ICU annually ($n = 142$ spec.)	>2,500 patients 11%; $n = 16$	1,001–2,500 patients 36%; $n = 51$	501–1,000 patients 27%; $n = 38$	251–500 patients 18%; $n = 26$	≤250 patients 8%; $n = 11$
Types of ICU ($n = 185$ spec.)	Interdisciplinary ICU 60%; $n = 111$	Surgical ICU 15%; $n = 28$	Medical ICU 11%; $n = 19$	Cardiological ICU 3%; $n = 5$	Neurosurgical ICU 3%; $n = 5$
The head of ICU ($n = 160$ spec.)	Intensivist 58%; $n = 93$	Anesthesiologist 30%; $n = 48$	Internist 4%; $n = 7$	Surgeon 2%; $n = 3$	Other 6%; $n = 9$

3 Results

3.1 Panel demographics

A total of 219 participants from 40 countries (with the majority from Germany, 48%; $n = 105$) participated in the survey held between March and September 2022 (see Supplementary Table 1). As questions were allowed to be omitted, completeness percentages of datasets ranged from 2 to 98% (with an average of 52% and a median of 45%), leading to variations in the total number of answers per question. An overview of the survey panel demographics and hospital and unit characteristics of the panelists' workplaces is provided in Table 1. Some outstanding specifics of the panel demographics were highlighted, with 63% of the participants being—wherever sex was specified—male individuals. ICU physicians were the largest professional group with 68% of the participants, followed by ICU nurses (24% of $n = 200$). The panel consisted of very senior ICU practitioners, with 147 specified leadership positions and long-term work experience in the ICU environment, with 40% having more than 20 years and 15% having 16–20 years of ICU experience.

3.2 Hospital and unit characteristics

Two-thirds of the survey panelists worked in university and teaching hospitals. The largest group of panelists, constituting 25% of the total number of respondents ($n = 188$), worked in large hospitals with more than 900 beds. Small and medium-sized hospitals were equally represented. In total, 40% (of $n = 176$) of the participants worked in smaller ICUs with 6–12 beds and 29% worked in medium-sized ICUs with 13–20 beds. On average, 36% (of $n = 142$) of the panelists treated between 1,001 and 2,500 patients, and 27% of the panelists treated between 501 and 1,000 patients per year with their teams in their unit. The majority of the panelists worked in interdisciplinary ICUs (60% of 185). The units were mainly led by intensivists (58%) and anesthesiologists (30% of $n = 160$). When asked for other present units specialized in high-acute care in their hospitals, 153 panelists listed several other present units ($n = 451$ units listed), with the most commonly mentioned units being the intermediate care or step-down unit (24%) and the stroke unit (22%), followed by the palliative care unit (19%) and the chest pain unit (18%).

3.3 Performance metrics related to ICU discharge practice

The questions regarding routine ICU capacity utilization metrics revealed high ICU occupancy rates of ~90% ($n = 69$), with an ICU patient-to-nurse ratio of mainly 2 per day (44%) and 2–3 per night shift (49% of $n = 160$), an average ICU length of stay of ~4–5 days (41% of $n = 69$), and a readmission rate of ~5% ($n = 46$). Further metrics along the acute patient pathway were also high with a GW occupancy rate of ~90% ($n = 38$). In the GW, the patient-to-nurse ratios were observed to be 6–10 during the day (53% of $n = 132$) and 10–20 during the night shift (66% of $n = 62$). The average hospital length of stay was observed between 2.5 days and 10 days (67% of $n = 52$). About half of the participants that provided their ICU mortality stated it between 6% and 20% (51% of $n = 49$). Delirium rates were specified by 32 participants,

where half of them reported delirium rates between 11 and 30% in their ICUs.

3.4 Stakeholders and discharge decision makers

Multidisciplinary rounds were used by the majority of the respondents (78% of $n = 87$). Reported participants were doctors, ICU nurses and physiotherapists. Only 33% (of $n = 87$) of the respondents consulted other departments to come to a discharge decision. In most cases, the other decision makers were the receiving unit and/or an infectious disease specialist. However, the final discharge decision was mainly taken by the ICU clinician on duty (43% of $n = 190$ votes; multiple answers possible; $n = 91$ panelists).

3.5 Established discharge criteria in daily clinical routine

Nearly half of the respondents (49% of $n = 85$) had ADT guidelines established in their hospitals, whereas 37% had none (14% did not know or could not answer). When asked for specific discharge criteria from the ICU to the GW or other lower levels of care established in their unit, the majority of the participants had none (56% of $n = 85$) and 36% had some in place (7% did not know). The respondents, who mentioned that specific discharge criteria were established, listed the type of patient-specific criteria that are usually considered for a discharge decision: patient's current acuity level, neurological status, and laboratory data were considered the most, followed by the patient's independence and mobility, frailty, and specific clinical scores [such as Early Warning Score (EWS), Modified Early Warning Score (MEWS), Acute Physiological and Chronic Health Evaluation Index II (APACHE II), Sequential Organ Failure Assessment (SOFA), Glasgow Coma Scale (GCS), Richmond Agitation-Sedation Scale (RASS), Confusion Assessment Method for the ICU (CAM-ICU), and Clinical Pulmonary Infection Score (CIPS), specified by $n = 5$].

Furthermore, the panelists were asked for the type of organizational criteria that were usually considered for a discharge decision. Current bed availability, patient-to-nurse ratio, competencies, and available technology at the receiving unit were mentioned the most, followed by the current acuity level in the ICU, available palliative care pathway outside the ICU, the current ICU occupancy rate, and the operating room (OR) schedule. Healthcare economic factors were strongly reported as not being considered when making discharge decisions. Of the respondents who had ICU discharge criteria in place, the majority (75% of $n = 20$) agreed that these criteria were specific enough to evaluate individual discharge readiness and ensure a safe transition to a lower level of care.

3.6 Discharge planning and discharge process

Panelists reported that most patients were discharged to a GW (73% of $n = 84$), whereas 23% were discharged to a step-down/intermediate care unit. A discharge protocol or handover form was used by 58% of the respondents ($n = 49$), mainly in a digital or a paper-based format (51 and 37%, respectively). A liaison nurse to facilitate the patient's discharge was reported by only 36% of the respondents (n=82). The majority of the respondents (63% of $n = 82$) reported the presence of a care gap between the time when a patient is no longer in need of ICU care and when a patient can safely transition to a GW. The proposed measures to decrease this care gap are shown in Supplementary Table 2.

Advanced discharge planning was deemed feasible by 80% (of $n = 76$) of the respondents, where there was no consensus on the optimal time window. The answers (n =28) were scattered between $\leq$6 h and up to >24–$\leq$48 h. Panelists who considered that discharge planning was feasible more in advance were currently lacking certain requirements that are listed in Supplementary Table 3.

3.7 The occurrence of premature and delayed discharges

The majority of the participants did not observe premature discharges from ICUs (57% of $n = 83$), while the remaining participants reported some premature discharges. The top three underlying reasons for premature discharges were ICU capacity strain, admission of patients with higher acuity, and lack of objective discharge criteria or scoring systems. On the contrary, delayed ICU discharges were common (68% of $n = 82$). The most cited reasons for delayed discharge were as follows: no free bed at the receiving unit; patient flow and discharge management processes not synchronized with the receiving units; lack of set care goals that need to be met for discharge readiness, and lack of specific discharge criteria (Supplementary Figure 1). Multimorbidity, delirium, and communication difficulties with the patient were mentioned as the most occurring reasons for the presence of suboptimal discharges that may relate to suboptimal care at the receiving unit, readmissions, or preventable adverse events (Supplementary Figure 2).

4 Discussion

The main goal of the survey study was to gain detailed and structured insights into the current process reality of ICU patient care transitions and its specific framework conditions. Based on the findings presented in this study, we believe that our research can enhance comprehension of the current baseline situation and play a role in formulating more precise guidelines to standardize and improve the transition of care processes from the intensive care unit. Addressing a pressing topic, especially in the past COVID-19 pandemic, the survey received great support after being endorsed and distributed by several intensive care societies.

Additionally, the feedback received upfront on the survey content highlighted the need for more tangible insights into this area to establish standardized and cross-departmental acute patient flow management. This finding is supported by the related literature (5, 12–18), especially as study insights often result from rather small and regional to local cohorts. In many countries, the COVID-19 pandemic and retrospective analysis highlighted the present lack of clear discharge guidelines, specified admission criteria and acuity levels, and the match of acute care capacities with patient group needs (19–23). The survey was launched towards the end of the pandemic, and the ongoing appreciation for the topic was demonstrated by 219 participants from 40 countries, primarily holding senior positions and having long-term ICU work experience, who went through a list of 29 questions and provided quite a decent number of individual comments. In general, the participants' panel was dominated by ICU physicians with twice as many panelists as ICU nurses or other respondents. Academic hospitals represented most of the respondents' workplaces, and almost half of the panel worked in small units comprising 6–12 ICU beds. Interdisciplinary ICUs (60%) were the most common organizational form. ICUs were mainly led by intensivists or anesthesiologists. Intermediate care or step-down units, stroke units, and palliative care and chest pain units were common complementary units in the hospitals' high acuity area.

Based on the current literature, several performance metrics are associated with ICU discharge practice (1, 2, 24–30). Being asked about ICU performance metrics, acute care capacity strain with ICU and GW capacity rates of ∼90% is a daily struggle, leading to not only premature discharges (pressure to free up ICU beds) but also delayed transfers (no available GW beds and no or too few IMC beds). In discharge decision making, multidisciplinary rounds within the ICU team have been established; however, the ICU clinician on duty takes the final decision in most cases. Only one-third of the participants practices shared decision-making across departmental borders (for example, with the receiving units) and consultation with other experts such as antibiotic stewardship members. Although being asked toward the end of the COVID-19 pandemic, still only half of the panel had ADT guidelines established in their hospitals, and only one-third of the panel had some specific ICU discharge criteria implemented. The latter consists mainly of the patient's individual vital parameters and laboratory data, patient status and autonomy, and institution-specific criteria, such as capacity metrics of the ICU and the receiving units, as well as available support resources at the lower care levels. Interestingly, the listed organizational discharge criteria match the top-perceived discharge barriers, leading to the assumption that positive patient flow drivers such as IMC and GW bed availability, specialized care capabilities in lower care levels, timely synchronized ADT processes, and OR schedules are considered for decision-making but are not yet implemented in the daily clinical routine. For patient transfer, mainly a discharge protocol or a handover form is used in a digital or a paper-based format. Liaison nurses are less common, especially in German-speaking countries but are top-listed as a measure to close the widely perceived care gap between ICU and GW care levels, next to establishing or increasing IMC capacities. Furthermore, 80% of the panelists believe that patient discharges can be turned from *ad hoc*-actions to in-advance planning and preparation, given good transparency of lower care level capacity utilization, predictability, and availability, as well as a standardized and implemented discharge planning process along with interdisciplinary communication. Suboptimal discharges may relate to suboptimal care at the receiving unit, negatively affecting the patient outcome and patient flow (5). Suboptimal discharges were mainly due to multimorbidity, delirium, and communication difficulties.

4.1 Limitations

As a large group of German respondents dominates the insights of this study, it would be very valuable to replicate the survey in several other local healthcare systems. Furthermore, the survey was dominated by ICU physicians and ICU nurses, and especially, bed coordinators were underrepresented. No GW staff was included, which could have provided further insights from the perspective of the patient receiver, for example, regarding the existing monitoring and care infrastructure, available skill sets, and patient–nurse ratios in the receiving units. With as many as 29 questions, this survey was rather extensive, thus resulting in small numbers of answers toward the end of the survey. Part B included hospital size, type, and unit characteristics, and part C included variables related to the current ICU discharge practice. We used open-answer types for text entry in both parts and asked the panelists to relate the provided data to a period. This strategy resulted in numerous incomplete answers that were difficult to analyze and statistically interpret. Furthermore, additional questions regarding the different patient pathways (emergency vs. non-emergency and medical vs. surgical) could have delivered insights into patient group-specific process differences, which might then support more targeted process optimization. In general, these study results can be used as a starting point to explore certain topics more deeply, perhaps with future dedicated mix-method studies.

4.2 Outlook

Given this kaleidoscope of insights into current ICU discharge practices, this study emphasizes the need for step-by-step implementation research. Although the drivers of positive patient flow are known and considered in decision-making, structured implementation measures to support safe and timely transfers are often not yet implemented. Cross-departmental and interdisciplinary efforts are still necessary to define common patient care goals along the patient pathway, communicate these goals effectively, monitor progress, and align them in context of organizational care capabilities. In addition, continuous organizational performance data provision is widely lacking to measure change. In a plan-do-study-act manner (31), long-term, step-by-step implementation research with a multistakeholder approach is needed to improve the overall patient flow. This might involve measures such as shifting capacities from ICUs to IMC or GW units, introducing new roles such as liaison nurses and central bed managers, implementing capacity utilization dashboards

and clear discharge criteria checklists and handover forms, and aligning ADT planning and scheduling. Furthermore, the results could stimulate future research, for example, on collaboration and communication around care transitions within a hospital or even within regional care networks, discharge planning tools, process and performance benchmarking, and patient safety aspects associated with care transitions.

5 Conclusion

This survey study provided first insights into current ICU discharge practice on a broader multinational level. Critical issues, such as the pressure to free up intensive care beds and the lack of IMC and GW capacities, were listed by the majority of the participants. Furthermore, patients experienced rushed but also delayed discharges with all the negative side effects. For many study participants, established discharge criteria, cross-departmental decision-making, synchronized transfer processes, and adequate care capacity and quality at lower care levels were not the current reality in their daily clinical routine, although they were aware of its positive potential to improve care transitions. Here, good data on capacity utilization in acute medicine and insights into obstacles to patient flow can help to better control the use of existing capacities and align them with actual needs. To avoid bottlenecks in acute medicine and to improve patient flow, transfer processes should be managed proactively across departments based on structured and objective guidance. Gaps in care should be addressed by increasing IMC capacities and utilizing liaison nurses.

Data availability statement

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

Ethics statement

Ethical approval was obtained through a waiver by the Erasmus MC CRB (MEC-2022-0522), affiliated to the Erasmus Medical Center, being part of the Erasmus University Rotterdam. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft. CB: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft. MW: Conceptualization, Formal Analysis, Investigation, Methodology, Supervision, Validation, Writing – original draft. HB: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. AK: Formal Analysis, Validation, Writing – review & editing. JB: Conceptualization, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

Several national and international anesthesia and intensive care societies have assessed our study proposal and finally evaluated it as a valuable project to support knowledge generation in the field of intensive care patient transitions. We would like to acknowledge the following societies for endorsing and supporting our work by distributing our survey to their society members: ESICM, EfCCNa, DGF, DIVI, and DGAI. We would also like to thank all survey participants for their time and efforts on this topic.

Conflict of interest

MH completed this survey study as part of their PhD, being an external PhD student at the Erasmus University Rotterdam; throughout the phase of the PhD, MH was employed and salaried by Philips.

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

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1377902/full#supplementary-material

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