frontiers | Research Topics

Mechanisms and interventions for post-operative neurocognitive disorder and sleep disruptions

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Published in
Frontiers in Medicine
Frontiers in Neurology
Frontiers in Neuroscience

ISSN 1664-8714
ISBN 978-2-8325-7257-3
DOI 10.3389/978-2-8325-7257-3

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Mechanisms and interventions for post-operative neurocognitive disorder and sleep disruptions

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Citation

Chen, Q., Hu, Z., Yang, B., Cole, D., eds. (2025). *Mechanisms and interventions for post-operative neurocognitive disorder and sleep disruptions*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-7257-3

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frontiers | Frontiers in Neurology

TYPE Editorial
PUBLISHED 25 September 2025
DOI 10.3389/fneur.2025.1681931

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 08 August 2025
ACCEPTED 29 August 2025
PUBLISHED 25 September 2025

CITATION
Yang B, Chen Q and Hu Z (2025) Editorial: Mechanisms and interventions for post-operative neurocognitive disorder and sleep disruptions. *Front. Neurol.* 16:1681931. doi: 10.3389/fneur.2025.1681931

Editorial: Mechanisms and interventions for post-operative neurocognitive disorder and sleep disruptions

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KEYWORDS

neurocognitive disorder, sleep disruptions, post-operative, interventions, mechanism

Editorial on the Research Topic
Mechanisms and interventions for post-operative neurocognitive disorder and sleep disruptions

Introduction

Postoperative neurocognitive disorders (PNDs), encompassing postoperative delirium (POD) and postoperative cognitive dysfunction (POCD), represent a spectrum of cognitive impairments that occur following surgery, particularly in elderly populations. These conditions are associated with prolonged hospital stays, increased healthcare costs, and diminished quality of life. Sleep disturbances, often driven by disruptions to the circadian rhythm, are closely linked to PNDs, exacerbating cognitive decline through a vicious cycle of neuroinflammation and physiological stress. This Research Topic, Mechanisms and Interventions for Postoperative Neurocognitive Disorder and Sleep Disruptions, presents 17 cutting-edge studies exploring the underlying mechanisms and evaluating novel interventions. This review synthesizes these findings, categorizing the studies into those addressing mechanisms, interventions, or both. It also discusses their implications for clinical practice and future research.

PNDs mechanisms and sleep disruptions

Systemic and neuroinflammation factors

Neuroinflammation is a central mechanism driving PNDs. Gou et al. utilized transcriptomic analysis to identify differentially expressed genes (DEGs) such as COL18A1 and CXCL9 that interact with pro-inflammatory cytokines (e.g., IL-6, IL-1β) in elderly patients with POD. Their study employed correlation charts and immune infiltration plots to highlight the role of immune microenvironment interactions in neuroinflammation. Similarly, Liu Y. et al. developed a predictive model for postoperative pulmonary infections (PPI) in elderly orthopedic patients, identifying six clinical risk factors associated with

PNDs. Their model, validated through calibration curves and decision curve analysis, underscores systemic inflammation as a key driver, despite limitations from retrospective data collection.

Qin et al. further elucidated the role of inflammation by demonstrating that elevated preoperative high-sensitivity C-reactive protein (Hs-CRP) levels significantly increase POD risk, particularly in older and female patients. Their findings position Hs-CRP as a potential biomarker for early risk stratification. Wei et al. identified preoperative biomarkers, including the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune-inflammation index (SII) as predictors of post-stroke depression, which shares mechanistic overlap with PNDs, reinforcing the role of inflammatory pathways.

Cognitive reserve and demographic factors

Xiang et al. investigated the influence of cognitive reserve and found that lower educational levels were associated with an increased risk of POD in patients undergoing abdominal surgery (odds ratio: 0.6, 95% CI: 0.8–0.9). These results suggest that cognitive reserve modulates neurocognitive outcomes, highlighting the need for preoperative cognitive assessments. A meta-analysis by Wu et al. revealed sex-specific vulnerabilities in neurological outcomes, with forest plots indicating that sex differences may influence PNDs risk, necessitating tailored intervention strategies.

Circadian rhythm dysregulation

Ma et al. explored the interplay between postoperative pain, circadian rhythm disruptions, and neurocognitive outcomes. Their review highlights how pain-induced stress disrupts circadian rhythms, exacerbating PNDs through neuroinflammation and hormonal imbalances. These findings underscore the importance of effectively addressing pain management to mitigate sleep disturbances and cognitive decline.

Interventions for PNDs and sleep disruptions

Non-pharmacological interventions

Acupuncture has emerged as a promising non-pharmacological intervention for PNDs. A systematic review by Bu et al. demonstrated that acupuncture significantly reduced extubation time and stabilized hemodynamic parameters in postoperative settings, suggesting its efficacy in mitigating complications. Additionally, Wu et al. reported that electroacupuncture (EA) improved sleep duration and reduced the incidence of supraventricular tachycardia in patients undergoing thoracic surgery, likely by modulating autonomic nervous system activity.

Ultrasound-guided transversus abdominis plane (TAP) block also shows potential. A case report and literature review by Zhang et al. highlighted the ability of the TAP block to address anesthetic challenges in elderly patients with ovarian tumors and massive ascites, reducing postoperative neurocognitive complications by minimizing diaphragm elevation.

Pharmacological and perioperative strategies

A systematic review by Wang Y. et al. suggested that remimazolam, a novel benzodiazepine, may alleviate POD, as assessed by MMSE scores and funnel plots. This highlights the potential of remimazolam as a pharmacological intervention. A clinical trial by Luo et al. demonstrated that tailored positive end-expiratory pressure (PEEP) in robot-assisted surgeries reduces pulmonary stress, potentially mitigating PNDs and sleep disruptions by improving respiratory function.

Zheng et al. evaluated the use of noninvasive ventilation post-extubation in ICU settings, finding that it may reduce pulmonary complications and support neurocognitive outcomes; however, data limitations warrant further investigation. Zhao et al. explored intratumoral injections of cisplatin and Endostar combined with cryotherapy/hyperthermia for malignant tracheal stenosis, suggesting that relieving airway obstruction may reduce surgical stress and support neurocognitive recovery.

Tailored surgical and perioperative approaches

Wang Q. et al. compared the perioperative outcomes in 527 patients with and without pheochromocytoma, using odds ratios to assess the risk of complications. Their findings advocate for tailored surgical strategies to optimize perioperative conditions and reduce PNDs risk. A systematic review by Yang et al. emphasized the need for standardized guidelines for POD assessment, using a literature screening flowchart to ensure consistent diagnostic approaches, which are critical for effective management.

Discussion

The studies in this Research Topic highlight the multifactorial nature of PNDs and sleep disruptions, which are driven by neuroinflammation, systemic inflammation, and circadian dysregulation. Interventions such as acupuncture, ultrasound-guided nerve blocks, and novel pharmacological agents like remimazolam show promise in mitigating these complications. However, challenges remain, including the need for prospective studies to overcome the limitations of retrospective data (e.g., Liu J. et al.) and the need to standardize diagnostic criteria (e.g., Yang et al.). Future research should focus on validating biomarkers such as Hs-CRP and NLR, refining predictive models, and exploring personalized interventions based on demographic factors such as education and gender.

Conclusion

This Research Topic underscores the complex interplay between PNDs, sleep disturbances, and their underlying mechanisms, including neuroinflammation, systemic inflammation, and circadian misalignment. Innovative interventions, ranging from non-pharmacological approaches such as acupuncture and ultrasound-guided nerve blocks to pharmacological and perioperative strategies, offer promising avenues for improving postoperative outcomes. By addressing these challenges through rigorous research and tailored interventions, we can enhance recovery and quality of life for surgical patients, particularly those in vulnerable populations.

Author contributions

BY: Writing – original draft, Conceptualization. QC: Writing – review & editing, Conceptualization. ZH: Conceptualization, Writing – original draft.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was funded by the Fujian Research and Training Grants for Young and Middle-aged Leaders in Healthcare, the Natural Science Foundation of Fujian Province (2022J011369), and the Scientific and Technological Research Program of the Chongqing Municipal Education Commission (KJQN202300117).

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Publisher's note

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 26 September 2024
DOI 10.3389/fmed.2024.1481083

OPEN ACCESS

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RECEIVED 15 August 2024
ACCEPTED 11 September 2024
PUBLISHED 26 September 2024

CITATION
Zheng X, Lu L, Ma M and Lei X (2024) Effect of prophylactic noninvasive oxygen therapy after planned extubation on extubation failure in high-risk patients: a retrospective propensity score-matched cohort study. *Front. Med.* 11:1481083. doi: 10.3389/fmed.2024.1481083

Effect of prophylactic noninvasive oxygen therapy after planned extubation on extubation failure in high-risk patients: a retrospective propensity score-matched cohort study

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Background: Extubation failure (EF) is common in the intensive care unit (ICU) and is associated with poor prognosis, especially in high-risk patients. However, the efficacy of prophylactic noninvasive oxygen therapy (NIT), including noninvasive ventilation (NIV) and high-flow nasal cannula (HFNC), in reducing EF in high-risk patients remains controversial. Therefore, we aimed to evaluate the effect of post-extubation prophylactic NIT on EF in high-risk patients.

Methods: This was a retrospective observational study conducted in the ICU from March 2018 to December 2023. We included adult patients at high risk for reintubation who were mechanically ventilated for over 24 h and successfully passed the spontaneous breathing trial (SBT). Immediately after extubation, patients underwent NIT or conventional oxygenation therapy (COT). The primary outcome was the EF rate within 7 days after extubation.

Results: There were 440 patients in the NIT group and 274 in the COT group. After propensity-score matching, 227 subjects were enrolled in each group. NIT reduced the rate of EF (18.0% vs. 34.3%, $p < 0.001$) and reintubation (10.5% vs. 18.2% $p = 0.003$) compared with COT, which was confirmed in propensity-matched cohort (17.6% vs. 32.2%, $p < 0.001$; 11.5% vs. 19.8%, $p = 0.014$). Multivariate logistic regression analysis indicated that prophylactic NIT ($p = 0.001$) and higher ROX index ($p = 0.022$) were associated with reduced risk of EF. While higher fluid balance ($p = 0.013$), higher RSBI ($p < 0.001$), and the occurrence of delirium ($p = 0.032$) may be the risk factors for EF. Subgroup analysis showed that post-extubation NIT was more effective in elderly patients, and HFNC was non-inferior to NIV in reducing EF. While HFNC had a tendency to reduce the incidence of delirium.

Conclusion: Post-extubation prophylactic NIT is effective in reducing EF in high-risk patients, especially in the elderly patients. HFNC is an alternative treatment to NIV. Fluid balance, RSBI, ROX index, and delirium are associated with the occurrence of EF.

KEYWORDS

noninvasive oxygen therapy, extubation failure, high-risk patients, delirium, noninvasive ventilation, high-flow nasal cannula

1 Introduction

Extubation failure (EF) is common in the intensive care unit (ICU) and still occurs in 10–20% of mechanically ventilated patients who successfully complete the spontaneous breathing trial (SBT) (1). Among high-risk patients, that is, those older than 65 years or with any underlying chronic cardiac or respiratory disease, the EF rate is even as high as 48% (2). EF increases mortality by 25–50% and prolongs ICU stay and length of hospital stay (LOS) (3). Therefore, it is necessary to provide effective post-extubation respiratory support to prevent the occurrence of EF.

In addition to high-risk factors, delirium may also cause EF. Delirium is frequent in the ICU and may contribute to EF through altered consciousness, agitation and subsequent sedation, aspiration, and intolerance to noninvasive mechanical ventilation (NIV) (4). A reintubation rate of 22% has been reported among patients who developed delirium on the day of extubation (5). Identification of risk factors for EF is particularly important in predicting the occurrence of EF and reintubation.

NIV has been recommend for patients with hypercapnia. However, the effect of prophylactic use on reintubation and mortality in high-risk patients remains controversial (6, 7). In addition, NIV is susceptible to gastric distention, skin damage and claustrophobia, limiting its widespread use and reducing its efficacy in EF (8, 9). In contrast, high-flow nasal cannula (HFNC) improves patient comfort and tolerability (10). HFNC has also been reported to suppress delirium, which is a contributing factor to reintubation (11). In clinical practice, HFNC has emerged as a promising treatment strategy for patients with hypoxemic respiratory failure. In high-risk patients, HFNC was even comparable to NIV in preventing EF and reintubation (12). In recent years, an increasing number of studies referred to NIV and HFNC collectively as noninvasive oxygen therapy (NIT), and investigated its efficacy in ICU patients (13, 14).

A relevant randomized controlled trial (RCT) indicated that preventive use of NIT did not prevent reintubation compared with conventional oxygen therapy (COT) (15). However, the population was unselected and the efficacy of NIT in high-risk patients is unclear. Therefore, we conducted this retrospective observational cohort study to evaluate the efficacy of post-extubation prophylactic NIT to reduce EF in high-risk patients and to identify potential risk factors for EF.

2 Materials and methods

This was a retrospective observational cohort study conducted in the ICU of the First Affiliated Hospital of Chongqing Medical University from March 2018 to December 2023. The study was approved by the institutional ethics committee of the First Affiliated Hospital of Chongqing Medical University and registered with the Chinese Clinical Trial Registry (ChiCTR2200061820). Informed consent was waived because of the retrospective observational nature of the study. All records and data were anonymized and de-identified prior to analysis.

2.1 Study population

We reviewed the records of all adult patients ($\geq$ 18 years) admitted to the ICU and receiving MV for at least 24 h. In further screening, patients at high-risk of reintubation (7) who successfully passed the SBT and received post-extubation prophylactic NIV or HFNC and COT were included in the study. Patients were considered with high risk factors for reintubation if they fulfilled any of the following criteria as described in earlier studies: (1) age over 65 years; (2) had any underlying chronic cardiac or pulmonary disease. Underlying chronic cardiac diseases included left ventricular dysfunction, defined as left ventricular ejection fraction $\leq$ 45%; history of cardiogenic pulmonary edema; documented ischemic heart disease; or permanent atrial fibrillation. Underlying chronic pulmonary diseases included chronic obstructive pulmonary disease (COPD), obesity-hypoventilation syndrome, or restrictive pulmonary disease.

Exclusion criteria were as follows: (1) died before SBT or accidental extubation; (2) tracheotomy before weaning attempt; (3) intervention lasted less than 24 hours; (4) post-extubation surgery; (5) refusal of resuscitation and reintubation; (6) missing data.

2.2 Interventions

Patients who received prophylactic NIV (BiPAP Vision, Philips Respironics, USA) immediately after extubation were classified as the NIT group. The course of NIV was at least 24 h, but could be interrupted by drinking, feeding, and clearing secretions. Depending on patient respiratory status, NIV could be continued until complete recovery. Positive end-expiratory pressure (PEEP)

was set at 4–6 cmH_2O, and pressure-support level was initially set at 8 cmH_2O (titrated 1–2 cmH_2O) to obtain a tidal volume of about 6–8 mL/kg. Fractional inspiratory oxygen ratio (FiO_2) was adjusted to maintain peripheral capillary oxygen saturation (SpO_2) above 92%.

Patients in the NIT group could also be treated with HFNC (Optiflow, Fisher and Paykel Healthcare, Canada) immediately after extubation for at least 24 h. Flow was initially set at 10 L/min and titrated upwards in 5 L/min steps until patients experienced discomfort. FiO_2 was adjusted to maintain SpO_2 above 92%. To provide sufficient humidification, the temperature of the heated humidifier was set to 37°C.

Patients in the control group received COT via face mask or nasal cannula. FiO_2 was set to achieve SpO_2 over 92%. And COT was administered according to patient needs.

2.3 Study outcomes

The primary outcome was the rate of EF within 7 days following extubation. EF was defined as the need for reintubation or NIV rescue treatment (16). Secondary outcomes included reintubation within 7 days after extubation (2, 12), post-extubation respiratory failure (7), delirium on the day of extubation (17), in-hospital mortality, and post-extubation ICU stay and LOS. Patients were immediately reintubated if any of the following criteria was met: massive aspiration, uncontrollable agitation, sputum retention, hemodynamic deterioration unresponsive to vasoactive drugs, respiratory pauses with loss of consciousness or gasping for air, heart rate $<$ 50 beats per min with loss of alertness, and cardiac or respiratory arrest. And respiratory failure was defined as the presence of any of the criteria below: respiratory rate $>$ 35 breaths per minute, clinical signs suggesting respiratory distress, respiratory acidosis (pH $<$ 7.35 and PaCO2 $>$ 45 mmHg), hypoxemia (SpO2 $\leq$ 90% or PaO2:FiO2 ratio $\leq$ 120 mmHg at FIO2 $>$ 0.4), decreased level of consciousness (GCS $>$ 1 point decrease), and agitation. Delirium was defined as a disturbance of consciousness characterized by a sudden onset and a fluctuating course of attention accompanied by a change in perception or cognition. Delirium was routinely measured by ICU nurses using the Confusion Assessment Method for the ICU (CAM-ICU).

2.4 Data collection

The following data were collected retrospectively from the medical records: age, gender, underlying diseases, main reason for intubation, acute physiology and chronic health evaluation II (APACHE II) score at ICU admission and at extubation, duration of MV before extubation, fluid balance and secretion volume 24h before extubation, use of vasopressors at extubation, hemoglobin, and Glasgow Coma Score (GCS). Vital signs and arterial blood gas parameters were collected before SBT and at extubation, including mean arterial pressure, heart rate, respiratory rate, tidal volume, SpO_2, rapid shallow breathing index (RSBI), the ratio of SpO_2/FiO_2 to respiratory rate (ROX index), as well as pH, partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), the ratio of PaO_2 to FIO_2 (oxygenation index).

2.5 Subgroup analysis

Patients were divided into two subgroups based on age ($>$ 65 years and $\leq$ 65 years) to demonstrate the impact of prophylactic NIT on EF, particularly in elderly high-risk patients. And another subgroup analysis was performed in the NIT group to determine whether HFNC was noninferior to NIV in reducing EF rate.

2.6 Statistical analysis

Due to the retrospective design of the study, propensity score matching (PSM) was performed to reduce the effects of selection bias and possible confounding factors between the two groups. The following variables were selected to generate the propensity score: age, gender, underling diseases, intubation period, APACHE II score at ICU admission and at extubation, fluid volume, secretion volume, hemoglobin, GCS, and physiological parameters before SBT and at extubation. After calculating the propensity scores, we matched patients with similar propensity scores in each group in a 1:1 ratio using the nearest neighbor method, with the caliper width set to 0.1.

Data were summarized as mean ± standard deviation (SD) or median (25th percentile, 75th percentile) depending on distribution. The Mann-Whitney U test was used for group comparisons of continuous variables when the data were abnormally distributed; otherwise, Student's t-test was applied. Categorical variables were expressed as numbers (percentage) and compared using the chi-square test or Fisher's exact test as appropriate. Univariate logistic regression analysis was used to identify independent factors related to EF within 7 days after extubation. Variables with $p < 0.1$ in the univariate analysis and other clinically significant variables were included in the conditional stepwise multivariable logistic regression. All statistical tests were 2-sided and p-values $<$ 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics 26.0 (SPSS Inc., Chicago, IL, USA).

3 Results

3.1 Patient characteristics

Between March 2018 and December 2023, 3227 patients over 18 years old were admitted to the ICU receiving MV. Of these, 1746 patients were excluded due to MV duration less than 24 h. Among the remaining 1481 patients, 767 were excluded for the following reasons: death (n = 251) or tracheostomy (n = 61) before SBT attempt, accidental extubation (n = 75), without risk factors for reintubation (n = 225), receiving neither NIT nor COT intervention immediately after extubation (n = 17), duration of intervention less than 24 h (n = 48), refusal of resuscitation and reintubation (n = 33), post-extubation surgery (n = 21) and loss of information (n = 36). Overall, we analyzed data from 714 patients, including 440 patients in the NIT group and 274 patients in the COT group. The flow diagram is shown in Figure 1.

The baseline characteristics of both groups are presented in Table 1. There were more male patients in the NIT group than

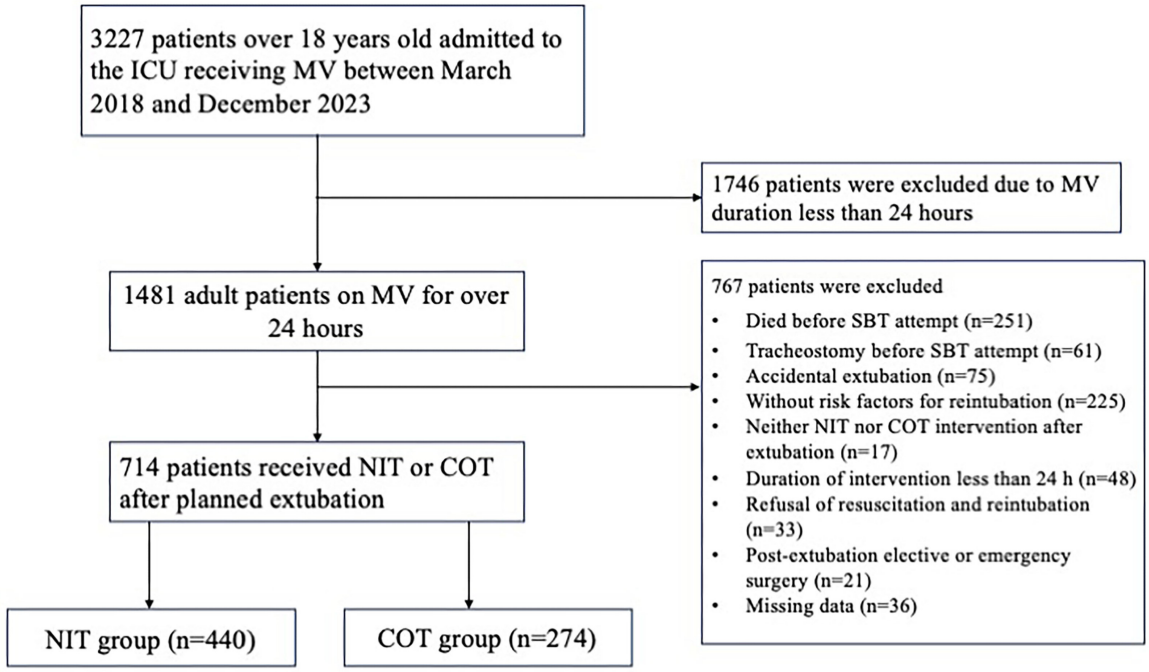

FIGURE 1
The flow diagram of study population. ICU, intensive care unit; MV, mechanical ventilation; SBT, spontaneous breathing trial; COT, conventional oxygen therapy; NIT, noninvasive oxygen therapy.

in the COT group (75.5% vs. 67.2%, p = 0.016). The NIT group had a higher proportion of patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) (52.0% vs. 21.9%, $p < 0.001$), and a lower proportion of patients with pneumonia or acute respiratory distress syndrome (ARDS) than the COT group (42.5% vs. 57.3%, $p < 0.001$). Patients receiving NIT had a longer intubation period than those in the COT group [6 (4, 10) vs. 5.5 (3, 7) d, $p = 0.001$]. The amount of secretion 24 h before extubation was significantly higher in the NIT group than in the COT group [64 (38, 78) vs. 41 (21, 61) ml, $p < 0.001$]. The pre-SBT tidal volume was greater in the NIT group compared to the control group (474.0 ± 83.1 vs. 450.9 ± 78.3 ml, $p < 0.001$). Patients receiving prophylactic NIT had higher $PaCO_2$ levels before SBT (48.7 ± 11.6 vs. 41.4 ± 9.4 mmHg, $p < 0.001$) and at extubation (47.1 ± 9.5 vs. 40.1 ± 5.9 mmHg, $p < 0.001$) than those in the COT group. After a 1:1 PSM, 227 matched subjects were included in each group. There were no significant differences in demographic and clinical characteristics between the two matched cohorts, except that patients in the NIT group had a higher secretion volume 24h before extubation (shown in Table 1).

3.2 Primary outcome

The occurrence of EF in both groups is summarized in Table 2. Of the 440 patients treated with prophylactic NIT, 79 failed to extubate, with a lower incidence than the control group (18.0% vs. 34.3%, $p < 0.001$). In the propensity-matched cohort, the EF rate in the COT group was 32.2%, nearly 2 times that of the NIT group ($p < 0.001$).

3.3 Secondary outcomes

In the overall cohort, NIT was associated with a lower reintubation rate (10.5% vs. 18.2%, $p = 0.003$) and in-hospital mortality (17.5% vs. 27.9%, $p = 0.001$) compared with COT. However, the incidence of respiratory failure and delirium were comparable between the two groups (39.1% vs. 43.6%, $p = 0.227$; 51.8% vs. 56.6%, $p = 0.213$). As shown in Table 2, NIT group had longer post-extubation ICU stay and post-extubation LOS than the control group [7(4, 11) vs. 5(3, 9) d, $p < 0.001$; 9 (6, 15) vs. 7 (4, 16) d, $p = 0.004$, respectively]. In the propensity-matched cohort, NIT reduced the incidence of reintubation compared with the COT (11.5% vs. 19.8%, $p = 0.014$). However, there were no significant differences in respiratory failure, delirium, in-hospital mortality, post-extubation ICU stay, and post-extubation LOS between the two matched cohorts.

3.4 Subgroup analysis

Among the 714 patients in the study, 512 were over 65 years old (as shown in Table 3). In this subgroup, NIT reduced the rate of EF (16.3% vs. 38.0%, $p < 0.001$) and reintubation (12.5% vs. 23.0%, $p = 0.002$) compared with COT, as confirmed in the propensity-matched cohort (13.9% vs. 37.3%, $p < 0.001$; 8.9% vs. 24.7%, $p < 0.001$, respectively). In both cohorts, there were no differences in respiratory failure, delirium, post-extubation ICU stay or post-extubation LOS between the two groups. In the non-elderly high-risk subgroup ($n = 202$), NIT was not superior to COT in reducing EF, reintubation, respiratory failure, delirium, and in-hospital

TABLE 1 Baseline characteristics of study population.

	Overall cohort			Propensity-matched cohort		
	COT *n* = 274	NIT *n* = 440	*P*-value	COT *n* = 227	NIT *n* = 227	*P*-value
Age (years)	69.3 ± 14.9	71.0 ± 11.6	0.101	69.9 ± 14.5	71.4 ± 11.2	0.219
Male	184 (67.2)	332 (75.5)	0.016	159 (70.0)	170 (74.9)	0.248
Underlying diseases						
AECOPD	60 (21.9)	229 (52.0)	< 0.001	49 (21.6)	64 (28.2)	0.103
Pneumonia/ARDS	157 (57.3)	187 (42.5)	< 0.001	144 (63.4)	137 (60.4)	0.499
CVD	124 (45.3)	219 (49.8)	0.240	117 (51.5)	128 (56.4)	0.300
Hypertension	140 (51.1)	198 (45.0)	0.113	86 (37.9)	95 (41.9)	0.388
Diabetes	82 (29.9)	108 (24.5)	0.114	63 (27.8)	65 (28.6)	0.835
Liver disease	34 (12.4)	42 (9.5)	0.228	16 (7.0)	12 (5.3)	0.435
Renal disease	40 (14.6)	61 (13.9)	0.784	26 (11.5)	36 (15.9)	0.172
Shock	81 (29.6)	130 (29.5)	0.996	57 (25.1)	48 (21.1)	0.316
Arrhythmia	11 (4.0)	19 (4.3)	0.844	8 (3.5)	15 (6.6)	0.134
PE	10 (3.6)	25 (5.7)	0.221	7 (3.1)	2 (0.9)	0.175
Asthma	9 (3.3)	13 (3.0)	0.804	4 (1.8)	7 (3.1)	0.360
APACHE II score at ICU admission	21.4 ± 5.6	21.3 ± 5.8	0.880	21.3 ± 5.5	21.2 ± 6.1	0.796
APACHE II score at extubation	14.1 ± 3.2	14.3 ± 3.2	0.390	14.1 ± 3.1	14.6 ± 3.1	0.083
Intubation period (days)	5.5 (3,7)	6 (4,10)	0.001	6 (3,7.5)	5 (4,9)	0.063
Main reason for intubation			0.063			0.477
Acute respiratory failure	145 (52.9)	260 (59.1)		126 (55.5)	139 (61.2)	
Coma	55 (20.1)	76 (13.6)		44 (19.4)	40 (17.6)	
Acute heart failure	3 (1.1)	12 (2.7)		2 (0.9)	6 (2.6)	
Surgery	29 (10.6)	32 (7.3)		21 (9.3)	17 (7.5)	
Airway protection	35 (12.8)	55 (12.5)		28 (12.3)	21 (9.3)	
Other	8 (2.9)	5 (1.1)		6 (2.6)	4 (1.8)	
Fluid balance 24h before extubation (ml)	688 (−325,1219)	345 (−297,1070)	0.010	619 (−325,1219)	381 (−318,1029)	0.247
Secretion volume 24h before extubation (ml) †	41 (21,61)	64 (38,78)	< 0.001	42 (21,61)	62 (47,75)	< 0.001
Use of vasopressors at extubation	40 (14.6)	52 (11.8)	0.281	32 (14.1)	19 (8.4)	0. 053
Hemoglobin (g/dL)	103.4 ± 4.7	102.2 ± 3.9	0.182	104.1 ± 4.0	103.4 ± 3.9	0.216
GCS	14.1 ± 1.3	14.5 ± 1.6	0.327	14.2 ± 1.7	14.1 ± 1.2	0.673
Physiological parameters before SBT						
Mean blood pressure (mmHg)	88.8 ± 13.3	89.8 ± 12.9	0.303	88.9 ± 12.8	88.7 ± 13.4	0.915
Heart rate (beats/min)	90.4 ± 14.1	90.7 ± 15.7	0.813	91.0 ± 14.0	91.0 ± 14.2	0.979
Respiratory rate (breaths/min)	20.4 ± 4.3	20.4 ± 6.0	0.868	20.5 ± 4.2	20.9 ± 4.3	0.365
Tidal volume (ml)	450.9 ± 78.3	474.0 ± 83.1	< 0.001	459.0 ± 78.6	464.6 ± 81.8	0.457
SpO_2 (%)	98.2 ± 1.3	97.9 ± 1.7	0.020	98.1 ± 1.3	97.9 ± 1.9	0.419
pH	7.4 ± 0.1	7.4 ± 0.1	0.022	7.4 ± 0.1	7.4 ± 0.0	0.484
PaO_2 (mmHg)	120.5 ± 33.9	113.8 ± 26.7	0.005	118.4 ± 33.9	114.0 ± 22.4	0.107
$PaCO_2$ (mmHg)	41.4 ± 9.4	48.7 ± 11.6	< 0.001	42.5 ± 9.1	43.5 ± 10.2	0.252
PaO_2/FiO_2	274.0 ± 77.6	262.2 ± 66.5	0.037	271.0 ± 75.7	262.4 ± 71.5	0.214
RSBI	46.6 ± 13.3	44.3 ± 14.2	0.033	46.1 ± 13.1	46.3 ± 13.2	0.874

(Continued)

TABLE 1 (Continued)

	Overall cohort			Propensity-matched cohort		
	COT *n* = 274	NIT *n* = 440	*P*-value	COT *n* = 227	NIT *n* = 227	*P*-value
ROX index	11.8 ± 4.0	11.9 ± 3.8	0.921	11.8 ± 4.0	11.3 ± 3.4	0.127
SBT protocol			0.132			0.125
PSV	228 (83.2)	384 (87.3)		192 (84.6)	203 (89.4)	
PS	10.5 ± 3.4	12.0 ± 4.0	< 0.001	10.6 ± 3.6	11.0 ± 3.7	0.425
PEEP	5.4 ± 1.6	5.8 ± 1.7	0.002	5.4 ± 1.7	5.6 ± 1.8	0.279
T-Piece	46 (16.8)	56 (12.7)		35 (15.4)	24 (10.6)	
Physiological parameters at extubation						
Mean blood pressure (mmHg)	87.7 ± 10.5	87.8 ± 12.3	0.879	87.1 ± 10.2	88.2 ± 11.7	0.302
Heart rate (beats/min)	89.9 ± 10.4	91.4 ± 12.7	0.083	90.2 ± 10.6	91.9 ± 13.0	0.141
Respiratory rate (breaths/min)	20.2 ± 3.6	20.6 ± 3.8	0.271	20.1 ± 3.6	20.6 ± 3.7	0.148
Tidal volume (ml) [‡]	406.6 ± 84.0	412 ± 63.8	0.404	409.9 ± 89.3	412.7 ± 61.7	0.716
SpO_2, %	97.3 ± 1.8	97.0 ± 1.9	0.013	97.3 ± 1.9	97.1 ± 2.0	0.225
pH	7.4 ± 0.0	7.4 ± 0.0	0.112	7.4 ± 0.0	7.4 ± 0.0	0.306
PaO_2 (mmHg)	106.9 ± 36.4	102.1 ± 28.5	0.065	105.6 ± 33.4	103.3 ± 29.5	0.444
$PaCO_2$ (mmHg)	40.1 ± 5.9	47.1 ± 9.5	< 0.001	41.0 ± 5.9	42.0 ± 6.5	0.068
PaO_2/FiO_2	258.4 ± 83.7	253.9 ± 76.0	0.466	256.7 ± 80.8	258.3 ± 77.4	0.830
RSBI [§]	51.4 ± 14.9	50.6 ± 12.9	0.542	50.9 ± 15.3	50.1 ± 11.6	0.562
ROX index	12.2 ± 2.8	12.2 ± 3.1	0.838	12.3 ± 2.9	12.3 ± 2.9	0.836

COT, conventional oxygen therapy; NIT, non-invasive oxygen therapy; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ARDS, acute respiratory distress syndrome; CVD, cardiovascular disease; PE, pulmonary embolism; APACHE II, acute physiology and chronic health evaluation II; SBT, spontaneous breathing trial; GCS, Glasgow Coma Score; RSBI, rapid shallow breathing index; ROX, the ratio of SpO_2/FiO_2 to respiratory rate; PSV, pressure support ventilation; PS, pressure support; PEEP, positive end-expiratory pressure. [†]Secretion volume was available for 368 patients in the overall cohort: 128 in the COT group and 240 in the NIT group. [‡]Pre-extubation tidal volume was available for 612 patients in the overall cohort: 228 in the COT group and 384 in the NIT group. Pre-extubation tidal volume was available for 198 patients in the propensity-matched cohort: 102 in the COT group and 96 in the NIT group. [§]Pre-extubation RSBI was available for 612 patients in the overall cohort: 228 in the COT group and 384 in the NIT group. Pre-extubation RSBI was available for 198 patients in the propensity-matched cohort: 102 in the COT group and 96 in the NIT group.

TABLE 2 Patient outcomes in the NIT and COT group.

	Overall cohort			Propensity-matched cohort		
	COT *n* = 274	NIT *n* = 440	*P*-value	COT *n* = 227	NIT *n* = 227	*P*-value
Extubation failure	94 (34.3)	79 (18.0)	< 0.001	73 (32.2)	40 (17.6)	< 0.001
Reintubation	50 (18.2)	46 (10.5)	0.003	45 (19.8)	26 (11.5)	0.014
Respiratory failure	107 (39.1)	192 (43.6)	0.227	81 (35.7)	99 (43.6)	0.084
Delirium	142 (51.8)	249 (56.6)	0.213	118 (52.0)	137 (60.4)	0.089
In-hospital mortality	76 (27.9)	77 (17.5)	0.001	60 (26.4)	45 (19.8)	0.095
Post-extubation ICU stay (days)	5 (3,9)	7 (4,11)	< 0.001	5 (3,12)	5 (4,11)	0.068
Post-extubation LOS (days)	7 (4,16)	9 (6,15)	0.004	9 (5,17)	10 (5,16.5)	0.114

COT, conventional oxygen therapy; NIT, noninvasive oxygen therapy; ICU, intensive care unit; LOS, length of hospital stay.

mortality, as demonstrated in the propensity-matched cohort. The LOS after extubation was 10.5d in the NIT group, 3.5d longer than in the COT group (p = 0.002). And in the propensity-matched cohort, NIT also prolonged post-extubation LOS compared with the control group [13 (9, 14) vs. 9 (3, 10)d, p = 0.017).

In the NIT group, 392 patients received prophylactic NIV after planned extubation and 48 patients received prophylactic HFNC. As illustrated in Table 4, HFNC was noninferior to NIV in reducing EF (p = 0.162), reintubation (p = 0.624), respiratory failure (p = 0.771), in-hospital mortality (p = 0.083), and shortening post-extubation ICU stay (p = 0.393) and post-extubation LOS (p = 0.754), which was also confirmed in the propensity-matched cohort. However, patients receiving HFNC had a lower incidence of delirium than those with NIV (35.4% vs. 59.2%, p = 0.002). After PSM, the rate of delirium was comparable between the two groups (46.7% vs. 62.4%, p = 0.100).

TABLE 3 Outcomes of patients > 65 years and ≤ 65 years of each group.

	Overall cohort			Propensity-matched cohort		
	COT *n* = 200	NIT *n* = 312	*P*-value	COT *n* = 166	NIT *n* = 158	*P*-value
Patients > 65 years (n = 512)						
Extubation failure	76 (38.0)	51 (16.3)	< 0.001	62 (37.3)	22 (13.9)	< 0.001
Reintubation	46 (23.0)	39 (12.5)	0.002	41 (24.7)	14 (8.9)	< 0.001
Respiratory failure	83 (41.5)	140 (44.9)	0.453	70 (42.2)	78 (49.4)	0.194
Delirium	127 (63.5)	218 (69.9)	0.133	105 (63.3)	113 (65.2)	0.113
In-hospital mortality	65 (32.5)	67 (21.5)	0.005	51 (35.5)	35 (18.4)	0.081
Post-extubation ICU stay (days)	6 (3,14)	7 (4,11)	0.092	5 (3,14.8)	8 (5,15)	0.179
Post-extubation LOS (days)	7 (4, 17)	9 (5, 14)	0.402	8.5 (4.3, 17.8)	10 (7, 17.5)	0.422
	Overall cohort			Propensity-matched cohort		
	COT *n* = 74	NIT *n* = 128	*P*-value	COT *n* = 61	NIT *n* = 69	*P*-value
Patients ≤ 65 years (n = 202)						
Extubation failure	18 (24.3)	28 (21.9)	0.689	11 (18.0)	18 (26.1)	0.271
Reintubation	4 (5.4)	7 (5.5)	0.985	4 (6.6)	12 (17.4)	0.061
Respiratory failure	24 (32.4)	52 (40.6)	0.247	11 (18.0)	21 (30.4)	0.101
Delirium	15 (20.3)	31 (24.2)	0.519	13 (21.3)	24 (34.8)	0.089
In-hospital mortality	11 (14.9)	10 (7.8)	0.114	9 (14.8)	10 (14.5)	0.966
Post-extubation ICU stay (days)	4 (2, 6.5)	6.5 (4, 9)	0.003	4 (2, 6)	6 (3, 13)	0.156
Post-extubation LOS (days)	7 (3, 9.5)	10.5 (6, 17)	0.002	9 (3, 10)	13 (9, 14)	0.017

COT, conventional oxygen therapy; NIT, noninvasive oxygen therapy; ICU, intensive care unit; LOS, length of hospital stay.

TABLE 4 Outcomes of patients receiving NIV and HFNC in the NIT group.

	Overall cohort			Propensity-matched cohort		
	NIV *n* = 392	HFNC *n* = 48	*P*-value	NIV *n* = 197	HFNC *n* = 30	*P*-value
Extubation failure	66 (16.8)	12 (25.0)	0.162	36 (18.3)	4 (13.3)	0.508
Reintubation	40 (10.2)	6 (12.5)	0.624	24 (12.2)	2 (6.7)	0.543
Respiratory failure	172 (43.9)	20 (41.7)	0.771	81 (41.1)	8 (26.7)	0.131
Delirium	232 (59.2)	17 (35.4)	0.002	123 (62.4)	14 (46.7)	0.100
In-hospital mortality	72 (18.4)	4 (8.3)	0.083	29 (14.7)	1 (3.3)	0.143
Post-extubation ICU stay (days)	7 (4, 11)	6.5 (5, 13.8)	0.393	8 (4, 13)	8 (5, 17)	0.628
Post-extubation LOS (days)	9 (6, 14)	9 (5, 18.5)	0.754	11 (7, 17)	17 (8, 19)	0.358

NIT, noninvasive oxygen therapy; ICU, intensive care unit; LOS, length of hospital stay; NIV, noninvasive mechanical ventilation; HFNC, high-flow nasal cannula.

3.5 Risk factors for EF

Univariate logistic regression analysis showed that there were significant differences in APACHE II score at extubation, fluid balance volume, secretion volume, intervention protocol, pre-SBT $PaCO_2$, ROX index, RSBI, PEEP and delirium between the failed extubation group and the successful extubation group. After the above variables were inserted into the multivariable logistic regression analysis (as shown in Table 5), we found that prophylactic NIT was a protective factor for EF, both in the overall cohort (odds ratio [OR] = 0.20, 95% confidence interval [CI]: 0.06–0.73, $p = 0.014$) and in the propensity-matched cohort (OR = 0.06, 95% CI: 0.01–0.30, $p = 0.001$). Higher fluid balance 24h before extubation (OR = 1.02, 95% CI: 1.00–1.03, $p = 0.002$, for the overall cohort; OR = 1.01, 95% CI: 1.00–1.02, $p = 0.013$, for the propensity-matched cohort) and higher pre-extubation RSBI (OR = 1.19, 95% CI: 1.10–1.28, $p < 0.001$, for the overall cohort; OR = 1.17, 95%CI: 1.10–1.24, $p < 0.001$, for the propensity-matched cohort) were associated with an increased risk of EF. Delirium on the day of extubation appeared to be a risk factor for EF, both in the overall cohort (OR = 1.96, 95% CI: 1.27–2.54, $p = 0.029$) and in the propensity-matched cohort (OR = 1.78, 95% CI: 1.32–1.94, $p = 0.032$). Higher pre-SBT ROX index appeared to be a protective factor against EF (OR = 0.80, 95% CI: 0.64–1.00, $p = 0.045$, for the

TABLE 5 Multivariate logistic regression analyses identify risk factors for extubation failure.

	Overall cohort		Propensity-matched cohort	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Prophylactic NIT	0.20 (0.06, 0.73)	0.014	0.06 (0.01, 0.30)	0.001
Fluid balance (ml)	1.02 (1.00, 1.03)	0.002	1.01 (1.00, 1.02)	0.013
Secretion volume (ml)	0.98 (0.96, 1.00)	0.010	0.97 (0.95, 0.99)	0.005
Pre-SBT ROX index	0.80 (0.64, 1.00)	0.045	0.59 (0.37, 0.93)	0.022
Pre-SBT RSBI	0.95 (0.90, 1.00)	0.033	0.95 (0.89, 1.01)	0.076
Pre-extubation RSBI	1.19 (1.10, 1.28)	<0.001	1.17 (1.10, 1.24)	<0.001
Delirium	1.96 (1.27, 2.54)	0.029	1.78 (1.32, 1.94)	0.032

NIT, noninvasive oxygen therapy; SBT, spontaneous breathing trial; RSBI, rapid shallow breathing index; ROX, the ratio of SpO_2/FiO_2 to respiratory rate.

overall cohort; OR = 0.59, 95% CI: 0.37–0.93, $p = 0.022$, for the propensity-matched cohort).

4 Discussion

In this cohort study, prophylactic NIT (including NIV and HFNC) was superior to COT in reducing the rate of EF within 7 days after extubation in patients at high-risk of reintubation, especially in those older than 65 years. HFNC was noninferior to NIV in high-risk patients. In addition, higher fluid balance 24 h before extubation, lower pre-SBT ROX index, higher pre-extubation RSBI, and delirium on the day of extubation increased the risk of EF.

NIT was associated with a lower incidence of EF and reintubation in high-risk patients. The high success rate may be due to the superiority of NIV and HFNC over COT. As we know, NIV administered following extubation opens the upper airway, prevents alveolar collapse, and improves oxygenation (18). In high-risk patients, inspiratory positive airway pressure (IPAP) can reduce respiratory workload and compensate for increased airway resistance (19). Expiratory positive airway pressure (EPAP) increases end-expiratory lung volume and decreases venous return, especially in patients with congestive heart failure (20). Compared with COT, HFNC provides more predictable FiO_2 and preserves the mucosal function (21). In addition, HFNC generates a positive airway pressure (between 2 and 8 cmH_2O at the pharyngeal level) similar to positive end-expiratory pressure (PEEP), which may benefit high-risk patients (22–24).

However, a recent RCT indicated that the application of NIT after extubation was not able to prevent reintubation compared with usual care, contrary to our results (15). The different findings may be related to the study population. In the study by Casey et al. (15), critically ill adult patients undergoing MV were included, whereas we only focused on mechanically ventilated patients with high-risk factors for reintubation. Moreover, in that study (15), patients in the usual-care group could also be treated with NIV or HFNC at the discretion of the attending physicians, which may reduce the occurrence of reintubation. Furthermore, in the study by Casey et al. (15), HFNC was predominantly used in the NIT group, which may influence the efficacy of NIT. Therefore, more studies are needed to investigate the effectiveness of NIT on reintubation and EF.

In the subgroup analysis, NIT immediately after extubation benefited elderly patients, which was consistent with a cohort study (25). However, we found no effect of NIT on EF and reintubation in non-elderly high-risk patients compared with COT. In fact, age is an important factor in reintubation (26). In addition to being older than 65 years, elderly patients are prone to be complicated with other risk factors, such as COPD and chronic heart failure. It has been suggested that patients with ≥ 4 risk factors may respond better to NIV (27), which may explain why NIT is more beneficial in older patients. In addition, the duration of prophylactic use of NIT varies by individual, which may affect the efficacy of NIT on EF and reintubation. Further studies are needed to determine the effect of the number of risk factors and duration of intervention on EF.

The respiratory support provided by HFNC is limited, as it may not provide stable positive pressure like NIV (27). However, subgroup analysis of the present study demonstrated that HFNC was noninferior to NIV in reducing EF, which was in accordance with the results of Hernández et al. (12). Numerous studies have confirmed that HFNC is significantly more comfortable and tolerable than NIV (12, 28, 29). In fact, the heating and humidification functions of HFNC allow gas delivery at an optimal humidity, effectively promoting secretion clearance while avoiding side effects such as mucosal dryness (30, 31). Interestingly, we found that HFNC tended to reduce the incidence of delirium, which was in agreement with the findings of Hernández et al. (12) and Stéphan et al. (28). Furthermore, HFNC has a CO_2 flushing effect on the nasopharyngeal space, thereby decreasing anatomical dead space ventilation and CO_2 rebreathing (32, 33).

In addition to prophylactic NIT, multivariate logistic regression analysis in our study showed that a higher ROX index before SBT was associated with a reduced risk of EF. The ROX index, defined as the ratio of SpO_2/FiO_2 to respiratory rate, is often used as a predictor of reintubation after HFNC failure, with moderate specificity (34, 35). An increasing number of articles have reported the role of ROX index in predicting NIV failure, but there is population heterogeneity, with different time periods for ROX index measurement (36, 37). A retrospective study showed that the ROX index at 6 h after ICU admission helped identify patients with ARDS at risk of NIT failure. Zablockis et al. (38) reported the role of ROX index within 24 h of admission in predicting NIV failure in patients with acute hypoxemic respiratory failure (38). To our knowledge, this study indicated for the first time that pre-SBT ROX index may be associated with the development of EF in high-risk

patients. More prospective studies are needed in the future to verify the validity of the ROX index in predicting EF at different time points and to find the best threshold.

In the present study, higher fluid balance 24 h before extubation increased the risk of EF in high-risk patients, which was in agreement with previous studies (39, 40). Weaning-induced pulmonary edema is a common reason for EF (41). And cardiac dysfunction can occur during decannulation owing to increased preload and afterload of the right and left ventricles, triggering EF, especially in high-risk patients (42). Therefore, restricted fluid therapy may be one of the key measures for successful extubation.

Delirium is a common medical problem that is often characterized by transient fluctuations in attention, confusion, and disturbance of thought (43). Delirium has been reported to occur in 50 to 80% of mechanically ventilated patients (44). The incidence of delirium was as high as 54.8% in the high-risk patients included in this study. Older age, ventilator use, and benzodiazepine use increased the risk of delirium in ICU patients (45). This was confirmed in our subgroup analysis, which showed a higher incidence of delirium in patients older than 65 years than in those aged $\leq$ 65 years. In addition, delirium is a risk factor for EF and reintubation, which was consistent with our results. This may be related to the fact that delirium impedes pulmonary rehabilitation and out-of-bed activities. Not only that, but patients who develop delirium are often treated with benzodiazepines, and the cumulative effect of these sedative drugs can impair mental status after tracheal intubation removal, leading to EF and reintubation.

Although early weaning from MV after successful SBT improves prognosis, EF is inevitable and significantly increases the rate of reintubation. Therefore, it is important to choose an appropriate respiratory strategy to prevent EF, especially for high-risk patients. To prevent EF and increase the success rate of extubation, the modalities of COT, HFNC, and NIV are commonly used to support breathing. In clinical practice, NIV or HFNC could be used prophylactically after planned extubation to reduce the risk of EF in high-risk patients. And NIT is more effective in those older than 65 years. Reducing the incidence of EF and reintubation, and shortening the length of hospital stay are not only beneficial to patients and their families, but also avoid the waste of medical resources. In addition, combinational use of HFNC and NIV seems to be a promising method in post-extubated patients because the addition of HFNC to NIV could, at least theoretically, further improve gas exchange and decrease the work of breathing. In the future, larger sample size randomized controlled trials are needed to explore the effect of combination therapy on extubation failure and reintubation in high-risk patients.

There are several limitations in the study. First, this was a cohort study conducted in a single center, limiting the generalizability of the results. Evaluation methods and parameter settings in different hospitals may affect the effectiveness of NIT on EF. In the future, we will conduct a related multicenter randomized controlled study to further explore the effect of NIT in high-risk patients. Second, due to the nature of retrospective study, there may be potential biases such as selection bias, recalling bias, and confounding factors. These biases may affect the validity of the findings. To address selection bias, we established clear inclusion and exclusion criteria and used uniform and accepted diagnostic criteria. However, PSM was performed in the study to reduce the effect of selection bias and possible confounders between the two groups. The possibility of residual confounding may still exist after PSM. To further control for confounders, other statistical methods can be used, such as stratified analyses or multivariate adjustment analyses, which can help to identify and control for additional confounders. Considering the limited sample size, only two subgroup analyses were performed in this study. Third, although the assessment of SBT is standardized, clinical guidelines are updated over time and the attending physicians make the final decision. Fourth, the small sample size, particularly in the subgroup analysis involving the efficacy of NIV and HFNC, may weaken the strength of the evidence. However, HFNC was proven to be noninferior to NIV in reducing reintubation in relevant multicenter RCTs. Finally, respiratory mechanics parameters such as cough peak expiratory flow (CPEF), peak inspiratory pressure and peak expiratory pressure were missed due to retrospective data collection from medical records. These relevant parameters may be associated with EF. And CPEF is considered to be a useful tool for predicting extubation (46). A CPEF of < 60 L/min was associated with a significantly increased risk of EF (47). The advantage of CPEF is that it is simple, inexpensive, portable, easy to repeat, and has the potential to prevent reintubation. More respiratory mechanical parameters are needed to predict extubation success or failure in the future.

5 Conclusion

In conclusion, prophylactic use of NIT following planned extubation is effective in reducing the rate of EF in high-risk patients, especially in those over 65 age of years. HFNC is an alternative treatment to NIV in high-risk patients and increases patient comfort and tolerance. Furthermore, fluid balance, RSBI, ROX index and delirium may be good predictors of EF in high-risk patients.

Data availability statement

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

Ethics statement

The studies involving humans were approved by the institutional ethics committee of the First Affiliated Hospital of Chongqing Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal

guardians/next of kin because Informed consent was waived because of the retrospective observational nature of the study.

Author contributions

XZ: Writing – original draft. LL: Writing – original draft. MM: Writing – review and editing. XL: Writing – review and editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of the 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 25 October 2024
DOI 10.3389/fmed.2024.1479741

OPEN ACCESS

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RECEIVED 12 August 2024
ACCEPTED 11 October 2024
PUBLISHED 25 October 2024

CITATION
Zhao X, Zhou Z, Li Z, Hu Z and Yu Y (2024) Use of esketamine for tracheoscopic drug injection: a randomized controlled trial. *Front. Med.* 11:1479741. doi: 10.3389/fmed.2024.1479741

Use of esketamine for tracheoscopic drug injection: a randomized controlled trial

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Background: Sufentanil may induce hypotensive bradycardia and other adverse reactions in elderly patients during anesthesia, while esketamine exhibits sedative and analgesic effects with minimal impact on respiration and circulation. The objective of this study was to investigate the impact of these two anesthetics on vital signs in patients undergoing bronchoscopy and lavage under general anesthesia.

Method: This study was a randomized controlled trial with a parallel design. A total of 100 patients aged ≥60 years with ASAI or II who were undergoing bronchoscopy and lavage were randomly assigned to two groups: group A (esketamine, $n = 50$) and group B (sufentanil, $n = 50$). During anesthesia induction, both groups received intravenous infusion of propofol at a dose of 1.5 mL/kg and atracurium. In group A, esketamine at a dose of 0.3 mg/kg was injected; in group B, sufentanil at a dose of 0.2 μg/kg was injected intravenously. Subsequently, a laryngeal mask was inserted and connected to an anesthesia machine for mechanical ventilation. Anesthesia maintenance involved continuous intravenous infusion of propofol at a dose of 3 mL/kg. The mean arterial pressure (MAP), heart rate (HR), and blood oxygen saturation (SpO2) were recorded at various time points: before anesthesia injection (T0), after laryngeal mask insertion (T1), 5 min after the operation started (T2), 15 min after the operation started (T3), and before the end of the operation (T4). Additionally, the recovery time was recorded.

Results: The blood pressure of patients in the esketamine group exhibited higher levels compared to those in the sufentanil group at multiple time points during the operation, while maintaining a more stable intraoperative blood pressure and shorter postoperative recovery time than that observed in the sufentanil group. The blood pressure and heart rate of patients in the esketamine group exhibited significant fluctuations after laryngeal mask implantation compared to pre-anesthesia induction, with a statistically significant increase observed. Conversely, no significant changes were observed in the sufentanil group. The heart rate and oxygen saturation showed no significant differences between the two groups, nor did the amount of propofol administered during the procedure.

Conclusion: The utilization of esketamine during the induction phase of bronchoscopy and lavage under general anesthesia can enhance hemodynamic stability and reduce the occurrence of hypotension, thereby facilitating postoperative anesthetic recovery.

KEYWORDS

esketamine, sufentanil, tracheoscopy, curative effect, security

1 Introduction

Malignant tumor cells invade the trachea, leading to malignant tracheal stenosis, which can cause dyspnea and is considered a severe respiratory disease. Therefore, the treatment primarily aims to immediately eliminate airway obstruction. Previous studies have shown that the intratumoral injection of cisplatin and Endostar, especially when combined with cryotherapy and hyperthermia, under a bronchoscope can eliminate tumors, control tumor growth, maintain a smooth trachea and bronchial lumen in a timely manner, and prolong the time of tracheal restenosis (1, 2). However, it can also lead to several issues. Patients can feel uncomfortable during the treatment, particularly in the long-term treatment process, commonly patients cannot be treated or treatment fails because they cannot cooperate. To improve the comfort and efficacy of examination and treatment, general anesthesia is preferred. In this anesthetic method, sufentanil is commonly used in the induction stage. However, the use of sufentanil in elderly patients can often cause adverse events such as cough, chest wall stiffness, hypotension, and bradycardia (3), which can affect surgeries using a tracheoscope. Esketamine is the dextral structure of ketamine, which has effects including sedation, analgesia, and loss of consciousness. However, it has a minimal effect on respiration and circulation (4). Therefore, this study evaluated the efficacy and safety of ketamine combined with propofol for painless tracheoscopy in patients with tumors to provide a reference for clinical medication.

2 Methods

2.1 Clinical data

We collected the data of 100 patients who underwent painless bronchoscopy and received injection therapy from January 2022 to March 2023 at the Department of Respiratory and Critical Care Medicine, Qingdao Haici Hospital Affiliated to Qingdao University. All patients presented with The American Society of Anesthesiologists (ASA) classification I–II disease. However, none of the patients were at high risk for anesthesia. Inclusion criteria: The inclusion criteria were as follows: patients with lung cancer, lung metastases, and tracheal tumors confirmed on pathology and/or cytology who had central airway lesions that were intratracheal + wall or wall type, those who required painless bronchoscopy and injection therapy under a bronchoscope, and those aged over 60 years. Exclusion criteria: The exclusion criteria were as follows: patients allergic to narcotic drugs; those who refused to undergo tracheoscopy; those with uncontrolled hypertension, cerebral infarction within the last 3 months, oral anticoagulants, new cardiovascular events, and oral antiplatelet drugs that cannot be discontinued; those with severe respiratory insufficiency or cardiac insufficiency who could not tolerate tracheoscopy and treatment; and those with vital signs that changed due to excessive bleeding during surgery. The participants were randomly divided into group A who included patients receiving esketamine ($n = 50$) and group B who comprised patients receiving sufentanil ($n = 50$).

2.2 Anesthetic methods

During anesthesia induction, propofol at a dose of 1.5 mL/kg and atracurium at a dose of 0.4 mg/kg were intravenously administered. Group A received esketamine at a dose of 0.3 mg/kg intravenously. Group B received sufentanil at a dose of 0.2 μg/kg intravenously. A laryngeal mask was inserted and connected to the anesthesia machine for mechanical ventilation. The tidal volume was calculated based on the standard of 8–10 mL/kg, while end-tidal carbon dioxide levels were maintained within the range of 35–45 mmHg. Anesthesia was maintained via continuous intravenous infusion with propofol at a dose of 3 mg/kg.

2.3 Surgical method using the tracheoscope

The patients were treated with a bronchoscope injection needle (Shanghai Elton Model: af-d1810pn). Routine bronchoscopy was performed. After cutting the tumor under a bronchoscope, the needle was inserted into the residual tumor under direct visualization. Injection was performed at 4–6 points at the center and periphery of the tumor. The penetration depth was 3–4 mm. Endostar (15 mg) and cisplatin (20 mg) were diluted to 4 mL. Four to six parts of the tumor were injected alternately with 0.5 mL of drugs each time, twice a week for two consecutive weeks.

2.4 Observation index

The primary outcomes, including mean arterial pressure (MAP), heart rate (HR), and blood oxygen saturation, were recorded at multiple time points: before anesthesia injection (T0), after laryngeal mask insertion (T1), 5 min after the beginning of surgery (T2), 15 min after the beginning of surgery (T3), and before the end of surgery (T4). The secondary outcome, the time from the end of the procedure until the patient can open his eyes and cooperate with commands.

2.5 Quality control plan

All examinations were performed by the same physician and assistant and by the same anesthesiologist.

2.6 Sample size estimation

According to the results of the preliminary experiment, the mean arterial pressure (MAP) in the sufentanil group was 96 ± 10 mmHg after laryngeal mask airway (LMA) insertion. The predicted increase in MAP in the esketamine group was 7 mmHg (mean MAP value of 103 ± 10 mmHg), with a two-sided $\alpha = 0.05$ and a power of 90%. The sample size calculation using PASS 15 software yielded a requirement

Abbreviations: ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

of 88 subjects. Considering a potential dropout rate of 20%, at least 100 subjects were ultimately needed.

2.7 Statistical processing

SPSS 23.0 software was utilized for conducting statistical analysis. The Shapiro–Wilk test was employed to assess the normality of the data. The qualitative data are illustrated in the form of examples (%) and compared using chi-square or Fisher exact tests. Quantitative data were expressed as mean ± SD, with group comparisons conducted using t-tests and comparisons at different time points performed through repeated measures analysis of variance (ANOVA). The within-group comparisons were conducted using a multivariate analysis of variance. Statistical significance was defined as a p value less than 0.05.

3 Results

3.1 Demographic data and clinical characteristics

There were no significant differences in terms of age, sex, body mass index, and ASA classification (I/II) between the two groups ($p > 0.05$), as shown in Table 1.

3.2 Recovery time for anesthesia

The recovery time from anesthesia in group A was lower than that in group B ($p < 0.05$). There was no significant difference in terms of surgical duration between the two groups ($p > 0.05$), as shown in Table 2.

3.3 Hemodynamics

The two groups exhibited statistically significant differences in mean arterial pressure (MAP) at various time points, as well as in terms of time and interaction effects ($F_{group} = 18.315$, $p < 0.01$; $F_{time} = 5.019$, $p < 0.05$; $F_{group \times time} = 7.412$, $p < 0.05$). Prior to anesthesia administration, there was no significant disparity observed in MAP between the two groups ($p > 0.05$). Group A demonstrated higher MAP values than group B at T1, T2, T3, and T4 ($p < 0.05$). The MAP at T2, T3, and T4 did not show any statistically significant difference in group A compared to the T0 ($p > 0.05$). However, significant differences were observed at T2, T3, and T4 in group B ($p < 0.05$). No notable distinctions were found between the two groups regarding heart rate and blood oxygen saturation across different time points. as shown in Table 3.

4 Discussion

Endotracheal interventional therapy under a bronchoscope is safe, effective, and minimally invasive. It has increasingly prominent advantages for treating airway tumors. For patients with definite malignant intratracheal tumors, intratumoral injection of chemotherapy drugs combined with cryotherapy and hyperthermia can play a synergistic role. In previous studies, our team confirmed that drug injection under a bronchoscope can immediately and effectively remove the airway tumor and prolong the time of airway restenosis. However, because bronchoscopy should go deep into the human body, it is an invasive examination that can cause significant discomfort, not only cough but also dyspnea and other serious complications (5). It also leads to operational difficulties and risks to the medical staff (6).

Laryngeal mask airway anesthesia can ensure the airway patency of patients. Hence, they can complete the surgery comfortably. The anesthesia operation stimulation is minimal (7), particularly after applying lidocaine cream. Moreover, the insertion and removal of a laryngeal mask has minimal effects on circulation. General anesthesia can relax the pharyngeal muscles and shorten the surgical duration. At present, opioids are commonly used. However, in the process of anesthesia induction, the blood pressure of patients with hypotension and low HR decreases significantly. Further, vasoactive drugs are required to maintain blood pressure within the normal range.

The sedative and analgesic effects of ketamine have been utilized in clinical anesthesia for over 50 years; however, its prominent side effects, including elevated blood pressure or intracranial pressure, increased airway secretions and heart rate, as well as dizziness and vomiting, have led to its gradual replacement by alternative anesthetic drugs (8). Esketamine is the dextrorotatory enantiomer of ketamine, and its pharmacological properties closely resemble those of ketamine. Both compounds exert anesthetic, amnesic, analgesic, anti-hyperalgesic, and antidepressant effects by inhibiting N-methyl-D-aspartate (NMDA) receptors. Studies have demonstrated that esketamine

TABLE 1 Preoperative demographics and characteristics.

Baseline indicators	Group A	Group B	p
Sex (M/F)	32 (64)/18 (36)	29 (58)/21 (42)	0.681
Age (years)	66.9 ± 4.8	68.1 ± 6.5	0.405
BMI (kg/m^2)	23.2 ± 2.3	23.6 ± 2.7	0.427
ASA I/II	19 (38)/31 (62)	22 (44)/28 (56)	0.068

BMI, body mass index; ASA, American Society of Anesthesiologists physical status. Sex and ASA were expressed as number of patients (%), Age and BMI as mean ± SD. The significance level of $p < 0.05$ indicates a statistically significant difference between the two groups.

TABLE 2 Perioperative related indicators.

Group	Number of cases	Dosage of propofol (mg)	Surgical duration (min)	Anesthesia recovery time (min)
A	50	77.0 ± 10.2	23.7 ± 5.7	3.6 ± 1.3
B	50	80.3 ± 10.1	22.6 ± 6.3	4.1 ± 1.1
P		0.051	0.329	0.040

The intraoperative propofol dosage, operation time, and postoperative recovery time were compared between the two groups. All data are presented as mean ± SD. A significance level of $p < 0.05$ was considered to indicate a statistically significant difference.

TABLE 3 Vital signs recorded at different time points.

Vital signs	Group	Number of cases	T0	T1	T2	T3	T4
MAP	A	50	89.8 ± 10.34	105.1 ± 10.4[a]	93.6 ± 7.4	93.7 ± 8.0	94.1 ± 6.6
(mmHg)	B	50	91.6 ± 8.9	80.7 ± 3.4[b]	74.3 ± 10.6[ab]	78.3 ± 11.5[ab]	77.7 ± 10.6[ab]
HR	A	50	75.6 ± 10.4	91.9 ± 11.1[a]	82.9 ± 13.2	79.7 ± 12.1	79.9 ± 11.4
(bpm)	B	50	75.6 ± 4.4	86.4 ± 13.0	75.0 ± 9.2	77.2 ± 8.2	77.4 ± 8.0
SpO2	A	50	96.6 ± 0.7	95.6 ± 0.7	96.8 ± 0.5	97.9 ± 0.7	97.7 ± 0.5
(%)	B	50	97.3 ± 0.6	96.9 ± 0.5	96.8 ± 0.3	97.1 ± 0.2	97.0 ± 0.3

MAP, mean arterial pressure, HR, heart rate, SpO_2, blood oxygen saturation. Data are presented as mean ± SD. Compared with T0, [a]$p < 0.05$; Compared with Group A, [b]$p < 0.05$.

exhibits approximately three times higher affinity for NMDA receptors compared to ketamine, resulting in a potential 2–3 fold increase in its anesthetic potency (9). The use of esketamine in pediatric short surgery offers several advantages, including the preservation of respiratory muscle tension and protective airway reflexes. Its potent sedative effect effectively caters to the requirements of pediatric surgical procedures. Additionally, its rapid onset and metabolism make it highly suitable for anesthesia in pediatric short surgeries (10, 11). The utilization of esketamine in adult surgery can effectively maintain hemodynamic stability. In comparison to the induction of anesthesia using propofol and sufentanil in elderly surgical patients, the combination of propofol and esketamine exhibits superior hemodynamic stability, while also enhancing surgical stress and inflammation management, as well as reducing anesthesia recovery time. Furthermore, there is no significant difference in the incidence of adverse reactions between sufentanil alone and its combined use with esketamine (12, 13). Other studies have demonstrated that esketamine can partially mitigate the incidence of postoperative cognitive dysfunction in elderly patients undergoing general anesthesia (14). In addition, certain surgical procedures such as breast disease surgery and laparoscopic hysterectomy can impose significant psychological burden on patients. The administration of esketamine following anesthesia induction can effectively enhance postoperative mood in the short term while also exhibiting commendable analgesic properties (15, 16). In this experiment, the intraoperative hemodynamics of patients in the esketamine group exhibited greater stability and a reduction in postoperative recovery time. However, there was a significant elevation in heart rate and blood pressure observed after laryngeal mask placement in the esketamine group. This can be attributed to the systemic release of catecholamines by esketamine, which inhibits norepinephrine reuptake by peripheral nerves, cardiomyocytes, and other neuronal tissues. Additionally, esketamine suppresses vagus nerve activity while enhancing sympathetic nerve excitability. These factors collectively contribute to an increase in heart rate and blood pressure (17, 18). In addition to elevating blood pressure and heart rate, esketamine can also induce an increase in cerebral blood flow, consequently leading to a rise in intracranial pressure. However, under normal circumstances, controlled ventilation or hyperventilation can mitigate the escalation of intracranial pressure caused by esketamine (19, 20). The selection should be made based on the specific conditions of patients in clinical practice.

Sufentanil, an opioid, takes effect 1.5 min after one injection and lasts approximately 40 min. If the dose exceeds the recommended dose, transient respiratory depression may occur. Combined with propofol, it can increase respiratory and circulatory depression, thereby indicating dose-dependent tolerance (21). The advantages of this controlled trial are as follows: First, the analgesic effect is accurate, and a single injection can meet the operation requirements. Second, the recovery of spontaneous respiration was almost unaffected, and recovery was not delayed. However, the main adverse reactions of sufentanil are hypotension and bradycardia (22). In this study, several disadvantages were observed. That is, the blood pressure of patients had a downward trend from anesthesia induction to the end of the surgery.

In this clinical study, the time from anesthesia induction to laryngeal mask insertion to the beginning of surgery was extremely short. Therefore, there was no observation time point between anesthesia induction and the start of interventional surgery.

5 Conclusion

Both ketamine and sufentanil can be used as anesthesia for injection therapy under an electronic bronchoscope. However, the effects of these two drugs on blood pressure and HR differ. In clinical practice, the appropriate compatible drug can be selected based on the patient's vital signs. Therefore, patients can undergo a smoother and more comfortable surgery.

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 Ethics Committee of Qingdao Haizi Hospital affiliated to Qingdao University (2020HC12LS011). 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

XZ: Writing – original draft. ZZ: Investigation, Writing – original draft. ZL: Data curation, Formal analysis, Writing – original draft. ZH: Supervision, Writing – review & editing. YY: Conceptualization, Investigation, Methodology, Supervision, 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.

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 06 November 2024
DOI 10.3389/fmed.2024.1499122

OPEN ACCESS

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RECEIVED 20 September 2024
ACCEPTED 28 October 2024
PUBLISHED 06 November 2024

CITATION
Wang Q, Huang F, Wei K, Wang J, Zhu X, Xiong Q and Liu D (2024) Association between duration of phenoxybenzamine use and postoperative delirium in suspected adrenal pheochromocytoma: a retrospective cohort study.
Front. Med. 11:1499122.
doi: 10.3389/fmed.2024.1499122

Association between duration of phenoxybenzamine use and postoperative delirium in suspected adrenal pheochromocytoma: a retrospective cohort study

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Background: At present, the available evidence regarding the relationship between duration of phenoxybenzamine use and postoperative delirium is inadequate in suspected adrenal pheochromocytoma.

Objective: To understand how changes in the duration of phenoxybenzamine use may affect postoperative delirium. The secondary objective of this study is to explore how the duration of phenoxybenzamine use may jointly influence postoperative delirium together with other interacting variables.

Methods: We conducted a retrospective cohort study involving 527 participants with a preoperative diagnosis of suspected pheochromocytoma. CT characteristics, preoperative preparation, intraoperative infusion, estimated bleeding, use of intraoperative vasoactive drugs, and outcomes were obtained from all participants. Logistic regression and interaction effects were utilized to substantiate the research objectives.

Results: A total of 108 (20.5%) developed postoperative delirium, which was seen in 37 (18.0%) in the pheochromocytoma group and 71 (22.0%) in the non-pheochromocytoma group. The incidence of postoperative delirium showed no statistically significant differences in the two groups. A positive association between the duration of phenoxybenzamine use and the risk of postoperative delirium was observed (OR = 1.05, 95%CI = 1.03–1.08, $p < 0.01$), independent of confounders. The relationship between the duration of phenoxybenzamine use and postoperative delirium differed according to the presence or absence of pheochromocytoma, suggesting an interactive effect ($p < 0.05$).

Conclusion: This study highlights the influence of inappropriate duration of phenoxybenzamine use on the risk of incident postoperative delirium, independent of confounders. The effect of duration of phenoxybenzamine use causes a further increase in the risk of postoperative delirium, especially in non-pheochromocytomas.

KEYWORDS

phenoxybenzamine, pheochromocytoma, postoperative, delirium, adrenal

Highlights

- *Question:* There was a lack of research on whether the duration of preoperative phenoxybenzamine use leaded to postoperative delirium.
- *Findings:* Prolonged preoperative use of phenoxybenzamine increases the probability of postoperative delirium.
- *Meaning:* Preoperative medication may be altered for patients with a low likelihood of a preoperative diagnosis of pheochromocytoma.

Introduction

Pheochromocytomas are rare neuroendocrine tumors that originate from chromaffin cells in the adrenal medulla that produce catecholamines. The primary treatment is surgical excision of the tumor. Hemodynamics, however, can alter dramatically and quickly during surgery, which significantly raises a patient's risk of experiencing a potentially fatal complication (1). Studies have shown that preoperative alpha blockade significantly improves intraoperative hemodynamics and reduces postoperative morbidity and mortality in patients undergoing surgery for pheochromocytoma (2, 3).

At our institution, preoperative treatment with alpha blockade was a routinely required for suspected pheochromocytoma. Meanwhile, preoperative diagnosis of pheochromocytoma is not easy (4–6), which creates uncertainty about the length of preoperative preparation. Phenoxybenzamine, one of the alpha blockade agents commonly used in the preoperative treatment of pheochromocytoma, was effective in reducing the incidence of intraoperative hemodynamics instability (7, 8). According to current guidelines, patients should receive at least 7 days of preoperative alpha blockade (9). Nevertheless, the duration of Phenoxybenzamine was not entirely in line with the guidelines due to inconsistent standardization of management (10). The use of alpha blockade increased the risk of hypotension and prolonged the duration of hypotension (11, 12). The intraoperative hypotension was more harmful and was associated with increased mortality at 30 days postoperatively (13).

Postoperative delirium is one of the common postoperative complications that can prolong hospitalization and increase the financial burden on the healthcare system. Some studies had shown that intraoperative hypotension was associated with postoperative delirium in surgical patients (14, 15). Nevertheless, whether prolonged hypotension causes postoperative delirium remains controversial (16).

Prolonged administration of Phenoxybenzamine may cause an increase in the duration of intraoperative and postoperative hypotension, and it is not known whether this further contributes to an increased risk of postoperative delirium. At present, the available evidence regarding the relationship between phenoxybenzamine duration and postoperative delirium is inadequate. Based on the above studies, we hypothesized that the duration of phenoxybenzamine use may be an important indicator of postoperative delirium. This study aimed to demonstrate the correlation between phenoxybenzamine duration and postoperative delirium. The secondary objective of this study is to investigate the combined effects of phenoxybenzamine duration and interacting factors on postoperative delirium.

Methods

Study design, setting, and participants

The Ethics Committee of the First Affiliated Hospital of Chongqing Medical University approved permission for this prospective observational study (registration number: 2023–367), which was carried out at the hospital. Informed consent was waived by the Ethics Committee for this investigation because it was retrospective.

We reviewed the clinical information (taken from patient records) of all the patients with adrenal tumors who had surgery from July 2018 to June 2023. Suspected pheochromocytoma was considered when the CT value of adrenal tumor is >10HU on CT plain scan and the CT shows marked enhancement of the mass shadow after intravenous contrast injection; it could also be combined with positive plasma fractionated metanephrines analogues determination. Patients with a preoperative diagnosis of suspected pheochromocytoma were included, and those with a definitive preoperative diagnosis of adenoma, hypercortisolism, primary aldosteronism, ASA grade V or higher, emergency surgery, and missing data were excluded. Also, patients with a preoperative diagnosis of delirium, dementia, or mild cognitive impairment were excluded. The guidelines for Strengthening the Reporting of Observational Studies in Epidemiology were adhered to in all papers.

Preoperative and intraoperative management

All patients included in the study were treated with alpha blockade (Phenoxybenzamine) preoperatively.

Phenoxybenzamine was started at the time of outpatient diagnosis of suspected pheochromocytoma. Then waiting for admission to the hospital for surgery, the waiting period was inconsistent for various reasons. Following admission, the dosage of phenoxybenzamine was adjusted and sustained. This was done to keep the patient's blood pressure from rising over 130/80 mm Hg. Once alpha blockade was established, a beta blockade was added when following the achievement of alpha blockade, a beta blockade was introduced when needed to keep the heart rate (HR) below 80 beats per minute (beats/min). Fluid therapy was also administered, and some patients underwent plasma infusion.

Before anesthetic induction, all patients in the operating room had their blood pressure continuously monitored using an intra-arterial catheter. Other intraoperative monitoring included an electrocardiogram, pulse oximetry, end-expiratory carbon dioxide, nasopharyngeal temperature, urine output, and Electroencephalographic monitoring (Nacrotrend). Peripheral and central venous lines were established. All patients had general anesthesia with tracheal intubation. In general, propofol, sufentanil, and vecuronium were used to induce anesthesia, and anesthesia was maintained using propofol infusion and/or sevoflurane inhalation, as well as sufentanil and/or remifentanil. The anesthesiologist decided on the intraoperative use of vasoactive medications and/or beta-blockers. Vasodilators were often used when the systolic blood pressure (SBP) was >160 mm Hg and vasopressors when the SBP was <90 mm Hg. Phentolamine was the preferred vasodilator, with

nicardipine and uradil as adjuncts. In terms of vasopressors, norepinephrine was the preferred therapy, epinephrine, phenylephrine, ephedrine, and dopamine were also employed. Esmolol was administered when the heart rate exceeded 90 beats per minute. Rehydration and blood transfusions were delivered by standard procedure. Depending on the surgeon's preferences, the surgical procedure could be either laparoscopic or robotic-assisted; huge tumors might require open surgery, but laparoscopic to open surgery was also a possibility. Postoperatively, the patient was transferred to the post-anesthesia care unit (PACU) and, if necessary, to the intensive care unit (ICU). Patient-controlled analgesia (PCA) or multimodal analgesia was used in the postoperative period.

Outcome measures and definition

The primary outcome was delirium within 7 days after surgery. Delirium was diagnosed using the Confusion Assessment Method (CAM). If the description in the medical record or in the nursing record matched the CAM, it was still recorded as 1 case of postoperative delirium.

The duration of phenoxybenzamine use was the duration of out-of-hospital preparation added to the duration of post-hospital administration of phenoxybenzamine. However, the duration of preoperative treatment with phenoxybenzamine was not uniform for various reasons. At the study center, surgeons tended to give phenoxybenzamine (10–15 mg, 3 times daily) for potentially longer (>7 days) in patients with a greater likelihood of pheochromocytoma (with typical symptoms, larger tumor size, and/or higher catecholamine levels). At our center, preoperative treatment with phenoxybenzamine was done out of the hospital to shorten the number of hospital days. Which had become one of the reasons for the inconsistency in the length of time phenoxybenzamine was used. Phenoxybenzamine was taken immediately when the diagnosis of suspected pheochromocytoma was made, and phenoxybenzamine was discontinued when catecholamine results ruled out pheochromocytoma. In patients with atypical symptoms who were also not tested for catecholamines, the duration of treatment may be shorter and variable. It depends on the experience of the physician. Phenoxybenzamine dosage statistics were the combination of daily usage.

The diagnosis of pheochromocytoma was determined by postoperative pathology. Suspicious pheochromocytoma was considered in patients with paroxysmal hypertension; typical triad of headache, sweating, and tachycardia; or adrenal incidentalomas with CT plains suggestive of lack of lipids and a CT value >10 HU.

Intraoperative hypotensive was defined as at least one episode of mean arterial pressure below 55 mmHg (17, 18). Intraoperative hypotension was usually treated with fluids, norepinephrine, epinephrine, dopamine, phenylephrine, or ephedrine. The need for blood transfusion depends on the amount of hemoglobin and the experience of the anesthesiologist.

Collection of clinical characteristics

By reviewing the patient's medical records during hospitalization, clinical characteristics were collected, including age, weight, height, ASA classification, type of adrenal tumor, and preoperative comorbidities; and perioperative indicators, including anesthetic drugs (midazolam, sufentanil, vecuronium, etc), type of surgery, length of anesthesia, length of surgery, estimated intraoperative blood loss, fluid therapy, the incidence of admission to the intensive care unit (ICU), postoperative complications, and length of hospital stay. In addition, intraoperative use of antihypertensive and antihypertensive drugs was evaluated. The worst pain score over the first postoperative 7 days was also collected.

Tumor size and enhanced versus unenhanced CT values were measured by reviewing patients' adrenal CT images completed by an attending radiologist with more than 5 years of experience.

Statistical analyses

Histogram distribution was used to determine whether variables were normally distributed. All normally distributed continuous variables were expressed presented as mean ± SD, and skewed continuous variables were described as median [interquartile range (IQR)]. Categorical variables were presented as frequencies (%). Comparison of continuous variables among groups was performed with the use of the independent samples Student's *t*-test or Mann–Whitney *U*-test depending on the normality of the distribution, and categorical data were compared by chi-square or Fisher's exact test as appropriate.

The effect of days of phenoxybenzamine use on postoperative delirium was evaluated using binary logistic regression models [odd ratio (OR) and 95% confidence interval (CI)] with adjustment for major covariables. We selected these confounders based on judgment, previous scientific literature, all significant covariates in the univariate analysis, or their associations with the outcomes of interest or a change in effect estimate of more than 10%. We constructed 2 models: Model 1 adjusted for age, sex, and BMI. Model 2 was additionally adjusted for Preoperative comorbidities, CT characteristics, types of surgery, duration of surgery, estimated bleeding, and transfusions.

Subgroup analysis examined the relationship between Days of Phenoxybenzamine use and postoperative delirium according to Subgroup variables, especially between the pheochromocytoma group and the non-pheochromocytoma group. Interaction across subgroups was tested using the likelihood ratio test. Missing data accounted for <5% of the data set and were handled by list-wise deletion on an analysis basis. All analyses were performed using R Statistical Software (Version 4.2.2,[1] The R Foundation) and Free Statistics analysis platform (Version 1.9, Beijing, China).[2] A two-sided $p < 0.05$ was considered statistically significant.

Results

A total of 527 patients were included after strict screening according to the inclusion and exclusion criteria. Of these, 205 cases (38.9%) were definitively diagnosed as pheochromocytoma (Figure 1).

1 https://www.R-project.org

2 https://www.clinicalscientists.cn/freestatistics

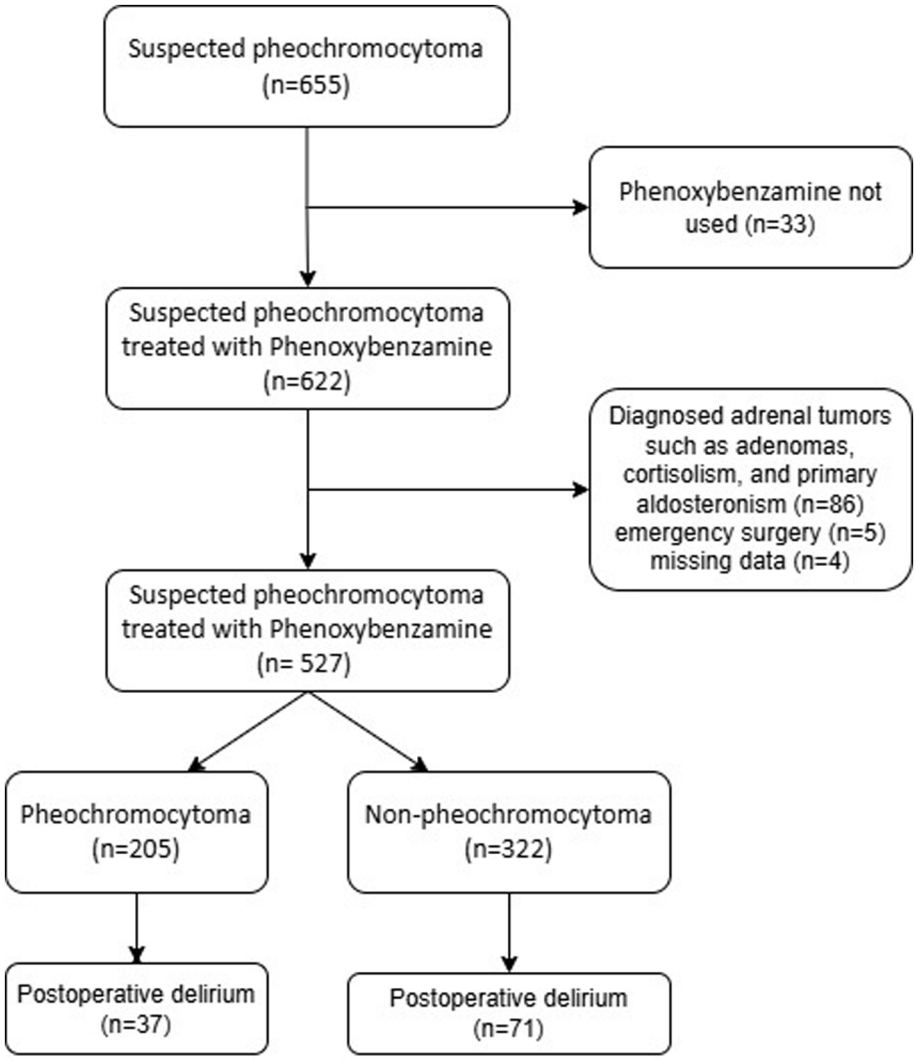

FIGURE 1
The flow chart of the study.

A total of 108 (20.5%) developed postoperative delirium, which was seen in 37 (18.0%) in the pheochromocytoma group and 71 (22.0%) in the non-pheochromocytoma group. Table 1 shows the baseline characteristics of the subjects included in the final analysis. Table 2 shows the differences in perioperative correlates between the pheochromocytoma group and the non-pheochromocytoma group.

Figure 2 shows a linear relationship between the duration of phenoxybenzamine use and the risk of postoperative delirium. In univariate logistic regression analyses, the duration of phenoxybenzamine use was expressed as a continuous variable (Per 1 day was positively associated with the probability of postoperative delirium) (OR = 1.04, 95% CI = 1.02–1.06, $p < 0.001$). This association was stable and remained statistically significant (OR = 1.05, 95% CI = 1.03–1.08, $p < 0.001$), independent of potential confounders (Table 3, model 2).

We also performed stratified analyses according to pheochromocytoma and non-Pheochromocytoma. We found that the relationship between the duration of phenoxybenzamine use and postoperative delirium was statistically significant across the subgroups (the p-value for the interaction likelihood ratio test was $p < 0.001$). In the non-pheochromocytoma group, each additional day of preoperative phenoxybenzamine use was associated with an 18% increase in the probability of postoperative delirium (OR = 1.18, 95% CI = 1.1–1.25, $p < 0.001$) (Figure 3).

Discussion

In these patients with a preoperative diagnosis of suspected pheochromocytoma retrospective cohort study, we first demonstrated that the duration of phenoxybenzamine use was independently associated with an increase in the risk of developing postoperative delirium. It is worth mentioning that an interaction was also observed between the duration of phenoxybenzamine and pheochromocytoma and non-pheochromocytoma in their influence on postoperative delirium ($p < 0.05$).

Our study observed positive associations of duration of phenoxybenzamine use with postoperative delirium in the context of

TABLE 1 Patient demographic information.

Variables	Total (n = 527)	Non-pheochromocytoma (n = 322)	Pheochromocytoma (n = 205)	p
Age (y), Mean ± SD	52.8 ± 12.7	53.3 ± 12.4	51.9 ± 13.2	0.206
Height (cm), Mean ± SD	160.6 ± 11.1	160.9 ± 9.3	160.3 ± 13.4	0.537
Weight (Kg), Mean ± SD	62.6 ± 12.5	63.9 ± 12.0	60.6 ± 12.9	0.003
BMI (Kg m^{-2}), Mean ± SD	26.7 ± 40.1	25.4 ± 20.6	28.7 ± 58.9	0.358
ASA, n (%)				< 0.001
I	2 (0.4)	2 (0.6)	0 (0)	
II	197 (37.4)	170 (52.8)	27 (13.2)	
III	317 (60.2)	149 (46.3)	168 (82)	
IV	11 (2.1)	1 (0.3)	10 (4.9)	
Type of diseases, n (%)				< 0.001
Pheochromocytoma	205 (38.9)	0 (0)	205 (100)	
Adenoma	277 (52.6)	277 (85.7)	0 (0)	
Hyperaldosteronism	6 (1.1)	6 (1.9)	0 (0)	
Cortisolism	21 (4.0)	21 (6.5)	0 (0)	
Cyst	8 (1.5)	8 (2.5)	0 (0)	
Hemangioma	9 (1.7)	9 (2.8)	0 (0)	
Teratoma	1 (0.2)	1 (0.3)	0 (0)	
Hypertension, n (%)	307 (58.3)	176 (54.7)	131 (63.9)	0.036
DM, n (%)	112 (21.3)	54 (16.8)	58 (28.3)	0.002
Dislipidemia, n (%)	45 (8.5)	30 (9.3)	15 (7.3)	0.423
Cerebral infarction, n (%)	18 (3.4)	15 (4.7)	3 (1.5)	0.049
Other combidity, n (%)	145 (27.5)	87 (27)	58 (28.3)	0.75
CT diameter (cm), Median (IQR)	3.9 (2.6, 5.5)	3.0 (2.3, 4.1)	5.1 (4.3, 6.3)	< 0.001
CT unenhanced, Median (IQR)	25.0 (14.0, 38.5)	16.0 (9.0, 24.0)	39.0 (35.0, 43.0)	< 0.001

BMI, body mass index; ASA, American Society of Anesthesiologists; DM, Diabetes mellitus; CT, computerized tomography.

patients with preoperative diagnosis of suspected pheochromocytoma, especially in the non-pheochromocytoma subgroup. Inadequate cerebral perfusion and impaired oxygenation were considered the most important contributing factors to postoperative delirium (14, 15). The occurrence of postoperative delirium may be related to intraoperative and postoperative hypotension. Kim (19) team found that alpha blockade was a predictor of intraoperative hemodynamic instability. The choice to treat normotensive pheochromocytomas with phenoxybenzamine before surgery may result in dangerously low blood pressure (11). According to Groeben et al. (20), receiving alpha blockade medication before surgery increased the need for vasopressors and intraoperative hypotension (21). Not singly but in pairs, Groeben et al. (20) similarly questioned the role of preoperative alpha blockade in preventing intraoperative hypertension, and preoperative use of alpha blockade may be associated with a higher incidence of complications related to hemodynamic instability (20). Our findings further confirm the higher risk of postoperative delirium in the intraoperative hypotensive population.

Furthermore, we noticed variations in the relationships between the various durations of phenoxybenzamine use and postoperative delirium in strata with pheochromocytoma and those without. The risk of postoperative delirium was greater in the non-pheochromocytoma group. This may be explained by the fact that these biochemically silent "phaeochromocytomas" were not true pheochromocytomas, did not secrete catecholamines, and did not constrict blood vessels throughout the body. Alpha-blocker use may result in alterations to vascular tone response (19). In the non-pheochromocytoma group, Hypotension lasted longer. This type of vessel wall responds more poorly to vasoconstrictors and requires higher doses of vasoconstrictors to maintain blood pressure, including phenylephrine. A study suggests that phenylephrine impairs cerebral perfusion by constricting cerebral blood vessels leading to an increased risk of postoperative delirium (16). This was confirmed in our study, where a greater amount of phenylephrine was used in the non pheochromocytoma group, with an increased risk of postoperative delirium.

However, for non-pheochromocytomas that cannot be definitively diagnosed preoperatively, the use of alpha-blockers was still necessary if these procedures were not undertaken in specialized adrenal centers (22). For the preparation of such patients, short-acting alpha-blockers are more appropriate than phenoxybenzamine (23). Other medications such as calcium channel blockers may also provide options (24). Possibly similar to the mechanism in dopamine-only pheochromocytomas, a shorter preoperative preparation time has been suggested (23). Therefore, preoperative preparation should be individualized for this group of patients (23). For patients with a

TABLE 2 Perioperative information of patient.

Variables	Total (*n* = 527)	Non-pheochromocytoma (*n* = 322)	Pheochromocytoma (*n* = 205)	*p*
Preoperative treatment				
Phenoxybenzamine duration (day), Median (IQR)	7.0 (4.0, 11.0)	6.0 (4.0, 8.0)	9.0 (5.0, 17.0)	< 0.001
Phenoxybenzamine (mg), Median (IQR)	290.0 (150.0, 625.0)	210.0 (112.5, 360.0)	480.0 (270.0, 1070.0)	< 0.001
RBC transfusion, *n* (%)	44 (8.3)	13 (4)	31 (15.1)	< 0.001
Plasma transfusion, *n* (%)	27 (5.1)	7 (2.2)	20 (9.8)	< 0.001
Intraoperative information and treatment				
Surgery type, *n* (%)				< 0.001
Laparoscopic	401 (76.1)	270 (83.9)	131 (63.9)	
Robotic-assisted	103 (19.5)	40 (12.4)	63 (30.7)	
Open surgery	20 (3.8)	9 (2.8)	11 (5.4)	
Intermediate open	3 (0.6)	3 (0.9)	0 (0)	
Midazolam, *n* (%)	455 (86.3)	318 (98.8)	137 (66.8)	< 0.001
Sufentanil (ug), Median (IQR)	40.0 (35.0, 45.0)	40.0 (35.0, 45.0)	40.0 (35.0, 45.0)	0.661
Remifentanil (mg), Median (IQR)	1.2 (1.0, 1.7)	1.2 (0.9, 1.4)	1.5 (1.2, 2.0)	< 0.001
Vecuronium (mg), Median (IQR)	10.0 (9.0, 11.7)	9.7 (8.5, 10.7)	11.0 (9.7, 12.8)	< 0.001
Introperative hypotension, *n* (%)	96 (18.2)	49 (15.2)	47 (22.9)	0.025
Phenylephrine (ug) Median (IQR)	200.0 (150.0, 250.0)	250.0 (200.0, 300.0)	100.0 (100.0, 150.0)	< 0.001
Norepinephrine, *n* (%)	394 (74.8)	223 (69.3)	171 (83.4)	< 0.001
Epinephrine, *n* (%)	27 (5.1)	3 (0.9)	24 (11.7)	< 0.001
Phentolamine, *n* (%)	68 (12.9)	0 (0)	68 (33.2)	< 0.001
Dopamine, *n* (%)	22 (4.2)	10 (3.1)	12 (5.9)	0.124
Esmolol, *n* (%)	57 (10.8)	1 (0.3)	56 (27.3)	< 0.001
RBC transfusion, *n* (%)	24 (4.6)	7 (2.2)	17 (8.3)	0.001
Plasma transfusion, n (%)	14 (2.7)	5 (1.6)	9 (4.4)	0.048
Anesthesia duration (min), Median (IQR)	150.0 (120.0, 200.0)	140.0 (105.0, 170.0)	180.0 (140.0, 235.0)	< 0.001
Surgery duration (min), Median (IQR)	110.0 (80.0, 155.0)	100.0 (73.5, 135.0)	130.0 (95.0, 190.0)	< 0.001
Estimate blood loss (ml), Median (IQR)	200.0 (100.0, 300.0)	200.0 (100.0, 300.0)	200.0 (100.0, 350.0)	0.017
Urine volume (ml), Median (IQR)	200.0 (100.0, 400.0)	200.0 (100.0, 300.0)	300.0 (150.0, 500.0)	< 0.001
Postoperative information				
Neostigmine (mg), Median (IQR)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	0.014
PACU duration (min), Median (IQR)	70.0 (60.0, 90.0)	65.0 (60.0, 80.0)	80.0 (60.0, 100.0)	< 0.001
ICU, *n* (%)	11 (2.1)	2 (0.6)	9 (4.4)	0.004
Postoperative delirium, *n* (%)	108 (20.5)	71 (22)	37 (18)	0.267
Infection, *n* (%)	10 (1.9)	4 (1.2)	6 (2.9)	0.198
Thrombsis, *n* (%)	15 (2.8)	7 (2.2)	8 (3.9)	0.245
Adrenal crisis, *n* (%)	2 (0.4)	2 (0.6)	0 (0)	0.524
Postoperative NRS $_{max}$, Median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	3.0 (2.0, 4.0)	< 0.001
Hospital duration (day), Median (IQR)	5.0 (4.0, 6.0)	4.0 (3.0, 5.0)	5.0 (4.0, 7.0)	< 0.001

RBC, Red blood cell; PACU, post-anesthesia care unit; ICU, intensive care unit; NRS, numerical rating scale.

low likelihood of pheochromocytoma, the duration of preoperative preparation should be minimized by using short-acting drugs or other drug alternatives. For institutions with specialized adrenal centers, there are more possibilities for preoperative medication choices (22).

This is the first time that the latest summary-level data have been applied to explore the connections between the duration of phenoxybenzamine use and postoperative delirium. The research perspective taken in this study was genuine, and it had excellent

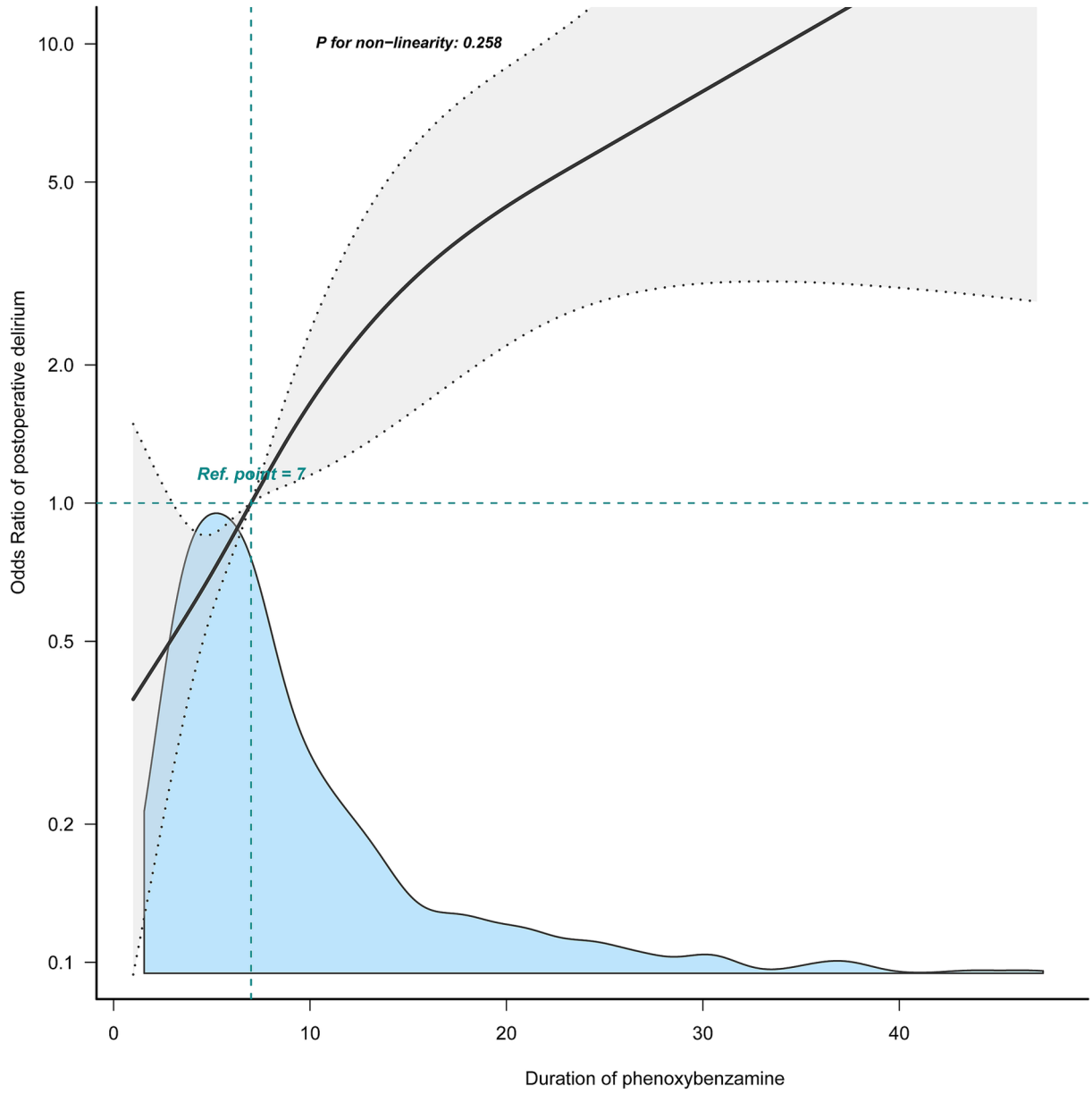

FIGURE 2
The relationship between the duration of phenoxybenzamine use and the risk of postoperative delirium.

TABLE 3 **Multivariate analysis of postoperative delirium.**

Outcome	Non-adjusted model		Model I		Model II	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Duration of phenoxybenzamine	1.04 (1.02–1.06)	<0.001	1.06 (1.03–1.08)	<0.001	1.05 (1.03–1.08)	<0.001

Model I: Adjust for sex, age, and BMI; Model II: Adjust for Model I + ASA, Cerebral infarction, Midazolam, Sufentanil, neostigmine, Anesthesia duration, estimated blood loss, and postoperative VAS max.

novelty and therapeutic application value. The current study provides robust evidence of the relationship between the duration of phenoxybenzamine use and the risk of postoperative delirium in patients with suspected pheochromocytoma through a thorough consideration of potential sources of confounding and biases. Nevertheless, several limitations merit consideration. First, as an observational study, we cannot establish a causal relationship between the duration of phenoxybenzamine use and the risk of postoperative delirium in the suspected pheochromocytoma population. The sample size in this study was relatively small, which limited the statistical power and exploration of interactions. The results should be interpreted with caution. Our basis for determining postoperative

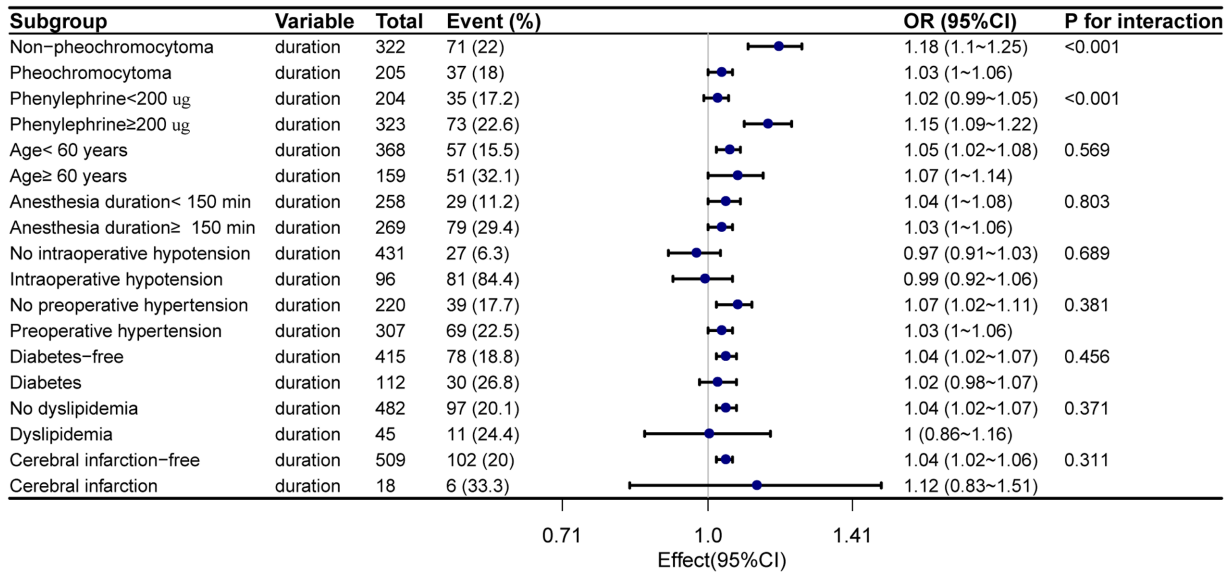

FIGURE 3
Relationship between the duration of preoperative phenoxybenzamine administration and postoperative delirium in subgroup. Adjust for Sex, BMI, ASA, neostigmine, postoperative NRS $_{max}$, Midazolam, Sufentanil, and estimated blood loss.

delirium is not a universal standard. We considered patients who matched the description of CAM in the medical record or the nursing record as postoperative delirium, which may have resulted in more cases of delirium than the actual number of cases. Also, there may be unmeasured selection bias with confounding factors due to incomplete information on some patients in the database, our exclusion of some patients, and the inability of the database to provide additional baseline data, such as Catecholamine secretion levels.

Conclusion

This cohort study found that positive relationship between the number of days of phenoxybenzamine use and postoperative delirium in suspected pheochromocytomas. Furthermore, this relationship is further enhanced in the non-pheochromocytoma subgroup. The findings of this study require further validation and confirmation.

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 humans were approved by The First Affiliated Hospital of Chongqing Medical University. 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

QW: Conceptualization, Data curation, Investigation, Writing – original draft. FH: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing. KW: Conceptualization, Formal analysis, Software, Validation, Writing – review & editing. JW: Data curation, Formal analysis, Investigation, Software, Validation, Writing – original draft. XZ: Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft. QX: Data curation, Formal analysis, Resources, Software, Validation, Writing – original draft. DL: Data curation, Investigation, Validation, Writing – original draft.

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.

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frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 13 January 2025
DOI 10.3389/fmed.2024.1502619

OPEN ACCESS

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RECEIVED 27 September 2024
ACCEPTED 20 December 2024
PUBLISHED 13 January 2025

CITATION
Bu F-d, Si S-k, Zhang D-b and Chi Y-l (2025) Effect of invasive acupuncture on awakening quality after general anesthesia: systematic review and meta-analysis.
Front. Med. 11:1502619.
doi: 10.3389/fmed.2024.1502619

Effect of invasive acupuncture on awakening quality after general anesthesia: systematic review and meta-analysis

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Background: The process of waking up from general anesthesia is still not well understood, and recovery issues such as delayed awakening, agitation, postoperative cognitive dysfunction, continue to be a challenge for anesthesiologists. Currently, the treatment of these complications is mainly achieved through the antagonistic action of specific drugs, but sometimes the antagonistic drugs are not as effective as they should be and can add to the financial burden of the patient. Acupuncture, a common treatment in Traditional Chinese Medicine, is widely used around surgery. However, there is no enough evidence to show it improves recovery after anesthesia. To explore this, we reviewed relevant randomized trials and conducted a meta-analysis.

Objective: This systematic review was conducted to explore the effect of perioperative application of invasive acupuncture on the quality of postoperative awakening after general anesthesia.

Methods: By searching PubMed, Embase, Cochrane Clinical Trials Center, China Knowledge Network (CNKI), China Biomedical Database (CBM), Wanfang Medical Database, Weipu Database, to include randomized controlled trials of invasive acupuncture applied perioperatively. Search is limited from the build-up of the database to March 2022. The statistical analysis was conducted using RevMan 5.3. Quality assessment of the included research literature using Cochrane-recommended risk of bias assessment tool.

Results: 18 randomized controlled trials were included with 1,127 patients. 565 patients in invasive acupuncture intervention group, 562 patients in control group. Results showed that invasive acupuncture group had a shorter eye opening time than control group (MD = −6.42, 95% CI [−8.17, −4.66], $p < 0.001$), shorter extubation times (MD = -5.84, 95% CI [−8.12, −3.56], $p < 0.001$), lower MAP at extubation (MD = −18.54, 95% CI [−22.69, −14.39], $p < 0.001$), lower HR at extubation (MD = −14.85, 95% CI [−23.90, −5.81], $p < 0.001$). No statistical difference in the occurrence of POCD (OR = 0.56, 95% CI [0.28, 1.11], $p = 0.10$) and postoperative agitation (OR = 0.42, 95% CI [0.11, 1.65], $p = 0.21$).

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/, CRD42023410260.

KEYWORDS

invasive acupuncture, general anesthesia, awakening, systematic review, meta-analysis

1 Introduction

The period of awakening after general anesthesia is both crucial and potentially hazardous (1). Complications such as delayed awakening, emergence agitation (EA), and cardiovascular issues can increase the risk of patient harm. Reports indicate that approximately 19% of adults experience EA following non-cardiac surgeries (2), EA is typically characterized by irritability, purposeless movements, and heightened arousal during the early recovery phase from anesthesia (3). Unlike postoperative delirium (POD), EA involves aggressive behaviors that can pose significant risks to healthcare professionals (4). The process of awakening includes the removal of the tracheal tube, which can activate the sympathetic catecholamine system, leading to increased oxygen consumption and the potential for brain damage (1). Current strategies for managing adverse reactions during this period primarily involve drug antagonism and enhanced analgesia. However, the administration of antagonistic drugs may result in additional complications, such as increased sedation during surgery in patients with EA, which could cause delays in awakening.

Invasive acupuncture, which includes techniques such as hand-twisting and electroacupuncture, is rooted in traditional Chinese medicine. It is thought to regulate the balance between the sympathetic and parasympathetic nervous systems and has demonstrated anti-inflammatory effects through various signaling pathways (5, 6). Owing to its safety, convenience, and fewer side effects, invasive acupuncture is commonly used in clinical settings (7–9).

While invasive acupuncture is commonly employed, there is still a considerable gap in meta-analyses examining its effects on the quality of recovery from general anesthesia. Thus, this study aims to perform a meta-analysis of randomized controlled trials (RCTs) to investigate if invasive acupuncture can affect the quality of awakening. The ultimate goal is to provide an evidence-based framework for clinical decision-making aimed at improving recovery quality during the awakening phase and providing higher-quality evidence.

In this research, invasive acupuncture is defined as including both electroacupuncture and traditional acupuncture, with the intervention group receiving one of these treatments. The time to eye opening is defined as the period from the end of the procedure until the patient opens their eyes, while the time to extubation is defined as the interval from the end of the procedure until the endotracheal tube is removed. Postoperative cognitive dysfunction (POCD) was defined as a decrease of one standard deviation in the Mini-Mental State Examination (MMSE) score at 3 days postoperatively compared to the baseline score obtained 1 day preoperatively. The control group was given either a blank control or a sham intervention.

1.1 Objectives

The aim of this study was to assess the impact of the application of invasive acupuncture on the quality of awakening in postoperative patients undergoing general anesthesia.

2 Methods

2.1 Inclusion criteria

(1) Study type: RCT including the effect of invasive acupuncture (Electroacupuncture, acupuncture) on the quality of postoperative awakening after general anesthesia; language is not limited. (2) Study population: The study included patients who underwent surgery under general anesthesia and received either invasive acupuncture or blank/sham stimulation during the perioperative period. No limitations were placed on age, gender, or nationality. (3) Interventions: Invasive acupuncture group received electroacupuncture, or acupuncture. The control group was not subjected to acupuncture stimulation, nor did they receive stimulation at non-meridian or non-acupuncture points.

2.2 Exclusion criteria

(1) Studies involving patients undergoing surgeries without general anesthesia or receiving other interventions were included in the analysis. (2) Original text was inaccessible or if the outcome indicators were incomplete. (3) Studies from non-RCTs, systematic evaluations or reviews, mechanistic studies, conferences and animal trials.

2.3 Information sources

BF and SS searched Chinese and English databases on 2022/03/24, included PubMed, Embase, Cochrane Clinical Trials Center, Chinese National Knowledge Infrastructure (CNKI), Wei-pu Database (VIP), Chinese Biomedical Database (CBM), Wan-fang Database, and article were searched from the time of database creation to March 2022.

2.4 Search strategy

The Chinese search terms included: "general anesthesia," "awakening," "recovery of consciousness," "open eyes," "extubation," "post-anesthesia monitoring treatment room," "acupoint ", "acupuncture," "electroacupuncture," "needle acupuncture," "randomized controlled trial." English search terms included: "general anesthesia," "awakening," "emergence," "recovery," "eye-opening," "extubation," "PACU," "acupoint," "acupuncture," "electroacupuncture," "randomized controlled trial." The formula can be viewed in the Supplementary material S1.

2.5 Selection procedures

After de-duplication, two people initially screened by looking at titles and abstracts, and then they reviewed the full article. Key data, such as author names, publication years, sample sizes, interventions, and outcome indicators, were extracted from the

final set of screened studies for analysis. If there was any disagreement, the corresponding author was consulted for resolution.

2.6 Data collection and data items

The data of the study was extracted by two independent persons (BF, SS) and the extracted data was saved in an Excel sheet. When there were doubts about the data in the study, they negotiated to resolve them. If data were not available for the outcome of interest, we contacted the authors of the data for information. The names and definitions of the extracted data are given in Supplementary material S2.

2.7 Study risk of bias assessment

Two researchers independently assessed the quality of the studies included in the review using a specific tool and criteria recommended by the Cochrane systematic review manual. The assessment focused on key elements including randomization, blinding, incomplete outcome data, and other potential sources of bias. The findings were classified into three categories: "low risk", "high risk", or "unclear". Methodological and qualitative evaluation of the included literature was as follows. If a study lacks relevant information, the two individuals will contact the corresponding author of the relevant study to enquire. GRADE was also applied to assess the quality of evidence.

2.8 Outcomes

Time to open eyes, Time to extubation, MAP immediately after extubation, HR immediately after extubation is a continuous variable are continuous variables, statistical description and effect sizes were combined using Mean difference (MD), along with their corresponding 95% confidence interval (CI). Incidence of POCD and Agitation are dichotomous variables, statistical description and effect sizes were combined using Odds ratio (OR), along with their corresponding 95% confidence interval (CI).

2.9 Data synthesis

Review Manager 5.3 was applied for data analysis. All outcomes were analyzed using an intention-to-treat analysis. We evaluated the results using MD, OR values, and their 95% CI. A p-value of less than 0.05 was regarded as indicative of a statistically significant difference. Heterogeneity was evaluated using the chi-square test with a significance threshold of $\alpha = 0.1$, and the extent of heterogeneity was quantified by the I^2 statistic. When heterogeneity is obvious ($I^2 \geq 50\%$), random effects model is used. When heterogeneity is low ($I^2 < 50\%$), using fixed effects model. The results of each synthesis are presented in the form of a forest plot. Funnel plots were used to evaluate publication bias when a sufficient number ($n \geq 10$) of studies were available for analysis. A balanced distribution of points on the center line was considered a low level of publication bias. Egger's test was employed to evaluate the presence of publication bias when there was a lack of sufficient study ($n < 10$). $p < 0.05$ suggests a publication bias.

2.10 Subgroup analysis

Based on age classification, we performed subgroup analyses of eye-opening time. One group is age >60, another group is age ≤ 60. Based on the type of surgery, we performed subgroup analyses of time to extubation. One group is minor surgery and one group is major surgery.

2.11 Sensitivity analysis

When $I^2 \geq 50\%$, a sensitivity analysis of the literature was performed, the sensitivity analysis was done by excluding studies where the MD deviated more from the center in the forest plot produced by Review manager 5.3. A larger deviation means that more heterogeneity is likely to be produced. Re-perform sensitivity analysis until I^2 is stable.

3 Results

3.1 Eligible studies and study characteristics

A total of 2,043 relevant literature was obtained from the search, 784 duplicates were excluded, 1,004 were excluded based on the title and abstract, After the full-text assessment, 18 studies meeting the study requirements were included, involved a total of 1,127 patients, 565 cases in invasive acupuncture group and 562 cases in control group. Figure 1 illustrates the literature screening process, Tables 1, 2 display the study characteristics and interventions details of the included studies. Good results in quality grading of evidence from included studies (see Supplementary material S3 GRADE).

3.2 Bias assessment results

The assessment of bias for the included studies is shown in Figure 2. The overall risk of bias of the included studies showed good. Results of publication bias test in Supplementary material S4.

3.3 Effect of invasive acupuncture on eye opening time

10 studies mentioned time to open eyes. Included 677 patients, 340 in invasive acupuncture group, 337 in control group. Heterogeneity test $I^2 = 90\%$ and random effects model was used to synthesize the data. Result shows that invasive acupuncture group had a shorter eye-opening time than control group (MD = −6.42, 95% CI [−8.17, −4.66], $p < 0.001$), as shown in Figure 3.

3.4 Effect of invasive acupuncture on extubation time

12 studies mentioned the time to extubation. Included 745 patients, 373 in invasive acupuncture group, 372 in control group. $I^2 = 93\%$, with high heterogeneity, random effects model data synthesis results show that invasive acupuncture group has a shorter extubation

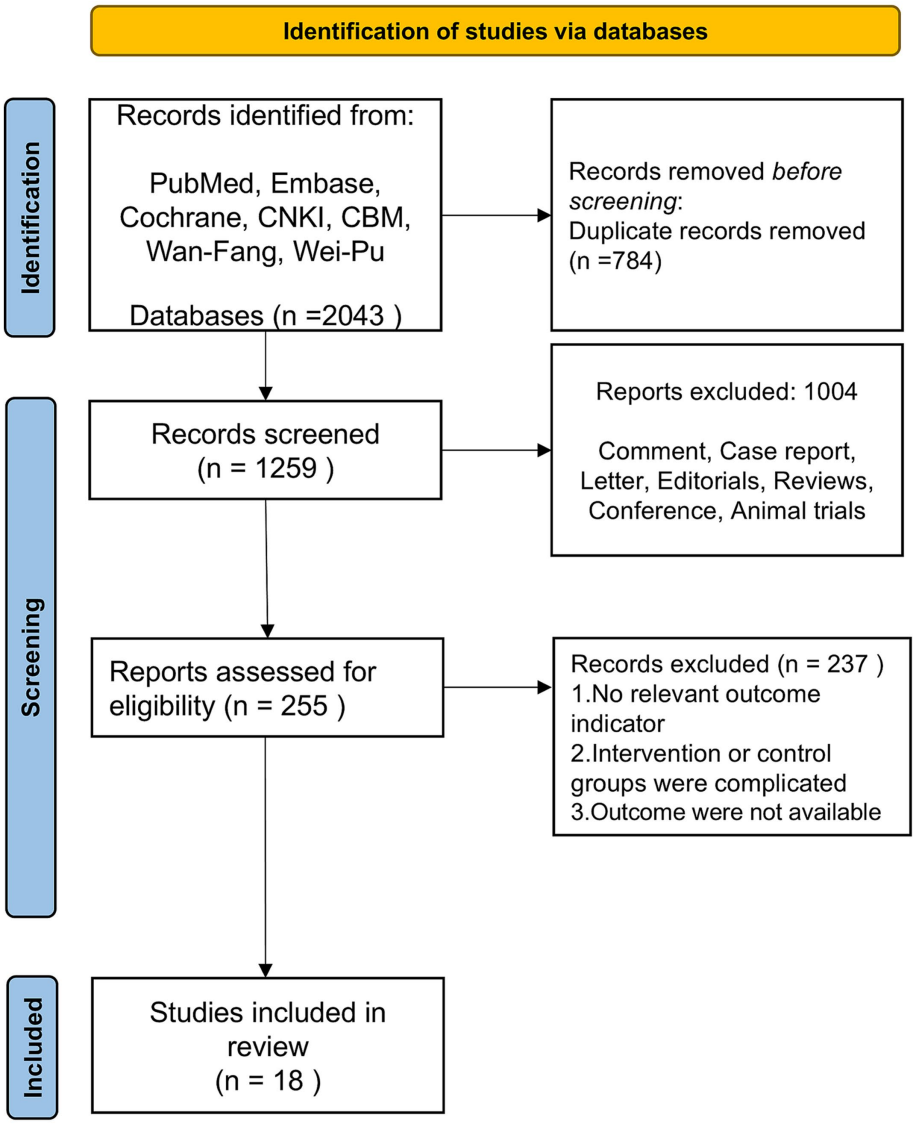

FIGURE 1
Flow chart of literature screening.

time compared to control group (MD = -5.84, 95% CI [−8.12, −3.56], $p < 0.001$), as illustrated in Figure 4.

3.5 Effect of invasive acupuncture on MAP

3 studies mentioned the mean arterial pressure (MAP) immediately following extubation. 160 patients in total, 80 in invasive acupuncture group, 80 in control group. Heterogeneity test $I^2 = 56\%$, using random effects model for combining effect sizes. The MAP was lower in invasive acupuncture group than in the control group (MD = −18.54, 95% CI [−22.69, −14.39], $p < 0.001$), as shown in Figure 5.

3.6 Effect of invasive acupuncture on HR

4 studies mentioned heart rate (HR) at extubation. The synthesis included 184 patients, with 92 in the invasive acupuncture group and 92 in the control group. A heterogeneity test showed an I^2 value of 91%, and the results were analyzed using a random effects model. Showed that HR was lower in invasive acupuncture group at the moment of extubation (MD = −14.85, 95% CI [−23.90, −5.81], $p < 0.001$), forest plot in Figure 6.

3.7 Incidence of POCD and agitation

2 studies reported about the incidence of postoperative cognitive dysfunction (POCD). Included 158 patients, 80 in invasive acupuncture group while 78 patients in the control group. $I^2 = 0\%$, a fixed-effects model was used, the result showed that no statistical difference between invasive acupuncture group and control group on incidence of POCD (OR = 0.56, 95% CI [0.28, 1.11], $p = 0.10$), forest plot in Figure 7.

Three studies mentioned the incidence of postoperative agitation. 220 patients involved, 110 in invasive acupuncture group, 110 in control group. Heterogeneity was low ($I^2 = 18\%$), according to fixed effects model

TABLE 1 Study characteristics.

Authors, year	Country	Surgery	Anesthesia	Patient	Sample size		Outcome
					T	C	
Lu et al. (18)	China	PB	TIVA	Adult	30	30	①
Li et al. (19)	China	TEC	GA	Adult	30	30	③④
Yan et al. (20)	China	RREC	GA	Adult	20	20	②③④
Zheng et al. (21)	China	PE	TIVA	Adult	40	40	①
Liu et al. (22)	China	GTR	GA	Adult	30	30	①
Wang et al. (23)	China	LC	GA	Adult	30	30	②
Gemma et al. (24)	Italy	PAGA	GA	Adult	10	9	①②
Yang et al. (25)	China	LC	GA	Adult	50	50	②
Lin et al. (26)	China	GTR	GA	The aged	42	41	①
Yan et al. (27)	China	PN	GA	Adult	40	40	①②
Yu et al. (28)	China	UL	GA	Adult	20	20	①
Lin et al. (29)	China	BCR	GA	The aged	38	37	①
Yang et al. (30)	China	GL	GA	AF	30	30	①②③④
Fu et al. (31)	China	P	GA	Adult	12	12	④
An et al. (32)	China	STR	GA	Adult	40	40	①②
An et al. (33)	China	STR	GA	Adult	40	40	①②
Gu et al. (34)	China	C	GA	Adult	30	30	①②
Gemma et al. (35)	Italy	M	GA	Adult	33	33	②

AF, Adult females; TIVA, Total intravenous anesthesia; GA, general anesthesia; PB, Painless Bronchoscope; TEC, Thoracotomy for esophageal cancer; RREC, Radical resectionn of esophageal carcinoma; PE, Painless enteroscopy; GTR, Gastrointestinal tumor resection; LC, Laparoscopic cholecystectomy; PAGA, Patients after general anesthesia; PN, Percutaneous nephrolithotomy; UL, Unilateral lobectomy; BCR, Bowel cancer resection; GL, Gynecologic laparoscopy; P, Pneumonectomy; STR, Supratentorial tumor resection; C, Cholecystectomy; M, Microdiscectomy. ①: Time to open eyes; ②: Time to extubation; ③: MAP(immediately after extubation); ④:HR(immediately after extubation); ⑤:Adverse reaction，including POCD and agitation.

and effect size analysis no statistical difference was found on postoperative agitation (OR = 0.42, 95% CI [0.11, 1.65], $p = 0.21$), forest plot in Figure 8.

3.8 Subgroup analysis results

Based on age classification, we performed subgroup analyses of eye-opening time. One group is age >60, another group is age ≤ 60. Results suggests that heterogeneity may come from group age ≤ 60 ($I^2 = 91\%$). We performed subgroup analyses of time to extubation stratified by type of surgery (minor or major). The findings from these analyses suggest that the type of surgery does not appear to be a significant source of heterogeneity in the synthesized results for time to extubation, as shown in Figures 9, 10.

3.9 Sensitivity analysis results

For single studies with large heterogeneity, excluding any one evidence in Revman 5.3 had no effect on the overall effect. This suggests that the results of our study are robust and reliable. In the synthesized analysis of immediate heart rate at extubation, we observed that Yan 2021 has a great heterogeneity.

4 Discussion

All synthesized results show that perioperative application of invasive acupuncture accelerates awakening from general anesthesia and improves the quality of awakening. Both electroacupuncture and acupuncture require acupuncture needles to be inserted into the skin and their interventions are similar in nature, so the interventions included in this study were both of them. It is noteworthy that in both electroacupuncture and acupuncture they intervened 20–30 min before the start of surgery. This coincides with the timing of perioperative acupuncture application in recent years. For the selection of acupuncture points, most of the studies took PC6. This may suggest that stimulation of PC6 promotes the patient's awakening after general anesthesia.

Electroacupuncture, a technique that applies electrical stimulation through acupuncture needles, can activate different neurotransmitters in the brain based on the frequency of stimulation. Specifically, electroacupuncture administered at a frequency of 2/100 Hz can stimulate the release of three substances—endorphins, enkephalins, and prednisolone—in the spinal cord (10). This may also explain why the frequency of electroacupuncture in the literature included in this study is mostly 2/100 Hz.

For both papers involving POCD, postoperative MMSE scores declined in both the intervention and control groups compared to their preoperative levels, with the difference being apparent on the third postoperative day. The invasive acupuncture group had higher scores than control group. However, the impact of cognitive scores over a longer postoperative period is lacking and more high-quality, large sample size clinical studies are needed to add to the evidence.

It is important to acknowledge the potential side effects associated with acupuncture, considering its invasive nature. While bleeding stands as the most commonly reported adverse reaction, rare occurrences of pneumothorax (11), hemothorax (12), and even cases like the one documented by Abe Daishiro (13), involving vertebral artery perforation due to fractured and displaced silver needles,

TABLE 2 Details of interventions.

Authors, year	Operating model	Time point	Frequency (Hz)	Current (mA)	Acupoint
Lu et al. (18)	Acupuncture	30min before bronchoscopy	NA	NA	Bil (Area of 1,2,3)
Li et al. (19)	Electroacupuncture	30 min before the induction till the end	2	Unknown	Bil (SI3, SJ6, PC6, LI4)
Yan et al. (20)	Electroacupuncture	30 min before the induction till the end	Unknown	Unknown	Bil (Internal pitting, PC6)
Zheng et al. (21)	Electroacupuncture	30min before the induction till the end	2/100	Unknown	Until (ST36, GB34, ST37, SP6), Bil (Li4)
Liu et al. (22)	Electroacupuncture	30 min before the induction till the end of surgery	2/100	5~(X-1)	Bil (ST36, SP6)
Wang et al. (23)	Electroacupuncture	20min before the induction	30	Unknown	Bil (GB24, ST30, GB34)
Gemma et al. (24)	Acupuncture	After the surgery	NA	NA	Bil (KI1, DU6)
Yang et al. (25)	Acupuncture	10-20min before anesthesia induction, rotation stimulation every 10 minutes after injection until the end of the operation	NA	NA	Bil (LI4, LR3)
Lin et al. (26)	Electroacupuncture	30 min before the induction till the end of surgery	2/100	7~7.5	Bil (DU20, PC6, ST36)
Yan et al. (27)	Electroacupuncture	20 min before the induction till the end of surgery	2/100	7~7.5	Bil (PC6, Internal pitting, LI4, LI5RN3, ST30, LR10)
Yu et al. (28)	Electroacupuncture	30 min before the induction till the end of surgery	2/100	Unknown	Bil (PC6, LI3, SJ6, LI4)
Lin et al. (29)	Electroacupuncture	20 min before the induction till the end of surgery	4/20	7~7.5	Uk (DU20, PC6, ST36, SP6)
Yang et al. (30)	Electroacupuncture	20~30 min before the induction till the end of surgery	2/100	12~15	Bil (ST36, SP6, LI4, LR3)
Fu et al. (31)	Electroacupuncture	30 min before induction	Unknown	1-3	Bil (SI3, SJ6, LI4)
An et al. (32)	Electroacupuncture	From anesthesia beginning to the end of operation	2/100	Unknown	Uk (LI4, TE5, BL63, LR3, ST36, GB40)
An et al. (33)	Electroacupuncture	From the beginning of anesthesia induction to the end of surgery	2/100	0.3~2	Bil (GB20, BL2)
Gu et al. (34)	Electroacupuncture	15~30 min before the induction	4/20	X~5	Bil (LI4, PC6, ST36, GB34)
Gemma et al. (35)	Acupuncture	Unknown	NA	NA	Bil (K1, S36)

Bil, bilateral; Unil, unilateral; NA, not applicable. Uk (unknown): It was not clear whether it was unilateral or bilateral. Electroacupuncture: A needle that can be connected to a nerve stimulator for electrical stimulation. Acupuncture: Needles that require constant hand twisting to cause stimulation of acupuncture points. X: The intensity of the current that the patient has difficulty tolerating while no pain and other adverse reactions.

10.3389/fmed.2024.1502619

FIGURE 2
Risk of bias graph and risk of bias summary.

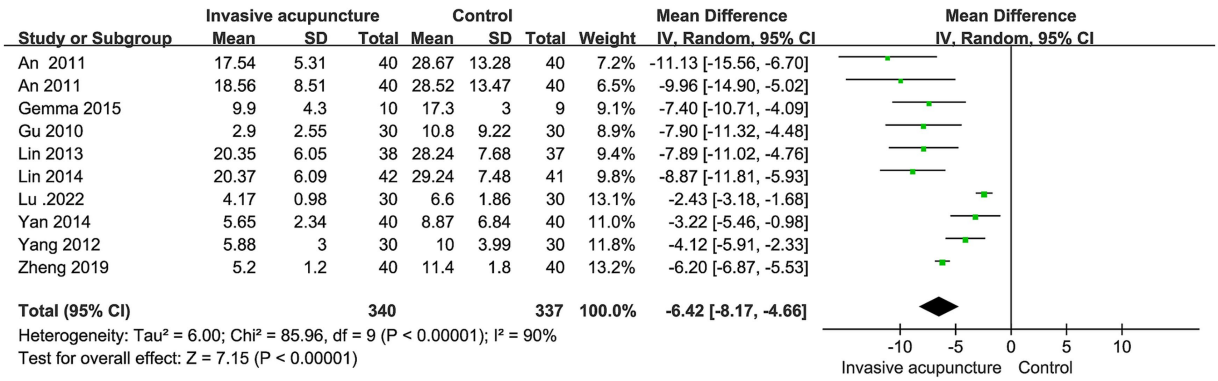

FIGURE 3
Synthesized results of eye-opening time.

emphasize the significance of proper training for acupuncture practitioners. The scarcity of experienced acupuncturists remains a notable concern raised by critics in surveys gauging the sentiments of healthcare professionals towards acupuncture in Australia (14).

Nevertheless, patients' enthusiasm for perioperative acupuncture remains undiminished. In a preoperative assessment survey conducted at the Mayo Clinic (15), a remarkable 68.4% of participants expressed keen interest in receiving acupuncture during the perioperative period. Notably, the approval rate for complimentary acupuncture services reached an impressive 86.7%, underscoring the substantial potential for the perioperative application of acupuncture in the Western world. This view was confirmed across the pond in European. Acupuncture is widely available and promoted in Switzerland and France. Switzerland's insurance is the most supportive of acupuncture in all of European, with reimbursement rates of up to 70–80%, and if the acupuncturist is a licensed Western medical practitioner, the patient can receive an even higher reimbursement rate. In France, due to the large number of acupuncture clinics, the competition between clinics has led directly to lower prices for acupuncture. It is easy to see how the low cost

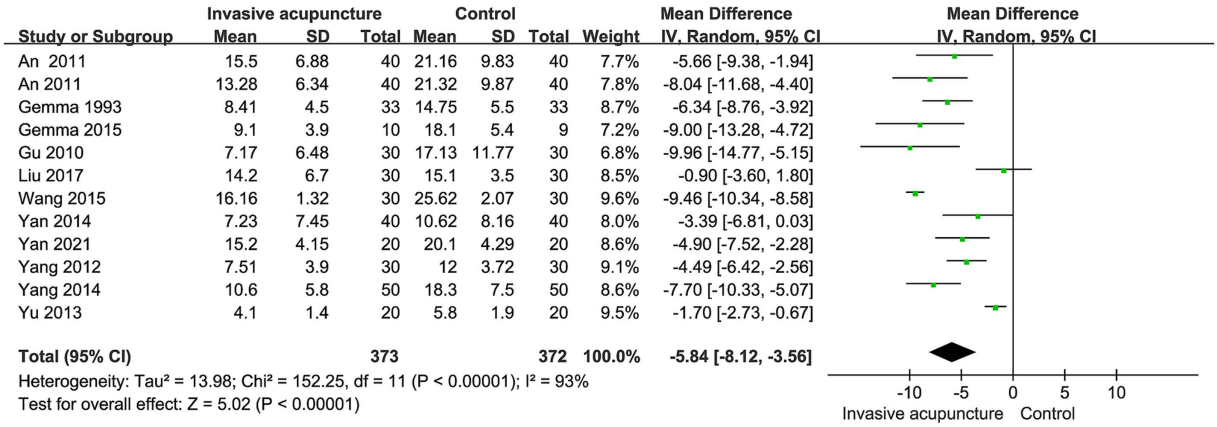

FIGURE 4
Synthesized results of extubation time.

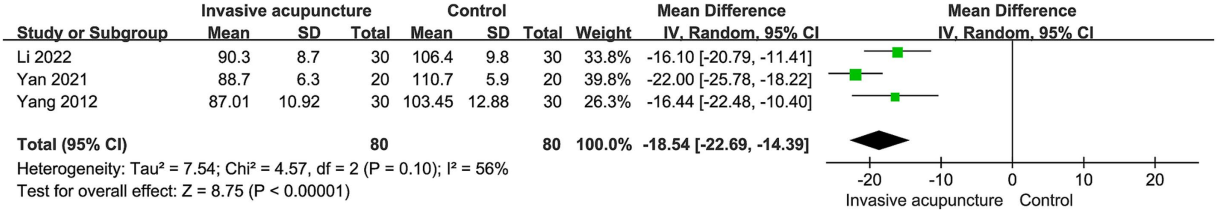

FIGURE 5
Synthesized results of MAP.

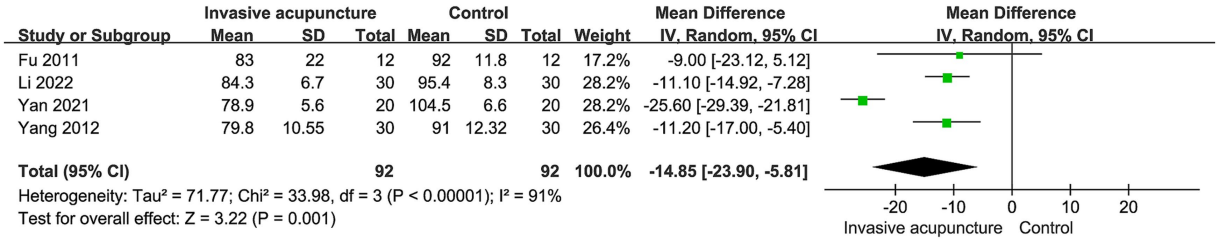

FIGURE 6
Synthesized results of HR.

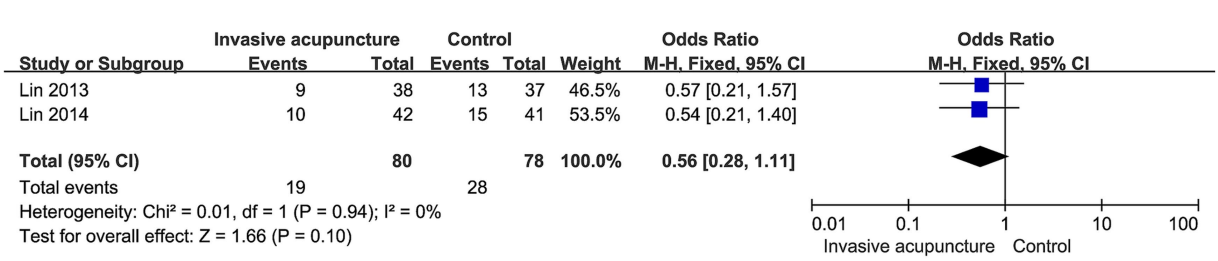

FIGURE 7
Synthesized results of POCD.

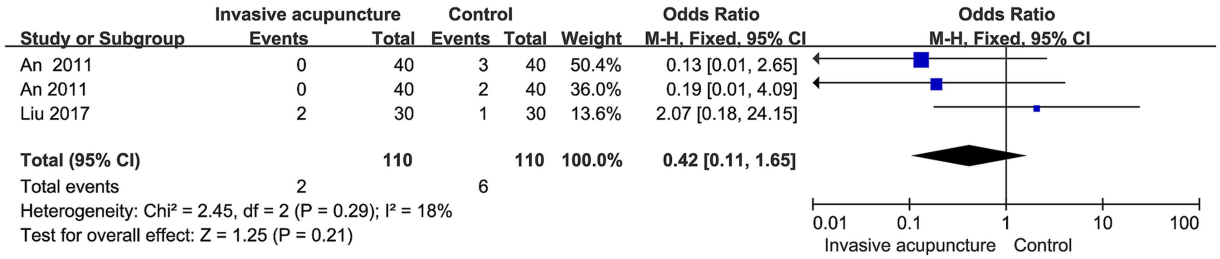

FIGURE 8
Synthesized results of agitation.

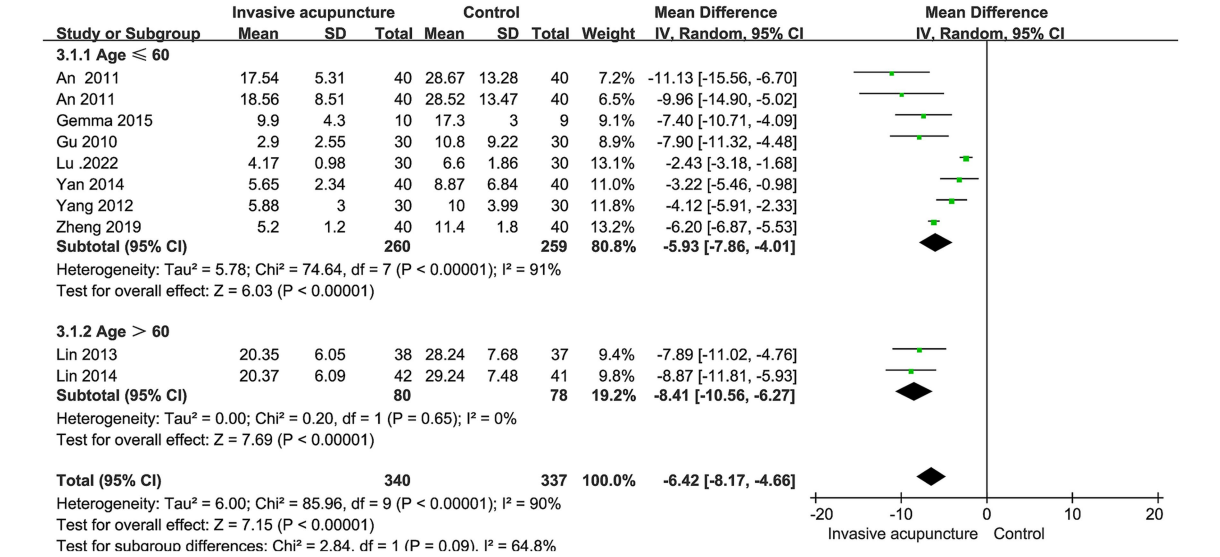

FIGURE 9
Subgroup analysis results of eye-opening time.

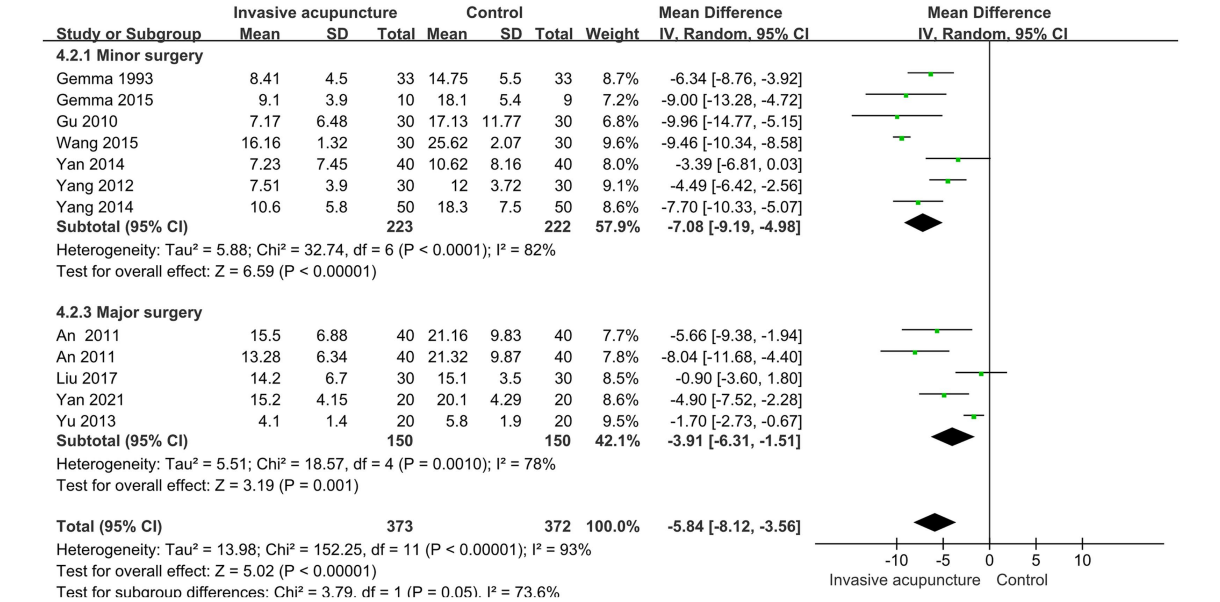

FIGURE 10
Subgroup analysis results of extubation time.

could greatly increase the acceptance of acupuncture by patients in the European and American countries.

Owing to linguistic barriers and other pertinent factors, the comprehensive adoption of traditional Chinese acupuncture in the Western world poses considerable challenges. Consequently, a process of localization has emerged, wherein dry needling therapy and battlefield acupuncture (16, 17) offer expedient and efficient means of attaining analgesic effects. As a result, these approaches find extensive utilization in the realms of combatting opioid abuse and managing pain in military settings.

4.1 Analysis of included literature

At the same time the subject of this literature is the awakening process after general anesthesia, and patients with non-general anesthesia do not exclude. The two papers included in this study had TIVA anesthesia although there was an anesthetic awakening process, but there was no use of inhalational anesthetics, which may increase the heterogeneity of the study when compared to anesthesia with a combination of sedation and suction and the difference in the type of intervention.

Of the types of surgeries included in these 18 articles in the literature, 7 were on the digestive system, which accounted for the largest proportion. Thoracic surgeries were next in importance with 5 articles. However, urological surgeries gynecological surgeries orthopedic surgeries neurological surgeries accounted for a lesser percentage. The patient population for these surgeries were all adults, so the findings of this study cannot be extended to the minor patient population.

There was variation in the neurostimulation instrumentation utilized within the electroacupuncture group, further contributing to heterogeneity. The absence of allocation concealment methods presents a direct risk to the research due to inadequate attention. Additionally, only some of the studies reported using blinding methods, which increases the risk of measurement bias. The absence of allocation concealment methods poses a direct risk to the research due to lack of attention.

The combined analysis of time to open eyes, time to extubation, and immediate heart rate at extubation demonstrated significant heterogeneity. To explore potential sources of this heterogeneity, we performed subgroup analyses for time to open eyes and time to extubation, along with sensitivity analyses for immediate heart rate at extubation. For the time to open eyes, subgroup stratification was based on age (≤60 years and >60 years), while for time to extubation, stratification was based on the type of surgery (minor or major). The findings revealed that heterogeneity for time to open eyes was 91% in the ≤60 years group and 0% in the >60 years group, suggesting that the younger age group (≤60 years) was likely responsible for the observed heterogeneity.

Extubation time was analyzed by categorizing surgeries into minor and major groups based on duration, with minor surgeries defined as lasting ≤2 h and major surgeries as lasting >2 h. The synthesized results demonstrated significant heterogeneity between the two groups, suggesting that surgery duration was not a contributing factor to the observed heterogeneity in extubation time. While subgroup analyses of time to open eyes and extubation time revealed considerable heterogeneity, the direction of the effect size was consistent across all groups. This consistency indicates that invasive acupuncture facilitates postoperative awakening and extubation in both minor and major surgeries, regardless of age group (≤60 years or >60 years).

Subgroup analyses demonstrated a reduction in heterogeneity across all subgroups, indicating that subgroup characteristics may contribute as a potential risk factor for the observed heterogeneity. However, this suggests that subgroup information alone is not the sole determinant of heterogeneity.

In the synthesized analysis of immediate heart rate at extubation, we observed that excluding one study (Yan, 2021) reduced the heterogeneity among the remaining three studies to 0%. This finding suggests that the Yan (2021) study contributed significantly to the observed heterogeneity. This may be explained by the fact that, in Yan's (2021) study, epidural analgesia was administered intraoperatively, effectively reducing the patients' pain response during the immediate extubation period. Since pain is a significant contributor to increased heart rate in the postoperative period, this intervention likely influenced the observed outcomes. Additionally, epidural anesthesia can slow heart rate if the level of anesthesia is excessively high (above T4), as it may block the cardiac sympathetic nerves.

The conclusions of the study should be viewed with caution due to the possible heterogeneity of the synthesized results. Future clinical studies of acupuncture should aim for multicenter, long follow-up periods, and standardized treatment protocols.

Data availability statement

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

Author contributions

F-dB: Conceptualization, Data curation, Formal analysis, Investigation, Validation, Writing – original draft. S-kS: Conceptualization, Data curation, Supervision, Writing – original draft, Writing – review & editing. D-bZ: Project administration, Supervision, Writing – review & editing. Y-lC: Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. Funded by Shandong Province Chinese Medicine Science and Technology Program (Grant number: Z-2022048).

Acknowledgments

Thanks to our colleagues for creating a great writing environment.

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.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1502619/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 24 January 2025
DOI 10.3389/fneur.2025.1530137

OPEN ACCESS

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RECEIVED 18 November 2024
ACCEPTED 09 January 2025
PUBLISHED 24 January 2025

CITATION
Wu J, Li S, Liang R, Wang Y, Shi F, Pan X and Chen X (2025) Risk factors for perioperative cerebral infarction in moyamoya disease: a meta-analysis.
Front. Neurol. 16:1530137.
doi: 10.3389/fneur.2025.1530137

Risk factors for perioperative cerebral infarction in moyamoya disease: a meta-analysis

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Background: The present study explored the risk factors for cerebral infarction perioperative moyamoya disease by meta-analysis.

Methods: The PubMed, Embase, Cochrane library, Web of science databases were searched for case–control/cohort studies on risk factors for the emergence of cerebral infarction perioperative moyamoya disease, the search was done from the database creation to June 1, 2024, and the data was analyzed by using stata15.0.

Result: Ten retrospective cohort studies (*N* = 3,239) were included. Meta-analysis results suggested posterior cerebral artery involvement [OR = 2.62, 95%CI (1.36, 5.06)], preoperative magnetic resonance angiography [OR = 2.81, 95%CI (1.27, 6.22)], previous infarction [OR = 2.52, 95% CI (1.69, 3.75)] were risk factor for the development of cerebral infarction perioperative moyamoya disease.

Conclusion: This study proves that posterior cerebral artery involvement and grade of preoperative magnetic resonance angiography is higher, and the previous infarction happened moyamoya disease a risk factor for cerebral infarction. Therefore, people with these risk factors should be intervened in advance to prevent the occurrence of perioperative cerebral infarction.

KEYWORDS

risk factors, cerebral infarction, meta-analysis, moyamoya disease, perioperative

Introduction

Moyamoya disease (MMD) is a chronic cerebrovascular disease with an unknown cause that involves progressive stenosis or occlusion of the ends of the internal carotid arteries (IC), anterior cerebral arteries (ACA), and the beginnings of the middle cerebral arteries (MCA) bilaterally, with the secondary formation of a smoky blood vessel network (1, 2). The age distribution of MMD has two peaks: around 10 years old and around 40 years old, but it is more common in adults (3). MMD can be categorized into ischemic and hemorrhagic types, with ischemic type being the most common. The main treatment means for this disease is intracranial and extracranial revascularization, which mainly includes direct bypass revascularization, indirect bypass revascularization and the combination of the two (4, 5). Bypass surgery can rapidly increase the cerebral blood flow in the anastomotic blood vessel supply area, improve the symptoms of cerebral ischemia, and reduce the probability of cerebral hemorrhage caused by rupture of collateral bypass vessels (6), which is significantly better than

other treatment modalities in preventing cerebral infarction or cerebral hemorrhage, and previous studies have pointed out that the efficacy of direct bypass surgery or direct combined with indirect bypass surgery (referred to as combined bypass surgery) for patients with MMD is better compared with indirect bypass surgery (7, 8), so it has become the main treatment method for MMD. Therefore, it has become the preferred treatment option for MMD. Some studies (9–11) have pointed out that the most common complication after bypass surgery in MMD patients is cerebral infarction, the incidence of which ranges from 1.7 to 13.0%, which seriously affects the quality of life of the patients after the operation, and the personalized perioperative blood pressure management can effectively reduce the incidence and severity of cerebral infarction in the patients after the operation (12). Study (13) have suggested that the posterior cerebral artery increases the risk of cerebral palsy in patients with MMD, other (14) has found the opposite conclusion, the risk factors of perioperative cerebral infarction in Moyamoya disease are still controversial (15), therefore, this study aims to explore the risk factors of perioperative cerebral infarction in Moyamoya disease by meta-analysis, and to provide guidance for the improvement of the prognosis and quality of life of these patients.

Materials and methods

Literature retrieval

Two authors searched PubMed, Embase, Cochrane library, and web of science databases from database creation to June 1, 2024, with the search terms cerebral Infarction, risk factors, and moyamoya disease, and the specific search strategy is described in Supplementary Table S1.

Literature selection

Inclusion criteria: adults who met the diagnostic criteria for moyamoya disease, exposure factor was perioperative cerebral infarction, primary outcome indicator was multivariate risk factors, and study type was case–control study or case–control study.

Exclusion criteria: duplicate articles, protocols, animal experiments, reviews, inaccessible full text, articles without usable data.

Data extraction

Two authors rigorously selected the literature based upon predetermined inclusion and exclusion criteria. In case of any disagreement, they resolved it through discussion or sought the opinion of a third party to negotiate and reach consensus. Information extracted from the included studies included the following key details: study, year, country, study design, sample size, cerebral infarction, gender (M/F), mean age, regression model.

Quality evaluation

The Newcastle-Ottawa Scale (NOS) (16) was used to evaluate case–control studies, including the selection of the study population (4 points), comparability between groups (2 points), and measurement of exposure factors or results (3 points). The total score of the scale is 9, with ≤4 indicating low quality, 5–6 indicating medium quality, and ≥ 7 indicating high quality. If the two researchers disagree on the evaluation process, they will discuss the decision or ask a third party to decide.

Statistical analysis

The data were statistically analyzed using Stata 15.0 software. The OR (Odds ratio) and 95% CI (confidence interval) of the risk factors included in the articles were extracted. Heterogeneity test (Q test) and I^2 statistic were used to select the appropriate model to calculate the combined OR. If $I^2 \geq 50\%$, a random effects model was used; if $I^2 \leq 50\%$, a fixed effects model was used. For $I^2 > 50\%$, we assessed the sensitivity of the literature using the leave-one-out method. In addition, we performed publication bias using the Egger test with the significance level set at $\alpha = 0.05$. p-value <0.05 was considered statistically significant.

Result

Literature screening results

A total of 492 articles were obtained by searching PubMed, Embase, Cochrane library, and web of science databases, and 10 retrospective cohort studies (14, 17–25) were finally included by removing 100 duplicates, 380 articles by reading the title and abstract, and 2 articles by reading the full text (Figure 1), of which all 10 studies were cohort studies, all from Asian. The NOS scores of the included studies were 7 for 4 articles (17, 20, 24, 25), 8 for 3 articles (18, 21, 22), and 9 for 3 studies (14, 19, 23). The basic characteristics of the included studies are shown in Table 1.

Meta-analysis results

Age

A total of seven studies mentioned age, in which heterogeneity was tested ($I^2 = 76.9\%$, $p = 0.001$) and therefore analyzed using a random-effects model, and the results of the analysis (Figure 2) suggested that age was not a risk factor for the development of cerebral infarction perioperative moyamoya disease [OR = 0.99, 95% CI (0.95, 1.03), $p = 0.14$].

Posterior cerebral artery involvement

A total of three studies mentioned posterior cerebral artery involvement, in which heterogeneity was tested ($I^2 = 0.0\%$, $p = 0.716$) and therefore analyzed using a fixed-effects model, and the results of the analysis (Figure 3) suggested that posterior cerebral artery involvement was a risk factor for the development of cerebral infarction perioperative moyamoya disease [OR = 2.62, 95% CI (1.36, 5.06), $p = 0.002$].

Preoperative MRA grade

A total of five studies mentioned preoperative magnetic resonance angiography (MRA) grade, in which heterogeneity was tested ($I^2 = 85.1\%$, $p = 0.001$) and therefore analyzed using a random-effects

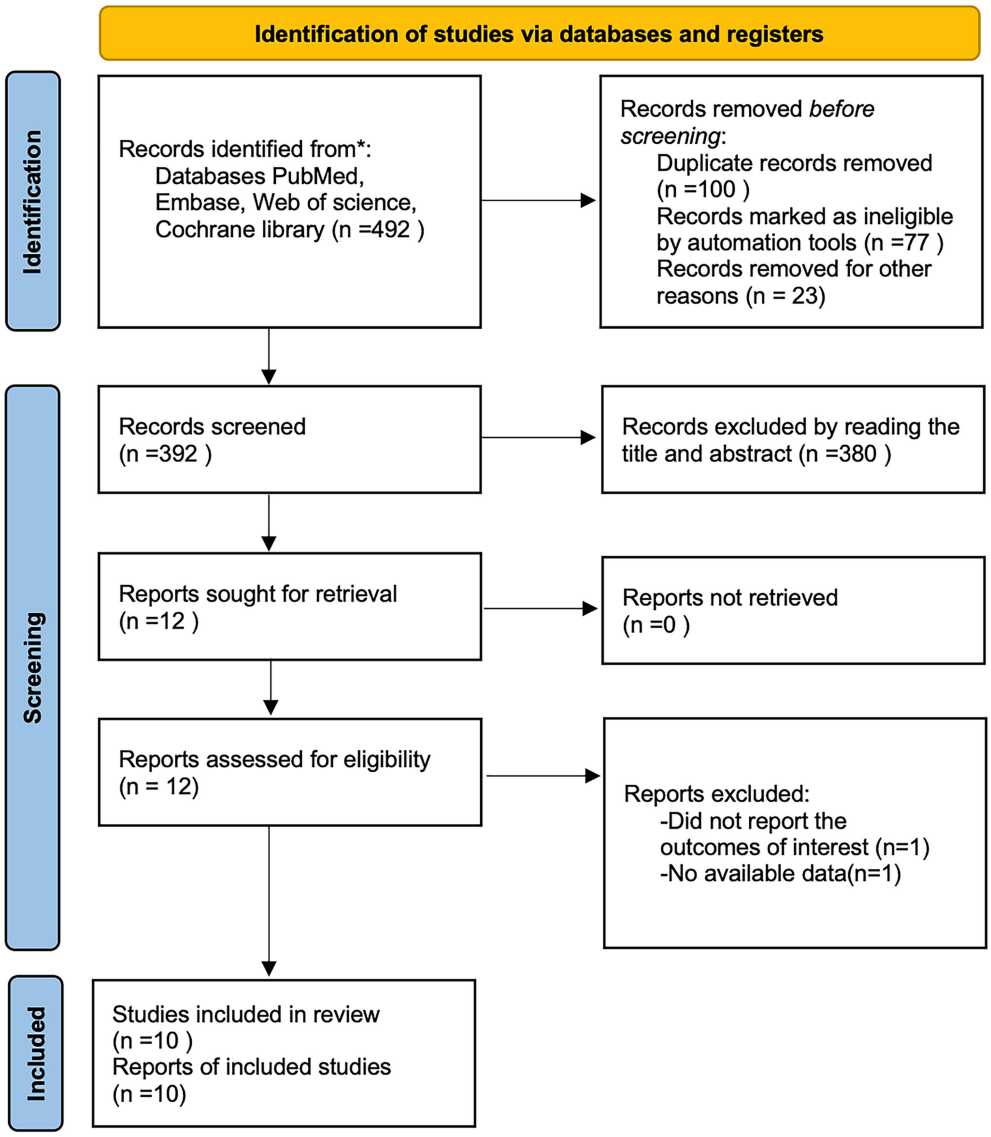

FIGURE 1
Literature search flow chart.

TABLE 1 Basic features of included literatures.

Study	Year	Country	Study design	Sample size	Cerebral infarction	Gender (M/F)	Mean age	Regression model	NOS scores
Araki	2022	Japan	Cohort study	39	7	NR	3.6	logistic Regression	7
Choi	2020	Korea	Cohort study	1,241	63	551/690	3.7	logistic Regression	8
Guo	2023	China	Cohort study	160	60	79/81	2.17	logistic Regression	9
Hao	2024	China	Cohort study	308	36	152/156	8.5	logistic Regression	7
Hayashi	2021	Japan	Cohort study	120	54	53/67	6.7	logistic Regression	8
Li	2020	China	Cohort study	312	52	149/163	39.18	logistic Regression	8
Park	2016	Korea	Cohort study	194	44	58/136	37.2	logistic Regression	9
Qian	2020	China	Cohort study	250	31	108/142	30	logistic Regression	9
Wang	2022	China	Cohort study	890	46	432/289	38	logistic Regression	7
Yu	2023	China	Cohort study	418	49	198/220	38.3	logistic Regression	7

M/F, Male/female; NOS, Newcastle-Ottawa Scale.

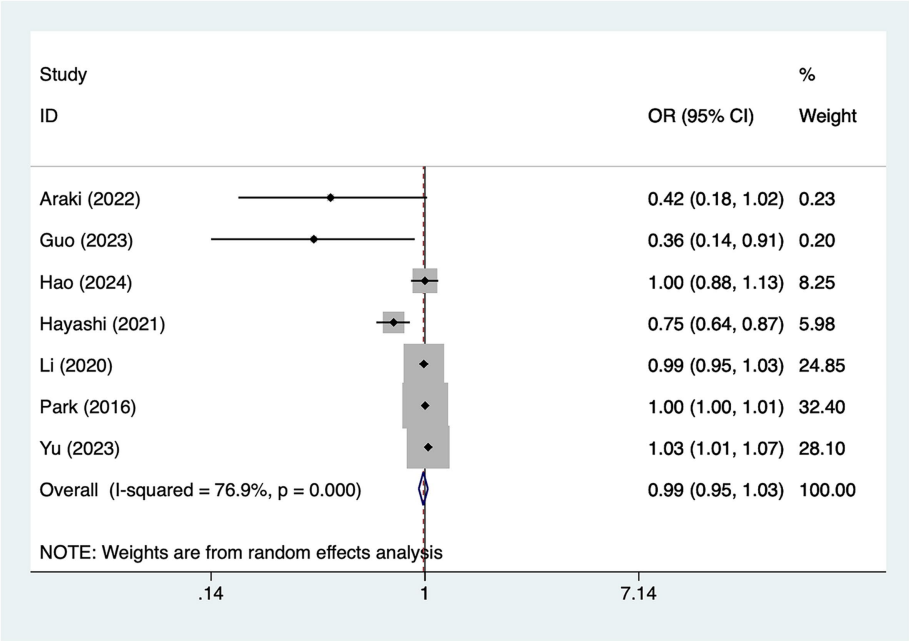

FIGURE 2
Forest plot of age meta-analysis.

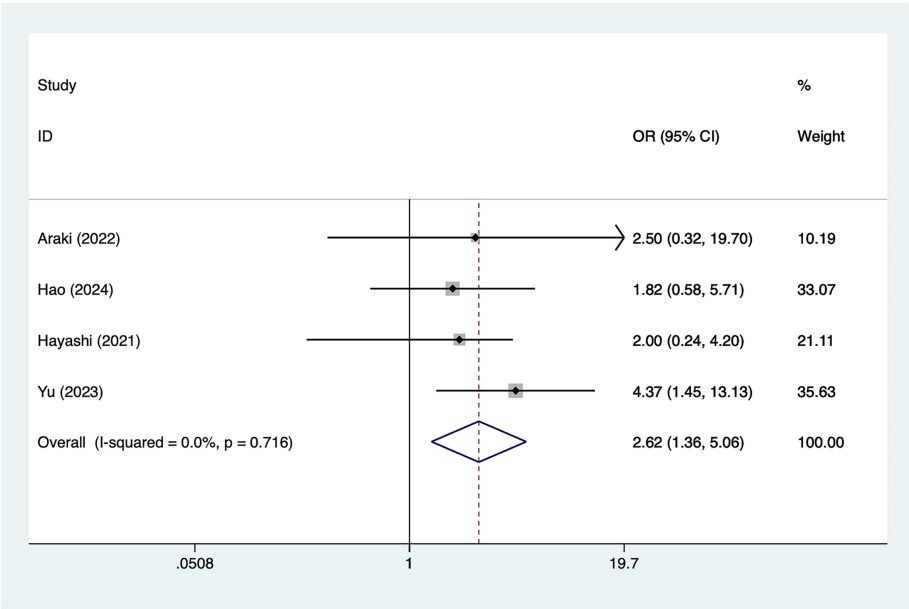

FIGURE 3
Forest plot of posterior cerebral artery involvement meta-analysis.

model, and the results of the analysis (Figure 4) suggested that preoperative MRA grade was a risk factor for the development of cerebral infarction perioperative moyamoya disease [OR = 2.81, 95% CI (1.27, 6.22), $p = 0.003$].

Previous infarction

A total of five studies mentioned previous infarction, in which heterogeneity was tested ($I^2 = 0.0\%$, $p = 0.668$) and therefore analyzed using a fixed-effects model, and the results of the analysis (Figure 5) suggested that previous infarction was a risk factor for the development of cerebral infarction perioperative moyamoya disease [OR = 2.52, 95% CI (1.69, 3.75), $p = 0.01$].

Female

A total of three studies mentioned female, in which heterogeneity was tested ($I^2 = 0.0\%$, $p = 0.405$) and therefore analyzed using a

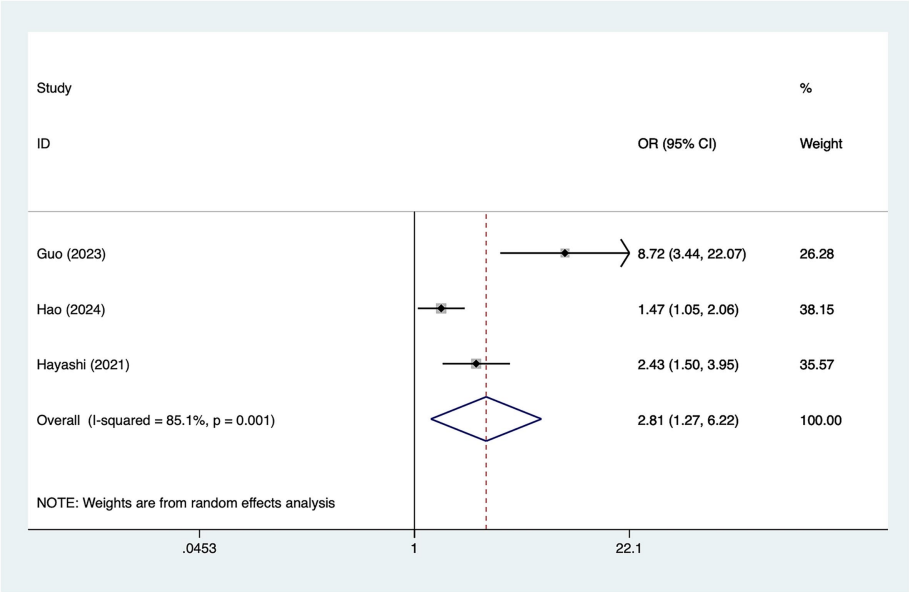

FIGURE 4
Forest plot of preoperative MRA grade meta-analysis.

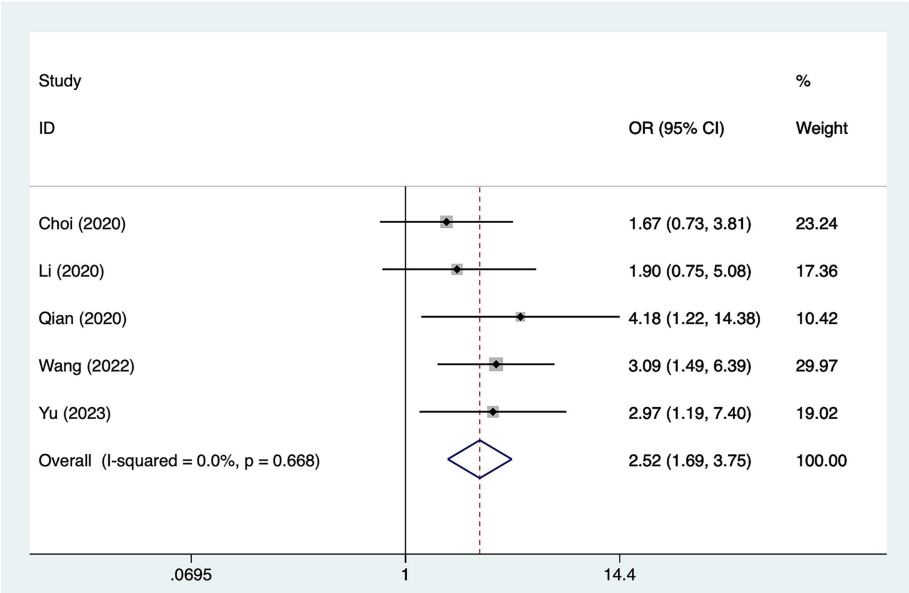

FIGURE 5
Forest plot of previous infarction meta-analysis.

fixed-effects model, and the results of the analysis (Figure 6) suggested that female was not a risk factor for the development of cerebral infarction perioperative moyamoya disease [OR = 1.48, 95% CI (0.86, 2.54), $p = 0.53$].

Hypertension

A total of three studies mentioned hypertension, in which heterogeneity was tested ($I^2 = 0.0\%$, $p = 0.653$) and therefore analyzed using a fixed-effects model, and the results of the analysis (Figure 7) suggested that hypertension was not a risk factor for the development of cerebral infarction perioperative moyamoya disease [OR = 1.40, 95% CI (0.76, 2.56), $p = 0.12$].

Publication bias

The included studies were analyzed for publication bias using Egger's test, which suggested the possibility of publication bias for age ($p = 0.51$), posterior cerebral artery involvement ($p = 0.13$), preoperative magnetic resonance angiography ($p = 0.45$), previous

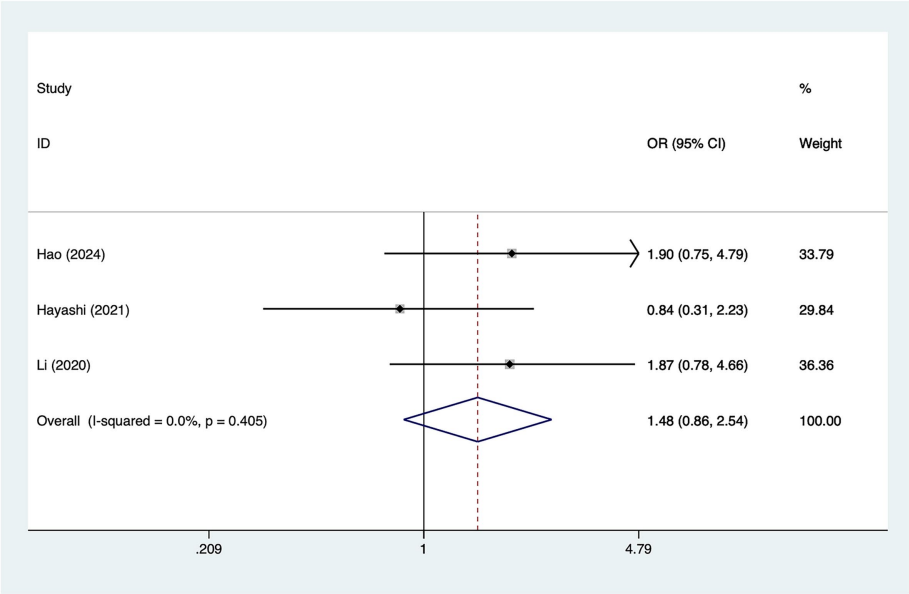

FIGURE 6
Forest plot of gender meta-analysis.

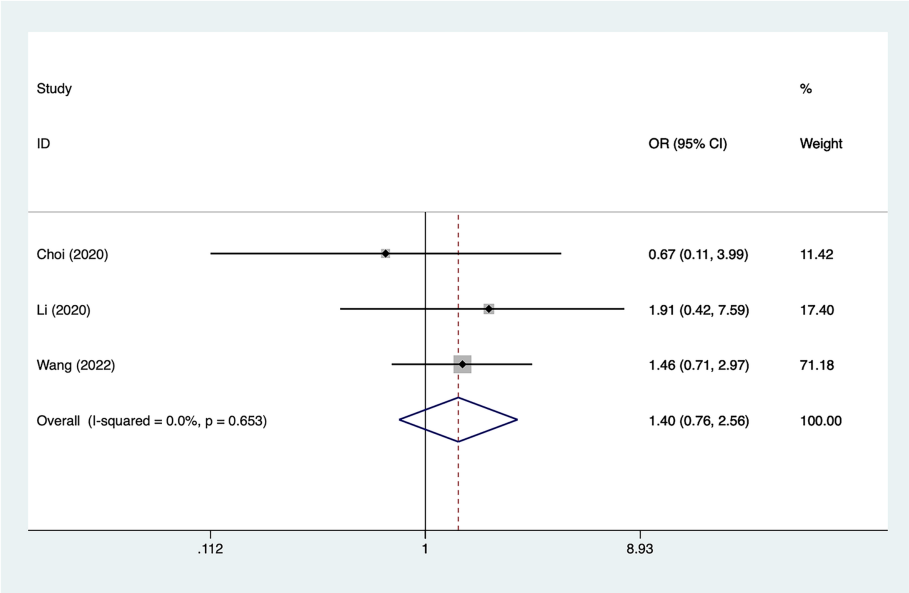

FIGURE 7
Forest plot of hypertension meta-analysis.

infarction ($p = 0.24$), gender ($p = 0.06$), hypertension ($p = 0.07$), previous infarction($p = 0.24$), female($p = 0.06$), hypertension($p = 0.07$) were less likely to have publication bias.

Discussion

MMD blood flow reconstruction surgery is difficult to operate and has a high risk of bleeding; surgical stress, depth of anesthesia, operator proficiency, degree of refinement, and the physical quality of the patient may all have an impact on blood pressure (26, 27); in addition, arteries need to be blocked in the course of the surgery, which further reduces the cerebral perfusion; and it is difficult to control the fluctuation of the patient's blood pressure in the course of the operation, making it difficult to ensure a stable perfusion of the brain tissue (28), and the patient's incidence of cerebral infarction in the perioperative period is risk is significantly elevated (29, 30).

This study is the first to explore the risk factors for cerebral infarction after MMD, and it was found that MMD patients with posterior cerebral artery involvement are more likely to have

cerebral infarction. First, stenosis or occlusion of the posterior cerebral artery occurs in the late Suzuki stage, and patients with this late stage have more severe intracranial stenosis, poorer cerebral perfusion, and more unstable hemodynamics (31, 32). Secondly, stenosis or occlusion of posterior cerebral artery involvement affects the compensatory capacity of collateral circulation in MMD patients, which is an important factor in maintaining cerebral perfusion in MMD patients, and furthermore, stenosis or occlusion of posterior cerebral artery involvement increases the risk of white blood clots (33). Furthermore, the relationship between posterior cerebral artery involvement stenosis or occlusion and revascularization is not only that posterior cerebral artery involvement stenosis leads to an increased risk of cerebral infarction in patients, but also that revascularization in patients with MMD may cause posterior cerebral artery involvement stenosis (34), therefore, for the population with posterior cerebral artery involvement, the progress of the disease should be closely monitored in clinical practice, and surgical intervention should be performed as early as possible to prevent the occurrence of cerebral infarction.

The study found that preoperative infarction is a risk factor for perioperative infarction in patients with MMD. Zhao et al. (35) proved that patients with preoperative ischemic manifestations had a significantly higher risk of perioperative ischemic complications through a study of 500 patients with MMD; Muraoka et al. (13) also proved that patients with preoperative cerebral infarction are more likely to have perioperative cerebral infarction than other, in fact, patients with preoperative ischemic attacks or cerebral infarction often had insufficient compensation of the side branches and extremely unstable cerebral hemodynamics, and mechanical damage to the compensated side branches during the surgical procedure and the sudden change of cerebral hemodynamics after revascularization were more likely to induce perioperative cerebral infarction (2, 36). In addition, transient ischemic attack can not only increase the occurrence of intravascular micro thrombosis but also increase the activity of serum inflammatory cytokines as well as related proteases, which further aggravates the occurrence of cerebral infarction (37), for MMD patients with preoperative infarction, life and exercise therapy should be carried out as early as possible to prevent postoperative cerebral infarction (38).

The current study found that higher Preoperative MRA grading was a risk factor for perioperative cerebral infarction in patients with MMD. The higher MRA stage on the non-operative side implies that the stenosis and occlusion of blood vessels on the non-operative side are more severe, and the ability of the non-operative side to compensate to the operative side is reduced, which is prone to cause perioperative cerebral infarction (39). Zhao et al. (35) showed that advanced MRA stage is a risk factor for ischemic complications in adult patients, therefore, for patients with higher grade of MRA before operation, early intervention and physical intervention should be performed to prevent the occurrence of cerebral infarction after operation (40).

The study still has the following limitations: first, fewer studies were included and the cut included studies were from Asia, which may affect the extrapolation of our conclusions; second, a part of the study population belonged to children and a part of the study population belonged to adults, which may be the source of our heterogeneity; third, some of the studies had a greater degree of heterogeneity but the test for heterogeneity was not able to find out the source of the heterogeneity.

Conclusion

The present study demonstrated that posterior cerebral artery involvement, higher preoperative magnetic resonance angiography grading, and previous infarction are risk factors for the development of cerebral infarction perioperative moyamoya disease. Therefore, people with a combination of these risk factors should be intervened in advance to prevent perioperative cerebral infarction. However, since study limitations exist, In the future, we hope to have more studies with different regions, multi-centers and large samples to support our views.

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

JW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SL: Conceptualization, Formal analysis, Investigation, Project administration, Resources, Software, Validation, Writing – original draft. RL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft. YW: Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft. FS: Conceptualization, Data curation, Investigation, Project administration, Validation, Writing – original draft. XP: Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft. XC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, 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

We would like to thank the researchers and study participants for their contributions.

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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1530137/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 31 January 2025
DOI 10.3389/fneur.2025.1516800

OPEN ACCESS

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RECEIVED 25 October 2024
ACCEPTED 20 January 2025
PUBLISHED 31 January 2025

CITATION
Qin X, Ren J, Xing C, Chen L, Wang R and Tian S (2025) Linear association between high-sensitivity C-reactive protein and postoperative delirium after general anesthesia: a cross-sectional study. *Front. Neurol.* 16:1516800. doi: 10.3389/fneur.2025.1516800

Linear association between high-sensitivity C-reactive protein and postoperative delirium after general anesthesia: a cross-sectional study

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Objective: To investigate the association between high-sensitivity C-reactive protein (Hs-CRP) levels and the risk of postoperative delirium (POD) following general anesthesia.

Methods: This retrospective cross-sectional study included 644 patients who underwent general anesthesia. Univariate and multivariate logistic regression analyses were performed to evaluate the relationship between Hs-CRP and POD, with subgroup analyses used to assess stratified associations. Receiver operator characteristic (ROC) curve analysis was employed to assess the predictive efficacy of Hs-CRP for POD. Restricted cubic spline (RCS) analysis was conducted to explore the linear relationship between the log-transformed Hs-CRP (Log_{10}Hs-CRP) and POD risk.

Results: The total population consisted of 644 individuals with a mean age of 64.02 ± 13.20 years, 506 (78.60%) of whom were male, and 114 patients (17.7%) had POD. Compared to the lower Hs-CRP group, patients in the higher Hs-CRP group exhibited higher age, heart rate, white blood cell count, blood urea nitrogen, creatinine, uric acid, fasting glucose, hemoglobin A1c, fibrinogen, D-dimer, and a higher prevalence of CKD, but lower hemoglobin, high-density lipoprotein cholesterol, albumin and estimated glomerular filtration rate. Additionally, the prevalence of POD was higher in the higher Hs-CRP group (24.7% vs. 9.5%, $p < 0.001$). Multivariate logistic regression confirmed that elevated Hs-CRP and its forms (Log_{10}Hs-CRP, standardized Hs-CRP, and higher Hs-CRP group) consistently increased the risk of POD across all adjusted models ($p < 0.05$). Stratified analyses further highlighted significant associations between Hs-CRP and POD in specific subgroups, notably in patients aged ≥65 years, female patients, and those with or without hypertension, diabetes, or stroke history, and without chronic kidney disease ($p < 0.05$). ROC curve analysis demonstrated that Hs-CRP had a significant predictive ability for POD in the overall population (AUC = 0.646), as well as in male (AUC = 0.644) and female patients (AUC = 0.654). Additionally, RCS analysis indicated a linear positive association between Log_{10}Hs-CRP and POD risk ($p = 0.003$, nonlinear $p = 0.896$).

Conclusion: Elevated Hs-CRP levels are significantly associated with an increased risk of POD following general anesthesia.

KEYWORDS

inflammation, high-sensitivity C-reactive protein, postoperative delirium, general anesthesia, restricted cubic spline

1 Introduction

Postoperative delirium (POD) is a common postoperative complication, particularly prevalent among elderly patients and those undergoing surgery with general anesthesia (1). POD typically manifests as confusion, inattention, and cognitive impairment, which not only hinders patient recovery but may also extend hospital stays, increase healthcare costs, and even elevate mortality rates (2–4). Therefore, identifying risk factors for POD and implementing early interventions is crucial for improving patient outcomes.

In recent years, the inflammatory response has been recognized as a key factor in the development of POD (5). Studies have shown that surgery and anesthesia can activate the inflammatory response, leading to the release of various inflammatory mediators, which may, in turn, affect the central nervous system (6, 7). High-sensitivity C-reactive protein (Hs-CRP), a sensitive marker of inflammation, is elevated in numerous acute and chronic inflammatory states (8). Hs-CRP is not only used to assess postoperative infection risk but is also considered to be associated with neuroinflammatory processes in certain neurological disorders (9, 10). Therefore, some researchers have begun to focus on the association between inflammation and POD. For example, several studies have indicated a close relationship between CRP and POD following surgery with general anesthesia in various populations (11–13). However, the correlation between Hs-CRP and POD in the context of surgery with general anesthesia has not yet been fully explored.

Therefore, to further clarify the relationship between Hs-CRP and POD risk, this study adopts a cross-sectional design to evaluate the association between Hs-CRP levels and POD occurrence in patients undergoing surgery with general anesthesia, aiming to provide new insights for the early prediction and intervention of POD.

2 Methods

2.1 Study population

This study received approval from the Ethics Committee of the Sixth Hospital of Shanxi Medical University, and all procedures strictly adhered to the ethical principles outlined in the Declaration of Helsinki to ensure the safety and rights of the study subjects. As this study was retrospective, utilizing data from previous medical records that have been de-identified, informed consent from patients was waived. This study was a cross-sectional analysis involving patients who underwent general anesthesia at the Sixth Hospital of Shanxi Medical University from January 2019 to January 2024. A total of 644 patients who met the inclusion criteria were enrolled. The inclusion criteria were as follows: patients aged ≥18 years who underwent general anesthesia for elective non-cardiac surgeries, such as general surgery, orthopedics, burns, and urology, and received a POD assessment. The exclusion criteria were: (1) patients with a history of severe mental illness or cognitive impairment; (2) patients who died due to intraoperative or postoperative complications; (3) patients who used medications prior to surgery that could affect the assessment of delirium (such as antipsychotics or sedatives); (4) patients with acute or chronic infections, malignant tumors, or other conditions that could significantly influence Hs-CRP levels; (5) patients who underwent surgery with cardiopulmonary bypass or experienced severe hypoxic events; (6) patients who were unable to complete the POD assessment during the study period; (7) patients with missing baseline Hs-CRP data; and (8) patients with other major missing baseline data.

2.2 Diagnosis of postoperative delirium

In this study, POD was diagnosed using the Confusion Assessment Method (CAM), a widely used clinical tool for rapid screening. CAM diagnoses delirium by assessing patients based on four criteria: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Specifically, if a patient meets the first two criteria and at least one of the latter two (disorganized thinking or altered level of consciousness), they are diagnosed with delirium (14). Due to its high sensitivity and specificity, CAM is recommended for the rapid assessment of postoperative patients and is simple to use, making it suitable for administration by trained healthcare professionals (15).

2.3 Covariate collection and assessment

This study collected and assessed various covariates, including demographic information (age and gender), lifestyle factors (smoking and drinking), comorbidities, biomarkers, and vital signs. Smoking status was defined as smoking at least one cigarette daily within the past year. Alcohol consumption was defined as consuming alcohol at least once per week within the past year. Comorbidity information included hypertension, diabetes, stroke history, and chronic kidney disease (CKD). Hypertension was defined based on medical history, with systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or current antihypertensive treatment (16). Diabetes was defined by medical history, glycated hemoglobin (HbA1c) level ≥ 6.5%, fasting glucose ≥7.0 mmol/L, or prior diagnosis and treatment (17). Stroke history included any type of stroke (such as ischemic or hemorrhagic) documented in the medical records. CKD was defined by an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 or a prior diagnosis of CKD (18). The eGFR was calculated using the CKD-EPI equation, which includes serum creatinine levels, age, and gender, to provide an accurate assessment of kidney function (19).

Body mass index (BMI) was calculated based on height and weight measurements, expressed in kg/m^2. Vital signs, including SBP, DBP, and heart rate, were measured preoperatively with an automated blood pressure monitor following standardized protocols. Blood samples were also collected preoperatively to measure biomarkers, including

hemoglobin, white blood cell count, platelet count, uric acid, creatinine, blood urea nitrogen (BUN), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, fibrinogen, D-dimer, fasting glucose, HbA1c and Hs-CRP. Hs-CRP levels were categorized into two groups based on the optimal cutoff value of 4.78 mg/L determined through receiver operating characteristic (ROC) curve analysis: lower Hs-CRP (Hs-CRP $\leq$ 4.78 mg/L) and higher Hs-CRP (Hs-CRP > 4.78 mg/L). All biomarkers, including Hs-CRP, were collected during routine preoperative examinations before surgery and sent to a clinical laboratory for measurement using standardized operating procedures and certified equipment to ensure accuracy and reproducibility.

2.4 Statistical methods

All statistical analyses were performed using SPSS 26.0, MedCalc 19.6.1, and R 4.1.3 software. Continuous variables were expressed as mean ± standard deviation or median (interquartile range), depending on the data distribution, and were compared between groups using the independent sample t-test or the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages, and comparisons were made using the chi-square test or Fisher's exact test. To assess the association between Hs-CRP and the risk of POD, univariate logistic regression analysis was initially conducted to calculate the odds ratios (OR) and their 95% confidence intervals (CI) for each variable. Subsequently, multivariable logistic regression analysis was performed with three different adjustment models: Model 1 adjusted for age and gender; Model 2 further adjusted for smoking, drinking, hypertension, diabetes, stroke, and CKD; and Model 3 included additional adjustments for SBP, DBP, hemoglobin, AST, total bilirubin, albumin, BUN, creatinine, eGFR, uric acid, HbA1c, and fibrinogen. To further explore the relationship between Hs-CRP and the risk of POD, we conducted stratified analysis and restricted cubic spline (RCS) analysis. Stratified analysis was performed based on age, gender, hypertension, diabetes, stroke history, and CKD, with adjustments for other variables to evaluate the association between Hs-CRP and POD within different subgroups. RCS analysis was used to evaluate the linear relationship between Log_{10}Hs-CRP and the risk of POD and to determine the nonlinear p value to assess the significance of any nonlinear associations. Finally, receiver operating characteristic (ROC) curve analysis was conducted to assess the accuracy of Hs-CRP in predicting POD in different gender groups and the overall population, with the area under the curve (AUC) and its 95% CI calculated. All statistical analyses were considered significant at a two-sided $p < 0.05$ level.

3 Results

3.1 Clinical data grouped by high-sensitivity C-reactive protein

As shown in Table 1, the total population consisted of 644 individuals with a mean age of 64.02 ± 13.20 years, 506 (78.60%) of whom were male, and 114 patients (17.7%) had POD. patients in the higher Hs-CRP group exhibited significant differences across several clinical indicators. Firstly, age was notably higher in this group (65.25 vs. 62.56 years, $p = 0.010$). Compared to the lower Hs-CRP group, the higher Hs-CRP group had a higher prevalence of CKD (26.4 vs. 10.1%, $p < 0.001$), elevated heart rate (85.11 vs. 79.26 bpm, $p < 0.001$), increased white blood cell count (10.91 vs. 9.08 $\times 10^9$/L, $p < 0.001$), BUN (6.15 vs. 5.30 mmol/L, $p < 0.001$), creatinine (84.00 vs. 73.50 μmol/L, $p < 0.001$), uric acid (374.57 vs. 340.60 μmol/L, $p < 0.001$), fasting glucose (6.56 vs. 6.13 mmol/L, $p = 0.012$), HbA1c (6.85 vs. 6.46%, $p = 0.012$), fibrinogen (4.27 vs. 3.37 g/L, $p < 0.001$), and D-dimer (217.50 vs. 145.00 μg/L, $p < 0.001$). However, levels of hemoglobin (132.53 vs. 142.18 g/L, $p < 0.001$), HDL-C (1.10 vs. 1.18 mmol/L, $p < 0.001$), albumin (36.88 vs. 38.93 g/L, $p < 0.001$), and eGFR (83.86 vs. 103.67 mL/min/1.73 m^2, $p < 0.001$) were significantly lower. Additionally, the prevalence of POD was higher in the higher Hs-CRP group (24.7% vs. 9.5%, $p < 0.001$).

According to the results in Table 2, there were significant differences in multiple clinical indicators between the POD group and the non-POD group. The average age of patients in the POD group was significantly higher than that in the non-POD group (74.61 years vs. 61.74 years, $p < 0.001$), and the proportion of females was also higher (36.80% vs. 18.10%, $p < 0.001$). Regarding lifestyle factors, the POD group had lower rates of smoking (39.50% vs. 59.60%, $p < 0.001$) and alcohol consumption (21.90% vs. 39.80%, $p < 0.001$). Comorbidity analysis showed that the prevalence of hypertension (86.80% vs. 68.30%, $p < 0.001$), diabetes (49.10% vs. 35.30%, $p = 0.006$), stroke history (40.40% vs. 20.60%, $p < 0.001$), and CKD (50.00% vs. 12.30%, $p < 0.001$) was significantly higher in the POD group. In terms of biomarkers, the POD group showed significantly higher levels of SBP, BUN, creatinine, uric acid, HbA1c, D-dimer, fibrinogen, and Hs-CRP compared to the non-POD group, while DBP, hemoglobin, ALT, AST, total bilirubin, albumin, and eGFR levels were significantly lower in the POD group ($p < 0.05$).

3.2 Logistic regression analysis of high-sensitivity C-reactive protein and postoperative delirium

In the univariate logistic regression analysis shown in Table 3, multiple variables were significantly associated with the occurrence of POD. Specifically, age (OR = 1.101, $p < 0.001$), female gender (OR = 2.637, $p < 0.001$), smoking (OR = 2.264, $p < 0.001$), alcohol consumption (OR = 2.355, $p < 0.001$), hypertension (OR = 3.063, $p < 0.001$), diabetes (OR = 1.771, $p = 0.006$), stroke (OR = 2.613, $p < 0.001$), CKD (OR = 7.154, $p < 0.001$), SBP (OR = 1.011, $p = 0.015$), DBP (OR = 0.982, $p = 0.023$), BUN (OR = 1.117, $p < 0.001$), creatinine (OR = 1.004, $p < 0.001$), uric acid (OR = 1.004, $p < 0.001$), and HbA1c (OR = 1.276, $p < 0.001$) all showed significant effects. Additionally, hemoglobin (OR = 0.964, $p < 0.001$), AST (OR = 0.998, $p = 0.011$), total bilirubin (OR = 0.959, $p = 0.008$), and albumin (OR = 0.851, $p < 0.001$) were negatively associated with POD. Furthermore, Hs-CRP (OR = 1.007, $p = 0.001$), its logarithmic transformation (Log_{10}Hs-CRP, OR = 1.972, $p < 0.001$), its standardized value (standardized Hs-CRP, OR = 1.335, $p = 0.001$), and the higher Hs-CRP group (OR = 3.142, $p < 0.001$) were all closely associated with an increased risk of POD.

In the multivariable logistic regression analysis presented in Table 4, Hs-CRP and its various forms were significantly associated with the risk of POD across different adjustment models. Specifically, in Model 1, which adjusts for age and gender, Hs-CRP (OR = 1.008, $p = 0.001$), Log_{10}Hs-CRP (OR = 1.920, $p < 0.001$), standardized

10.3389/fneur.2025.1516800

TABLE 1 Clinical data grouped by high-sensitivity C-reactive protein.

	All patients	Lower Hs-CRP	Higher Hs-CRP	*p* value
Age, years	64.02 ± 13.20	62.56 ± 12.98	65.25 ± 13.28	0.010
Gender, *n* (%)				0.509
Male	506 (78.60%)	236 (79.70%)	270 (77.60%)	
Female	138 (21.40%)	60 (20.30%)	78 (22.40%)	
Smoking, *n* (%)				0.333
Yes	283 (43.90%)	124 (41.90%)	159 (45.70%)	
No	361 (56.10%)	172 (58.10%)	189 (54.30%)	
Alcohol consumption, *n* (%)				0.364
Yes	408 (63.40%)	182 (61.50%)	226 (64.90%)	
No	236 (36.60%)	114 (38.50%)	122 (35.10%)	
Hypertension, *n* (%)				0.302
Yes	461 (71.60%)	206 (69.60%)	255 (73.30%)	
No	183 (28.40%)	90 (30.40%)	93 (26.70%)	
Diabetes, *n* (%)				0.275
Yes	243 (37.70%)	105 (35.50%)	138 (39.70%)	
No	401 (62.30%)	191 (64.50%)	210 (60.30%)	
Stroke, *n* (%)				0.087
Yes	155 (24.10%)	62 (20.90%)	93 (26.70%)	
No	489 (75.90%)	234 (79.10%)	255 (73.30%)	
Chronic kidney disease, *n* (%)				<0.001
Yes	122 (18.90%)	30 (10.10%)	92 (26.40%)	
No	522 (81.10%)	266 (89.90%)	256 (73.60%)	
Body mass index, kg/m^2	24.97 ± 3.59	25.04 ± 3.51	24.91 ± 3.66	0.656
Systolic blood pressure, mmHg	130.71 ± 22.58	131.39 ± 21.72	130.13 ± 23.30	0.479
Diastolic blood pressure, mmHg	77.73 ± 13.78	78.58 ± 13.35	77.01 ± 14.11	0.148
Heart rate, bpm	82.42 ± 16.33	79.26 ± 14.25	85.11 ± 17.49	<0.001
White blood cell count, 10^9/L	10.05 (7.61, 12.67)	9.08 (7.14, 11.83)	10.91 (8.24, 13.65)	<0.001
Hemoglobin, g/L	136.97 ± 22.60	142.18 ± 20.61	132.53 ± 23.28	<0.001
Platelet, ×10^9/L	220.04 ± 67.60	216.36 ± 59.68	223.17 ± 73.62	0.196
Triglycerides, mmol/L	1.38 (1.02, 1.99)	1.44 (1.02, 2.19)	1.37 (1.02, 1.86)	0.257
Total cholesterol, mmol/L	4.55 ± 1.16	4.61 ± 1.10	4.49 ± 1.21	0.187
LDL-C, mmol/L	2.76 ± 0.87	2.75 ± 0.78	2.77 ± 0.94	0.849
HDL-C, mmol/L	1.14 ± 0.25	1.18 ± 0.26	1.10 ± 0.25	<0.001
Alanine aminotransferase, U/L	33.00 (20.00, 54.00)	31.50 (20.00, 52.00)	34.50 (20.00, 56.25)	0.266
Aspartate aminotransferase, U/L	73.00 (29.00, 176.75)	75.50 (29.00, 188.75)	69.50 (29.00, 161.00)	0.624
Total bilirubin, umol/L	13.50 (9.90, 18.38)	13.80 (10.13, 17.60)	13.10 (9.33, 19.20)	0.504
Albumin, g/L	37.82 ± 4.13	38.93 ± 3.83	36.88 ± 4.15	<0.001
Blood urea nitrogen, mmol/L	5.70 (4.40, 7.50)	5.30 (4.20, 6.68)	6.15 (4.60, 8.60)	<0.001
Creatinine, umol/L	79.00 (66.00, 98.00)	73.50 (62.00, 89.00)	84.00 (69.00, 109.00)	<0.001
eGFR, mL/min/1.73 m^2	92.73 (68.68, 117.60)	103.67 (80.51, 126.15)	83.86 (58.20, 109.57)	<0.001
Uric acid, umol/L	358.95 ± 115.74	340.60 ± 102.36	374.57 ± 124.03	<0.001
Fasting glucose, mmol/L	6.42 (5.43, 8.31)	6.13 (5.26, 7.90)	6.56 (5.54, 8.65)	0.012
Hemoglobin A1c, %	6.66 ± 1.70	6.46 ± 1.48	6.85 ± 1.86	0.012
Fibrinogen, g/L	3.85 ± 0.99	3.37 ± 0.78	4.27 ± 0.96	<0.001

(Continued)

TABLE 1 (Continued)

	All patients	Lower Hs-CRP	Higher Hs-CRP	*p* value
D-dimer, ug/L	194.50 (89.00, 391.75)	145.00 (69.25, 288.75)	217.50 (118.00, 508.25)	<0.001
Postoperative delirium				<0.001
Yes	114 (17.70%)	28 (9.50%)	86 (24.70%)	
No	530 (82.30%)	268 (90.50%)	262 (75.30%)	

Lower Hs-CRP: Hs-CRP ≤ 4.78 mg/L, Higher Hs-CRP: Hs-CRP > 4.78 mg/L. Hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate.

Hs-CRP (OR = 1.399, $p = 0.001$), and the higher Hs-CRP group (OR = 2.930, $p < 0.001$) were all significantly associated with an increased risk of POD. In Model 2, which further adjusted for smoking, alcohol consumption, hypertension, diabetes, stroke, and CKD, Hs-CRP (OR = 1.006, $p = 0.012$), Log_{10}Hs-CRP (OR = 1.684, $p = 0.001$), standardized Hs-CRP (OR = 1.312, $p = 0.012$), and the higher Hs-CRP group (OR = 2.417, $p = 0.001$) maintained statistical significance. In Model 3, which included additional adjustments for SBP, DBP, hemoglobin, AST, total bilirubin, albumin, BUN, creatinine, eGFR, uric acid, HbA1c, and fibrinogen, Hs-CRP (OR = 1.007, $p = 0.037$), Log_{10}Hs-CRP (OR = 1.645, $p = 0.018$), standardized Hs-CRP (OR = 1.346, $p = 0.037$), and the higher Hs-CRP group (OR = 2.243, $p = 0.003$) remained significantly associated with POD.

3.3 Multivariable stratified association between high-sensitivity C-reactive protein and postoperative delirium

In the multivariable stratified analysis shown in Table 5, Hs-CRP was significantly associated with the risk of POD in several stratified variables. Specifically, in patients aged ≥65 years, higher Hs-CRP was significantly associated with POD (OR = 1.914, $p = 0.024$). In the gender stratification, the association between Hs-CRP and POD was significant in female patients (OR = 4.753, $p = 0.002$). Among the hypertension strata, the association was more pronounced in patients without hypertension (OR = 60.862, $p = 0.001$), while it also remained significant in those with hypertension (OR = 1.793, $p = 0.041$). In the diabetes stratification, Hs-CRP was significantly associated with POD in both non-diabetic patients (OR = 1.634, $p = 0.001$) and diabetic patients (OR = 3.349, $p = 0.004$). In the stroke stratification, significant associations were observed in both patients without a history of stroke (OR = 2.053, $p = 0.033$) and those with a history of stroke (OR = 2.655, $p = 0.024$). For the CKD stratification, Hs-CRP was significantly associated with POD in patients without CKD (OR = 1.645, $p < 0.001$).

3.4 Predictive value of high-sensitivity C-reactive protein for postoperative delirium across populations

Figure 1 presented the ROC curve analysis results of Hs-CRP in predicting the risk of POD. In the total population, the AUC for Hs-CRP was 0.646 (95% CI: 0.591–0.701, $p < 0.001$), indicating a significant predictive ability in the overall population. In the gender-stratified analysis, the AUC for male patients was 0.644 (95% CI: 0.601–0.686, $p < 0.001$), and for female patients, it was 0.654 (95% CI: 0.569–0.733, $p = 0.002$), showing that Hs-CRP was significantly associated with the occurrence of POD in both males and females.

3.5 Linear association between high-sensitivity C-reactive protein and postoperative delirium risk

Figure 2 presented the RCS plot of the linear association between the Log_{10}Hs-CRP and the risk of POD. The results showed a significant positive association between Log_{10}Hs-CRP and the risk of POD ($p = 0.003$), and this relationship was linear (nonlinear p value = 0.896). This indicated that as Log_{10}Hs-CRP increased, the risk of POD gradually rised.

4 Discussion

This study investigated the relationship between preoperative Hs-CRP levels and the risk of POD following general anesthesia. The results showed a significant positive association between elevated Hs-CRP levels and the occurrence of POD. Multivariate logistic regression analysis indicated that Hs-CRP, along with its logarithmic and standardized forms, and particularly the higher Hs-CRP group, were significantly associated with increased POD risk. Furthermore, stratified analyses revealed that the association between Hs-CRP and POD risk was more pronounced in certain subgroups, particularly in patients aged ≥65 years, female patients, and those with or without hypertension, diabetes, or stroke history, with an especially strong association observed in patients without CKD. ROC curve analysis indicated that Hs-CRP has moderate predictive value for POD in the overall population, with significant predictive capabilities in both male and female subgroups. RCS analysis further supported a linear positive association between Log_{10}Hs-CRP and POD risk, underscoring the importance of Hs-CRP as a potential marker for POD risk assessment.

Our findings are consistent with previous studies that consider CRP as an inflammatory marker associated with neurocognitive impairment, including POD. For example, in a prospective cohort study involving 547 patients aged 70 and older undergoing major non-cardiac surgery, Vasunilashorn et al. found a strong association between CRP and POD, though this association was influenced by genetic factors (11). In addition, in a retrospective study involving 643 colorectal cancer patients, Sun et al. found that a high CRP level on postoperative day 1 was an independent risk factor for POD (20). This suggests that postoperative CRP levels can serve as an independent predictor of POD in colorectal cancer patients, aiding clinicians in the early identification and intervention for high-risk POD patients among elderly colorectal cancer patients. Furthermore, in a nested

10.3389/fneur.2025.1516800

TABLE 2 Clinical data grouped by postoperative delirium.

	Non-POD	POD	*p* value
N	530 (82.30%)	114 (17.70%)	
Age, years	61.74 ± 12.78	74.61 ± 9.44	<0.001
Gender, *n* (%)			<0.001
Male	434 (81.90%)	72 (63.20%)	
Female	96 (18.10%)	42 (36.80%)	
Smoking, *n* (%)			<0.001
Yes	316 (59.60%)	45 (39.50%)	
No	214 (40.40%)	69 (60.50%)	
Alcohol consumption, *n* (%)			<0.001
Yes	211 (39.80%)	25 (21.90%)	
No	319 (60.20%)	89 (78.10%)	
Hypertension, *n* (%)			<0.001
Yes	362 (68.30%)	99 (86.80%)	
No	168 (31.70%)	15 (13.20%)	
Diabetes, *n* (%)			0.006
Yes	187 (35.30%)	56 (49.10%)	
No	343 (64.70%)	58 (50.90%)	
Stroke, *n* (%)			<0.001
Yes	109 (20.60%)	46 (40.40%)	
No	421 (79.40%)	68 (59.60%)	
Chronic kidney disease, *n* (%)			<0.001
Yes	65 (12.30%)	57 (50.00%)	
No	465 (87.70%)	57 (50.00%)	
Body mass index, kg/m^2	25.06 ± 3.52	24.49 ± 3.91	0.146
Systolic blood pressure, mmHg	129.70 ± 22.35	135.40 ± 23.16	0.014
Diastolic blood pressure, mmHg	78.31 ± 13.91	75.06 ± 12.87	0.022
Heart rate, bpm	81.95 ± 16.04	84.61 ± 17.54	0.114
White blood cell count, 10^9/L	10.19 (7.71, 12.81)	9.84 (7.41, 12.11)	0.414
Hemoglobin, g/L	140.31 ± 21.04	121.45 ± 23.18	<0.001
Platelet, ×10^9/L	219.19 ± 66.32	223.96 ± 73.46	0.495
Triglycerides, mmol/L	1.40 (1.03, 2.02)	1.31 (0.97, 1.88)	0.165
Total cholesterol, mmol/L	4.53 ± 1.10	4.61 ± 1.40	0.567
LDL-C, mmol/L	2.74 ± 0.83	2.84 ± 1.02	0.316
HDL-C, mmol/L	1.14 ± 0.25	1.15 ± 0.26	0.654
Alanine aminotransferase, U/L	36.00 (22.00, 56.00)	22.00 (15.00, 38.00)	<0.001
Aspartate aminotransferase, U/L	85.00 (31.00, 192.00)	41.00 (22.00, 104.00)	<0.001
Total bilirubin, umol/L	13.80 (10.05, 18.80)	11.80 (8.40, 15.75)	0.001
Albumin, g/L	38.30 ± 3.96	35.59 ± 4.20	<0.001
Blood urea nitrogen, mmol/L	5.40 (4.20, 6.90)	7.70 (5.60, 11.50)	<0.001
Creatinine, umol/L	76.00 (64.00, 92.00)	104.00 (81.00, 148.50)	<0.001
eGFR, mL/min/1.73 m^2	98.73 (77.00, 123.24)	59.67 (36.42, 84.64)	<0.001
Uric acid, umol/L	349.59 ± 109.93	402.47 ± 131.66	<0.001
Fasting glucose, mmol/L	6.37 (5.42, 8.07)	6.83 (5.40, 9.27)	0.117
Hemoglobin A1c, %	6.52 ± 1.55	7.33 ± 2.17	0.002
Fibrinogen, g/L	3.76 ± 0.96	4.28 ± 0.99	<0.001
D-dimer, ug/L	168.00 (78.50, 333.50)	309.00 (174.50, 694.50)	<0.001
Hs-CRP	4.41 (1.05, 18.82)	15.40 (4.51, 55.55)	<0.001

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein.

TABLE 3 The univariate logistic regression analysis of postoperative delirium.

	OR (95% CI)	*p* value
Age	1.101 (1.077, 1.125)	<0.001
Female	2.637 (1.698, 4.095)	<0.001
Smoking	2.264 (1.497, 3.424)	<0.001
Alcohol consumption	2.355 (1.462, 3.792)	<0.001
Hypertension	3.063 (1.727, 5.433)	<0.001
Diabetes	1.771 (1.178, 2.664)	0.006
Stroke	2.613 (1.701, 4.014)	<0.001
Chronic kidney disease	7.154 (4.563, 11.215)	<0.001
Body mass index	0.955 (0.897, 1.016)	0.146
Systolic blood pressure	1.011 (1.002, 1.020)	0.015
Diastolic blood pressure	0.982 (0.967, 0.998)	0.023
Heart rate	1.010 (0.998, 1.022)	0.115
White blood cell count	0.979 (0.930, 1.031)	0.426
Hemoglobin	0.964 (0.955, 0.973)	<0.001
Platelet	1.001 (0.998, 1.004)	0.494
Triglycerides	0.943 (0.780, 1.140)	0.542
Total cholesterol	1.060 (0.893, 1.257)	0.504
Low-density lipoprotein cholesterol	1.141 (0.910, 1.430)	0.253
High-density lipoprotein cholesterol	1.199 (0.543, 2.646)	0.653
Alanine aminotransferase	1.000 (0.998, 1.002)	0.961
Aspartate aminotransferase	0.998 (0.996, 0.999)	0.011
Total bilirubin	0.959 (0.929, 0.989)	0.008
Albumin	0.851 (0.807, 0.897)	<0.001
Blood urea nitrogen	1.117 (1.069, 1.168)	<0.001
Creatinine	1.004 (1.002, 1.006)	<0.001
eGFR	0.973 (0.967, 0.979)	<0.001
Uric acid	1.004 (1.002, 1.005)	<0.001
Fasting glucose	1.039 (0.998, 1.082)	0.065
Hemoglobin A1c	1.276 (1.125, 1.448)	<0.001
Fibrinogen	1.658 (1.352, 2.033)	<0.001
D-dimer	1.000 (1.000, 1.000)	0.352
Hs-CRP	1.007 (1.003, 1.011)	0.001
Log_{10}Hs-CRP	1.972 (1.498, 2.595)	<0.001
Standardized Hs-CRP	1.335 (1.124, 1.585)	0.001
Lower Hs-CRP	Ref	
Higher Hs-CRP	3.142 (1.985, 4.973)	<0.001

eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; OR, odd ratio; CI, confidence interval.

case–control study involving 566 patients aged 70 and older undergoing major non-cardiac surgery, Dillon et al. confirmed that elevated preoperative and postoperative CRP levels were closely associated with the occurrence of delirium, which suggests that CRP can serve as an early predictive marker for postoperative delirium in elderly surgical patients, aiding in the identification of high-risk individuals and the implementation of preventive measures (13). Moreover, Lozano-Vicario et al. included 60 patients aged 75 and older undergoing hip fracture repair surgery and found that although elevated CRP levels were associated with POD in elderly hip fracture patients, pre-existing cognitive impairment and infections were more significant risk factors (21). Furthermore, an observational study involving 314 patients from the SuDoCo trial found that elevated pre-operative CRP levels were independently associated with POD, but showed no significant association with post-operative neurocognitive disorder, which suggests that pre-operative CRP levels could serve as a predictive marker for POD risk, aiding clinicians in risk stratification among elderly patients and providing a basis for

TABLE 4 Multivariable logistic regression analysis of high-sensitivity C-reactive protein and postoperative delirium.

	Model 1		Model 2		Model 3	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Hs-CRP	1.008 (1.003, 1.012)	0.001	1.006 (1.001, 1.011)	0.012	1.007 (1.000, 1.013)	0.037
Log_{10}Hs-CRP	1.920 (1.415, 2.604)	<0.001	1.684 (1.223, 2.317)	0.001	1.645 (1.088, 2.487)	0.018
Standardized Hs-CRP	1.399 (1.145, 1.710)	0.001	1.312 (1.060, 1.623)	0.012	1.346 (1.018, 1.779)	0.037
Lower Hs-CRP	Ref		Ref		Ref	
Higher Hs-CRP	2.930 (1.788, 4.799)	<0.001	2.417 (1.442, 4.050)	0.001	2.243 (1.327, 3.793)	0.003

Model 1 was adjusted for age and gender; Model 2 was adjusted for age, gender, smoking, alcohol consumption, hypertension, diabetes, stroke, and chronic kidney disease; Model 3 was adjusted for all variables in Model 2, as well as systolic blood pressure, diastolic blood pressure, hemoglobin, aspartate aminotransferase, total bilirubin, albumin, blood urea nitrogen, creatinine, estimated glomerular filtration rate, uric acid, hemoglobin A1c, and fibrinogen. Hs-CRP, high-sensitivity C-reactive protein; OR, odd ratio; CI, confidence interval.

TABLE 5 Multivariable stratified association between Hs-CRP and postoperative delirium.

	Lower Hs-CRP	Higher Hs-CRP	*p* value
	OR (95% CI)	OR (95% CI)	
Age			
<65 years	Ref	4.262 (0.646, 28.126)	0.132
≥65 years	Ref	1.914 (1.088, 3.367)	0.024
Gender			
Male	Ref	1.268 (0.604, 2.659)	0.530
Female	Ref	4.753 (1.780, 12.691)	0.002
Hypertension			
Yes	Ref	1.793 (1.025, 3.136)	0.041
No	Ref	60.862 (5.750, 644.157)	0.001
Diabetes			
Yes	Ref	3.349 (1.471, 7.625)	0.004
No	Ref	1.634 (1.219, 2.190)	0.001
Stroke			
Yes	Ref	2.655 (1.139, 6.188)	0.024
No	Ref	2.053 (1.058, 3.983)	0.033
Chronic kidney disease			
Yes	Ref	1.255 (0.408, 3.855)	0.692
No	Ref	1.645 (1.277, 2.118)	<0.001

The multivariable stratified association was adjusted for age, gender, smoking, alcohol consumption, hypertension, diabetes, stroke, chronic kidney disease, systolic blood pressure, diastolic blood pressure, hemoglobin, aspartate aminotransferase, total bilirubin, albumin, blood urea nitrogen, creatinine, estimated glomerular filtration rate, uric acid, hemoglobin A1c, and fibrinogen except for the variable that was used for stratification. Hs-CRP, high-sensitivity C-reactive protein; OR, odd ratio; CI, confidence interval.

pre-operative interventions to reduce the occurrence of POD (22). In addition, another single-center cross-sectional study also found that higher levels of platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic inflammation index (SII) were independently associated with an increased risk of POD, suggesting that inflammation may play a crucial role in the development of POD (23). However, these studies primarily focus on traditional CRP, while research on Hs-CRP, a more sensitive measurement indicator, is limited in this field. The advantage of our study lies in the use of Hs-CRP, which enables the detection of low-level inflammation that may lead to POD, particularly in subclinical states. Additionally, the cross-sectional design of our study allowed us to adjust for multiple variables, providing a more comprehensive assessment of the relationship between Hs-CRP and POD. Through stratified analysis, we further revealed that Hs-CRP may serve as a powerful risk indicator for POD within specific subgroups, expanding the current literature on the role of Hs-CRP in POD risk across different patient populations. Furthermore, we not only confirmed the predictive value of Hs-CRP for POD in the overall population and among different gender groups but also established a positive linear correlation between Hs-CRP and POD. This provides new insights and theoretical support for the use of Hs-CRP in early pre-operative screening and management of POD.

However, although growing evidence in recent years indicates a close link between inflammation and POD, the pathophysiological mechanisms underlying this relationship remain incompletely understood (24). The potential mechanism by which elevated Hs-CRP contributes to POD may relate to its role as a marker of systemic

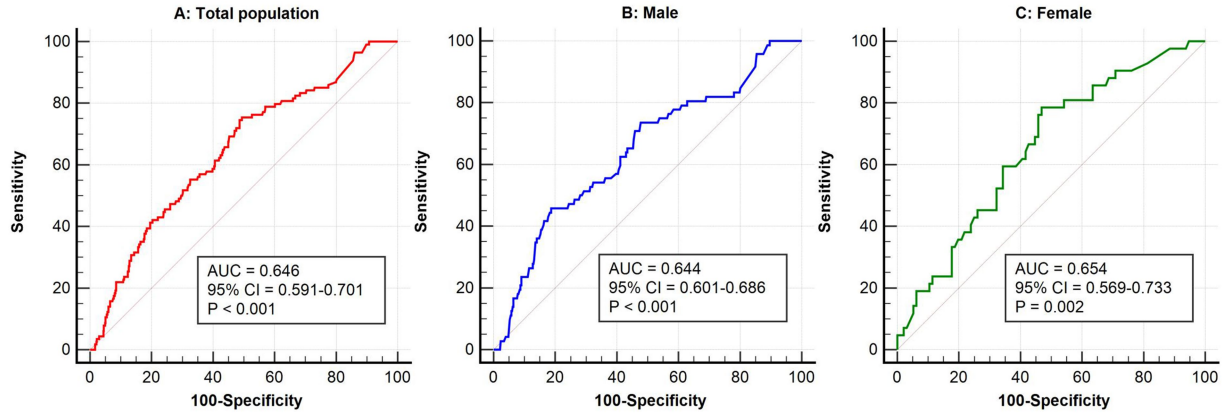

FIGURE 1
ROC analysis of high-sensitivity C-reactive protein in predicting postoperative delirium in the general population **(A)**, males **(B)**, and females **(C)**. ROC, receiver operator characteristic; AUC, area under the curve; CI, confidence interval.

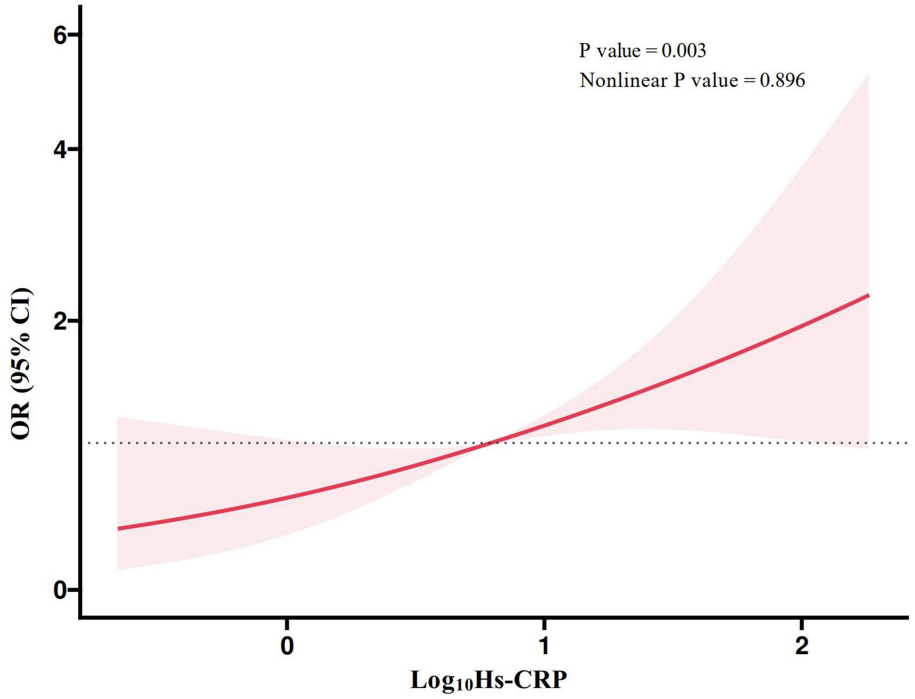

FIGURE 2
RCS plot of the linear association between high-sensitivity C-reactive protein and postoperative delirium. Hs-CRP, high-sensitivity C-reactive protein; RCS, restricted cubic spline; OR, odd ratio; CI, confidence interval.

inflammation. The inflammation induced by surgery and anesthesia can activate microglia, increase the release of pro-inflammatory cytokines, disrupt the blood–brain barrier, and subsequently trigger neuroinflammation, ultimately affecting cognitive function (25). Hs-CRP may reflect a state that exacerbates these inflammatory pathways. Research has shown that inflammation plays a key role in neurodegenerative diseases and cognitive impairment, supporting the hypothesis that elevated Hs-CRP increases susceptibility to POD through inflammation-driven neurobiological changes (26). Additionally, elevated Hs-CRP may promote POD by inducing oxidative stress. The inflammatory response triggered by surgery and anesthesia can increase the production of reactive oxygen species, heightening oxidative stress levels, which in turn damages neuronal function and further exacerbates neuroinflammatory responses (27, 28). Moreover, elevated Hs-CRP may be associated with the migration of peripheral immune cells into the central nervous system (29). Inflammatory responses may alter blood–brain barrier permeability, making it easier for peripheral immune cells (such as monocytes and neutrophils) to enter brain tissue, and the infiltration of these peripheral immune cells into the central nervous system can worsen

the local inflammatory environment, impair brain function, and increase the risk of POD (29–31). However, further research is needed to explore the underlying biological mechanisms of these associations.

Although this study reveals important findings, it has some limitations. Firstly, the average age of patients in the high Hs-CRP group was significantly higher than that in the low Hs-CRP group, and age is a known major risk factor for POD. This difference could act as a confounding factor, interfering with the independent association between Hs-CRP and POD risk. Secondly, the prevalence of CKD was significantly higher in the high Hs-CRP group. CKD can influence Hs-CRP levels through inflammation and metabolic disorders and may independently increase the risk of POD, posing challenges to the independent evaluation of the study results. Additionally, patients in the high Hs-CRP group exhibited significant differences in various physiological and metabolic indicators, including elevated heart rate, white blood cell count, BUN, creatinine, uric acid, fasting glucose, HbA1c, fibrinogen, and D-dimer levels, as well as reduced hemoglobin, HDL-C, albumin, and eGFR levels. These abnormalities may reflect inflammatory states, nutritional status, and systemic metabolic alterations, potentially contributing to the risk of POD and complicating the interpretation of results. Moreover, although the group differences were statistically significant, the clinical relevance of certain indicators may be limited; for example, some biochemical differences may not directly indicate substantial changes in POD risk. Therefore, future studies should further validate these findings and optimize study designs, such as through matching or stratified analyses, to better control potential confounding factors and improve the scientific rigor and clinical applicability of the research. Secondly, the cross-sectional design restricts our ability to determine a causal relationship between elevated Hs-CRP and POD. This limitation underscores the importance of longitudinal studies to clarify the temporal sequence and causative mechanisms underlying this association. Thirdly, while the sample size is relatively large, this is a single-center study, which may limit the generalizability of the results. Expanding this research to multi-center cohorts would strengthen the external validity of the findings. Additionally, relying solely on Hs-CRP as an inflammatory marker may not fully capture the underlying inflammatory processes associated with POD. Incorporating a panel of inflammatory biomarkers could provide a more comprehensive understanding of the inflammatory pathways involved in POD. Future research should consider longitudinal designs, multi-center involvement, and additional biomarkers to further validate and expand upon these findings.

5 Conclusion

In conclusion, this study indicates that elevated pre-operative Hs-CRP levels are significantly associated with an increased risk of POD following general anesthesia. These findings suggest that Hs-CRP could serve as a valuable marker for POD risk assessment in clinical settings. Early identification of high-risk patients using Hs-CRP levels could facilitate timely preventive measures and tailored interventions, potentially reducing the incidence of POD. Clinicians may incorporate Hs-CRP testing into pre-operative evaluations, particularly for high-risk patients, to identify and manage those most susceptible to POD. Future research should focus on exploring the mechanisms by which Hs-CRP contributes to POD and on investigating interventions that could mitigate this risk to improve postoperative outcomes in surgical patients. Additionally, further studies should assess the cost-effectiveness and feasibility of incorporating Hs-CRP testing into routine pre-operative workflows.

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 humans were approved by Ethics Committee of the Sixth Hospital of Shanxi Medical University. 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

XQ: Conceptualization, Data curation, Methodology, Software, Writing – original draft, Writing – review & editing. JR: Conceptualization, Writing – review & editing. CX: Conceptualization, Writing – review & editing. LC: Conceptualization, Writing – review & editing. RW: Conceptualization, Writing – review & editing. ST: Conceptualization, Funding acquisition, Project administration, Supervision, 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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Case Report
PUBLISHED 05 March 2025
DOI 10.3389/fmed.2025.1541462

OPEN ACCESS

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RECEIVED 07 December 2024
ACCEPTED 28 January 2025
PUBLISHED 05 March 2025

CITATION
Zhang L, Liu A, Wang L, Zhang Y and Hu Z (2025) Ultrasound-guided transversus abdominis plane block as an adjunctive anesthesia technique in elderly patients with combined massive ascites: a case report and literature review.
Front. Med. 12:1541462.
doi: 10.3389/fmed.2025.1541462

Ultrasound-guided transversus abdominis plane block as an adjunctive anesthesia technique in elderly patients with combined massive ascites: a case report and literature review

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The ultrasound-guided transversus abdominis plane (TAP) block has emerged as an effective adjunctive analgesic technique for abdominal surgery. However, its use in older patients with significant ascites has been rarely documented. This report presents the anesthetic management of an older patient with massive ascites undergoing open laparotomy for an ovarian tumor. Preoperatively, 30 mL of 0.2% levobupivacaine was injected into the TAP under ultrasound guidance. The procedure was uneventful, with approximately 9,000 mL of ascitic fluid drained, along with the removal of a 13 × 13 × 7-cm left ovarian mass, an 8 × 5.5 × 4-cm uterus, and a 3.5 × 1 × 0.5-cm right ovary. Throughout the surgery, the patient maintained hemodynamic stability, with no significant fluctuations in blood pressure or heart rate. Postoperatively, the patient reported minimal pain and experienced no adverse effects. These findings highlight the effectiveness of ultrasound-guided TAP block as an auxiliary anesthesia technique, providing enhanced analgesia, promoting hemodynamic stability, and improving overall anesthetic outcomes in older patients with substantial ascites.

KEYWORDS

ovarian tumor excision, transversus abdominal plane block, elderly, ascites, ultrasound, case report

Introduction

The transversus abdominis plane (TAP) block, introduced by Rafi (1), is a regional anesthesia technique that targets the thoracolumbar nerves originating from the T6–L1 spinal roots, which traverse the plane between the internal oblique and transversus abdominis muscles (2). Injecting a local anesthetic into this plane allows for the blockade of nerve afferents, providing effective analgesia to the anterolateral abdominal wall. Advances in ultrasound technology have improved the precision and safety of TAP blocks, leading to their increasing adoption as an adjunctive analgesic technique for abdominal surgeries. Over the past decade, growing evidence has demonstrated the efficacy of TAP blocks in various abdominal procedures, underscoring their integral role in multimodal analgesia (3, 4).

Patients with ovarian tumors and associated ascites often present unique anesthetic challenges due to coexisting comorbidities such as anemia and hypoproteinemia. Massive ascites can exacerbate these conditions by elevating the diaphragm, reducing thoracic cavity volume, and impairing ventilation, which may lead to hypoxia and hypercapnia. In addition, the prolonged compression of the abdominal aorta and inferior vena cava by the tumor and ascites can reduce venous return, resulting in hypotension and tachycardia. These hemodynamic changes are further complicated by the opening of lower limb vascular beds and the activation of collateral circulatory pathways in abdominal organs. Therefore, anesthetic management in these patients must prioritize maintaining hemodynamic stability and fluid balance to mitigate the risk of complications. Insufficient fluid resuscitation can lead to significant hypotension and impaired organ perfusion, while excessive fluid administration or frequent use of vasoactive drugs may precipitate acute pulmonary edema by increasing preload. Therefore, selecting an appropriate anesthetic technique is critical for optimizing perioperative outcomes in this patient population.

This report describes a case in which intravenous general anesthesia, combined with ultrasound-guided TAP block-assisted analgesia, was used successfully for open exploratory abdominal surgery in a patient with ovarian tumors, hypertension, and significant ascites (see Figures 1, 2).

Case report

A 63-year-old woman (163 cm, 78 kg) presented with progressive abdominal distension. Her medical history included uterine fibroids and grade II hypertension, with a maximum recorded blood pressure of 160/105 mmHg, which was treated with valsartan. Clinical examination revealed abdominal distension with increased wall tension, turbid percussion sounds, positive shifting dullness, and mild lower extremity edema. During hospitalization, the patient remained hemodynamically stable, with blood pressure ranging from 127 to 157/80 to 115 mmHg. Routine laboratory tests, including complete blood count, coagulation profile, and electrolytes, were unremarkable.

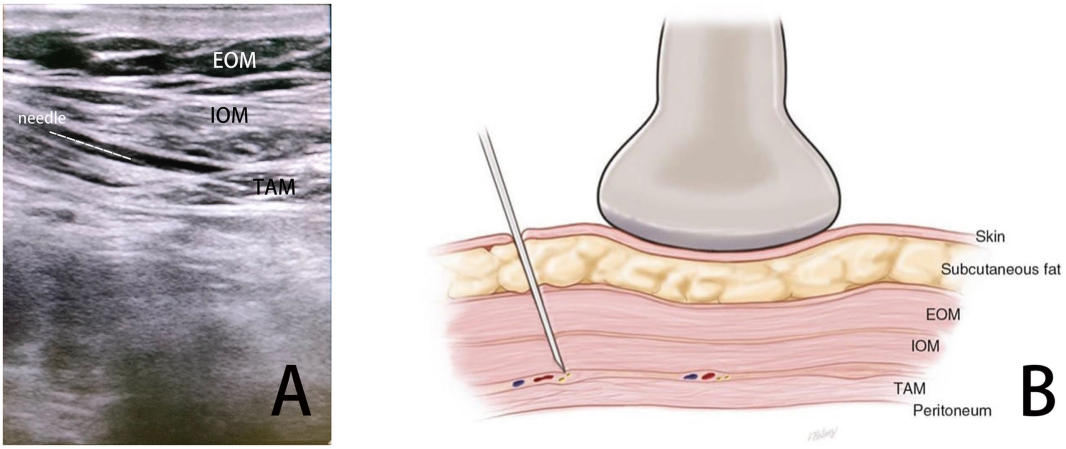

FIGURE 1
TAP block diagram. **(A)** Ultrasound imaging for TAP block. **(B)** Schematic representation of the TAP block.

FIGURE 2
Intraoperative images of the patient's lesions. **(A)** Image of ovarian tumor before removal. **(B)** Gross image after the removal of ovarian tumor. **(C)** Ovarian tumor profile.

Biochemical analyses showed hypoalbuminemia (albumin: 32 g/L and total protein: 55 g/L), elevated CA-125 level of 3,133 U/mL, and a thyroid-stimulating hormone (TSH) level of 9.06 μIU/mL. The cardiac evaluation revealed sinus tachycardia with ST-T abnormalities on electrocardiography and an ejection fraction of 70% on echocardiography, along with ventricular septal thickening and degenerative valvular changes. Imaging studies identified significant ascites, a pelvic mass, and associated findings, including hepatic cysts, right renal stones, uterine effusion, and bilateral pleural effusion. Gynecologic ultrasound suggested a follicular membranous cell tumor, while thoracic and abdominal CT showed coarse bilateral lung textures and irregular soft tissue density in the pelvis. A malignant pelvic tumor was strongly suspected, with an anticipated prolonged surgical duration. The combination of extensive ascites and hypertension presented the risks of intraoperative ventilation and circulatory instability, necessitating careful anesthetic planning. Therefore, the decision was made to administer intravenous general anesthesia in combination with ultrasound-guided TAP block-assisted analgesia to optimize hemodynamic stability.

The patient and her family were counseled preoperatively about the anesthetic plan, including the TAP block technique, its potential risks, and associated costs. Informed consent was obtained.

On the day of surgery, the patient was positioned supine in the operating room, and oxygen supplementation was initiated through a face mask. Routine monitoring was established, including electrocardiography, non-invasive blood pressure, pulse oximetry, bispectral index (BIS), and capnography. Lactated Ringer's solution was infused through intravenous access. Sedation was induced by administering midazolam (2 mg) and etomidate (5 mg). A bilateral TAP block was performed under ultrasound guidance, with 30 mL of 0.2% levobupivacaine injected on each side. The sensory block was confirmed 20 min later using needle testing, with the patient reporting no discomfort. General anesthesia was induced with etomidate (15 mg), vecuronium bromide (6 mg), and sufentanil (10 μg), followed by tracheal intubation. Maintenance anesthesia was provided with continuous infusions of propofol (20 mL/h) and remifentanil (3 mL/h). Vasoactive agents, including dopamine and atropine, were prepared as needed.

Surgery began at 09:05, with ascitic fluid drained incrementally in four sessions, totaling 9,000 mL over 45 min. Throughout the procedure, hemodynamic stability was maintained, with blood pressure ranging from 90/56 to 132/70 mmHg and heart rates between 76 and 99 bpm. Prophylactic dopamine (2 mg) was administered during the initial drainage to mitigate decompression-induced hypotension. At 10:00, brief episodes of atrioventricular block lasting 3–5 s were observed, with a minimum heart rate of 45 bpm. These episodes resolved after a single intravenous dose of atropine (0.3 mg), and no recurrence was noted. Blood gas analysis at 10:22 showed normal findings: pH 7.44, PCO_2 36 mmHg, PO_2 128 mmHg, potassium 3.5 mmol/L, sodium 137 mmol/L, calcium 1.13 mmol/L, glucose 5.8 mmol/L, and lactate 0.6 mmol/L. The surgery proceeded with a transabdominal hysterectomy and bilateral adnexectomy. Specimens included an 8 × 5.5 × 4-cm uterus, a 3.5 × 1 × 0.5-cm right ovary, and a 13 × 13 × 7-cm left ovarian mass. Intraoperative rapid cryopathological analysis confirmed a benign ovarian interstitial tumor. The operation concluded at 11:45, and the patient was extubated at 11:55 after regaining full consciousness. The total surgical duration was approximately 1 h and 40 min. Postoperative pain was assessed using a visual analog scale (VAS) over 2 days, with the patient reporting minimal pain and no adverse effects, such as nausea, vomiting, or respiratory depression. Overall, the patient expressed high satisfaction with the anesthesia protocol.

Discussion

With the global aging population on the rise, the demand for surgical treatments in older patients is increasing. However, these patients often have multiple comorbidities, which elevate the risks associated with perioperative anesthesia. Effective perioperative pain management is crucial for mitigating surgery-induced stress, minimizing postoperative complications, and promoting faster recovery.

The TAP block has become an integral component of multimodal analgesia in various abdominal procedures, including cesarean delivery, appendectomy, total abdominal hysterectomy, and laparoscopic cholecystectomy. Numerous studies have highlighted its effectiveness in reducing intraoperative and postoperative opioid consumption, lowering pain scores, and decreasing opioid-related side effects (5). For instance, a randomized controlled trial comparing bupivacaine and saline TAP blocks in patients undergoing cesarean delivery showed a > 60% reduction in total morphine consumption in the bupivacaine group, along with improved postoperative pain relief and fewer side effects, such as nausea and vomiting (6). Similarly, a study on laparoscopic cholecystectomy showed that patients who received TAP blocks experienced significantly lower postoperative pain scores, reduced analgesic requirements, and a lower incidence of nausea and vomiting than controls (4). Moreover, TAP blockade plays a key role in maintaining intraoperative hemodynamic stability. In a comparative study of anesthesia techniques, patients who received TAP block with the general anesthesia group exhibited fewer blood pressure fluctuations and a reduced need for phenylephrine than those who received general anesthesia alone or combined with epidural anesthesia (7). Another trial involving open gastric cancer surgery found that ropivacaine TAP blockade significantly lowered intraoperative systolic and diastolic blood pressure, heart rate fluctuations, and remifentanil use compared to saline TAP blockade (8). These findings highlight the role of TAP blockade in stabilizing vital parameters during surgery.

Ascites, characterized by the pathological accumulation of fluid in the peritoneal cavity, is typically classified into portal hypertensive ascites, non-portal hypertensive ascites, and mixed ascites (9). Ascites, which is frequently associated with cirrhosis and malignancies (10), causes a variety of debilitating symptoms, including dyspnea, abdominal pain, nausea, anorexia, and fatigue, all of which significantly impair quality of life (11). In the case presented, an older patient with an ovarian tumor and massive

ascites faced several physiological challenges. Ascites-induced compression of the abdominal vasculature worsens afterload, reduces venous return, and increases the risk of lower extremity thrombosis due to venous stasis. Diaphragmatic elevation further compromises ventilation, leading to hypoxia and hypercapnia. In addition, patients with ascites frequently exhibit malnutrition, anemia, hypoproteinemia, and electrolyte imbalances, necessitating a thorough preoperative evaluation and tailored anesthetic strategies.

Given the patient's condition, the dosage of general anesthesia was carefully reduced to prevent hemodynamic fluctuations during ascites drainage and tumor manipulation. To optimize analgesia and enhance perioperative stability, a multimodal approach combining general anesthesia with regional nerve blockade was used. Among the commonly used techniques, including TAP, erector spinae, and quadratus lumborum blocks, TAP blockade was preferred due to the patient's abdominal distension, massive ascites, and the ability to perform the block in the supine position. Studies have shown that these techniques provide comparable analgesic outcomes and opioid-sparing effects (12, 13). This multimodal regimen yielded excellent outcomes. First, the combination of TAP block with anesthesia induction, using 20 mg etomidate, 2 mg midazolam, and 10 μg sufentanil, effectively provided analgesia. Second, the patient's hemodynamics remained stable throughout ascites drainage, with no significant fluctuations in blood pressure or heart rate. The vasoactive agents, including dobutamine and atropine, were not required, except for a single prophylactic dose of 2 mg dobutamine to counteract decompression-induced hypotension. Finally, the patient experienced adequate postoperative pain control without adverse effects and expressed high satisfaction with the anesthetic technique.

In conclusion, ultrasound-guided TAP blockade provides substantial benefits as part of a multimodal analgesic strategy for patients with massive ascites. This approach reduces the need for anesthetic drugs, stabilizes intraoperative hemodynamics, and minimizes postoperative complications, ultimately improving patient outcomes and satisfaction. Advances in ultrasound technology have further improved the safety and applicability of TAP block, reinforcing its role in the perioperative management of complex cases such as this one.

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

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patient was not required to participate in this study in accordance with the national legislation and the institutional requirements. 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

LZ: Writing – original draft. AL: Data curation, Investigation, Writing – original draft. LW: Data curation, Investigation, Writing – original draft. YZ: Writing – review & editing. ZH: Writing – review & editing.

Funding

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

Acknowledgments

The authors would like to thank Yuanyuan YU of the Department of Anesthesiology, Qingdao Hiser Hospital, for her assistance in producing these texts.

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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1541462/full#supplementary-material

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frontiers | Frontiers in Neurology

TYPE Original Research
PUBLISHED 16 April 2025
DOI 10.3389/fneur.2025.1537780

OPEN ACCESS

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RECEIVED 27 February 2025
ACCEPTED 03 April 2025
PUBLISHED 16 April 2025

CITATION
Wei L, Zhu X, Zhao Y, Zou Y, Hu T, Huang Q, Li J, Pan B, Kong G, Tan S and Chen W (2025) Dynamic changes in peripheral inflammation as a risk factor for perioperative sleep disturbances in elderly patients undergoing laparoscopic hepatobiliary surgery. *Front. Neurol.* 16:1537780. doi: 10.3389/fneur.2025.1537780

Dynamic changes in peripheral inflammation as a risk factor for perioperative sleep disturbances in elderly patients undergoing laparoscopic hepatobiliary surgery

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Background: Elderly surgical patients are at high risk of perioperative sleep disturbances (PSD), and the underlying pathogenic mechanisms remain unclear. The relationship between peripheral inflammatory status and PSD pathogenesis currently lacks substantial clinical evidence.

Objective: This study aims to evaluate the association between peripheral inflammation indicators and PSD in elderly patients undergoing laparoscopic hepatobiliary surgery, and to analyze the dynamic changes in peripheral inflammation in PSD patients throughout the perioperative period.

Method and materials: Using retrospective data, this study compares peripheral inflammatory markers (NLR, MLR, PLR, SII, IL-6, and IL-10) in patients with PSD vs. those with normal sleep patterns before and after surgery. Receiver operating characteristic (ROC) curves were employed to evaluate the discriminative power of these indicators for PSD. Logistic regression models were employed to assess risk associations between inflammatory markers and PSD. Dynamic changes in peripheral inflammation were compared before surgery, on the day the surgery ended, and 1 day post-surgery between patients with PSD and those with normal sleep, exploring potential correlations with PSD pathogenesis.

Result: The study ultimately included clinical data from 156 patients. Findings indicated that elevated NLR and SII levels before and after surgery, alongside decreased plasma IL-10 levels post-surgery, are associated with a higher incidence of PSD. Peripheral inflammatory markers on the day of surgery were not significantly predictive of post-PSD. Multivariable logistic regression analyses identified NLR, SII, IL-6, and IL-10 as independent predictors of pre-PSD, while NLR, SII, and IL-10 remained independently associated with post-PSD.

Conclusion: Dynamic changes in peripheral inflammation during the perioperative period are associated with PSD in elderly patients undergoing laparoscopic hepatobiliary surgery. These findings may support the early identification and screening of high-risk PSD patients, providing new insights into the underlying mechanisms of PSD pathogenesis.

KEYWORDS

perioperative sleep disturbances, peripheral inflammation, surgery, immune cells, elderly

1 Introduction

The incidence of sleep disturbances increases with age, placing elderly surgical patients at particularly high risk for perioperative sleep disturbance (PSD) (1, 2). PSD has been linked to heightened perioperative pain sensitivity, reduced immunity, cardiovascular complications, postoperative delirium, and other severe outcomes (1, 3, 4). Clinically, PSD remains a dilemma due to insufficient attention from both healthcare providers and patients, overshadowed by the primary disease, and a limited understanding of PSD's underlying pathogenesis (5). Given PSD's association with serious clinical outcomes, including compromised patient recovery, addressing PSD preoperatively and managing postoperative sleep crises are crucial for promoting rapid recovery (6). Therefore, the prevention and treatment of PSD are urgent priorities, and further investigation into its pathogenic mechanisms could support early identification and targeted intervention.

The perioperative period is characterized by significant fluctuations in peripheral inflammation, and growing evidence suggests a link between peripheral inflammation and reciprocal modulation of cerebral neurological functions (7, 8). Sleep, a biologically conserved behavior across species, is regulated by the central nervous system; thus, impaired neurological function may present as abnormal sleep patterns (9–11). Current understanding of both the correlation between peripheral inflammation and PSD in elderly surgical patients, as well as the perioperative dynamic changes in peripheral inflammation among elderly PSD patients, remains relatively limited. To investigate the correlation between peripheral inflammation and PSD in elderly surgical patients, this study collected data on perioperative peripheral inflammation and sleep assessments at our institution. We compared peripheral inflammation levels between patients with PSD and those with normal sleep both preoperatively and postoperatively, analyzing the relationship between PSD and inflammatory status. Given that factors like surgical site and perioperative pain status can influence PSD and peripheral inflammation, we focused on patients undergoing laparoscopic hepatobiliary surgery, applying strict inclusion and exclusion criteria to control for confounding effects. Sleep data were collected using the Numerical Rating Scale for Sleep (NRS-S) and the Athens Insomnia Scale (AIS), both reliable tools for perioperative sleep assessment (12–14). Recent clinical evidence has established blood cell component ratios as sensitive markers of inflammation and stress, such as the neutrophil-to-lymphocyte ratio (NLR) and the systemic inflammation index (SII) (15). In this study, we assessed peripheral inflammation based on routine blood test results, calculating NLR, platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and SII, and measuring plasma interleukins (IL-6 and IL-10). This study aims to clarify the relationship between peripheral inflammation and PSD pathogenesis in elderly surgical patients, identifying peripheral blood cell types and molecules potentially involved in PSD pathogenesis. These findings are expected to enhance the understanding of PSD prevention and support strategies for improved postoperative recovery.

2 Methods and materials

2.1 Study population

Data for this study were retrospectively collected from patients undergoing laparoscopic hepatobiliary surgery at the First Hospital Affiliated to Hunan Normal University (Hunan Provincial People's Hospital) between December 1, 2022, and December 30, 2023, who had undergone perioperative sleep assessments. Ethical approval was obtained from the Ethics Committee of the First Hospital Affiliated to Hunan Normal University (Approval No. [2022]-114), granting permission to access medical records. Inclusion criteria were patients aged 65–90 years, classified as ASA I–III, and scheduled for elective laparoscopic hepatobiliary surgery. Exclusion criteria included the presence of hematologic disease; end-stage conditions such as severe organ failure; history or postoperative diagnosis of malignancy; severe psychiatric illness; chronic inflammatory disease; infections; history of substance abuse; BMI $\geq$ 30; ongoing antibacterial or antiviral therapy; hypersensitivity; decompensated cardiac, pulmonary, or cerebrovascular disease; blood transfusions; medications potentially affecting routine blood test results; incomplete data; obstructive sleep apnea syndrome (OSAS); history of epilepsy, thyroid disease, food or drug allergies, chronic pain, or Parkinson's disease; surgeries ending after 6:00 p.m.; and pre- or postoperative NRS-pain (NRS-P) scores $\geq$ 3, as well as postoperative neurocognitive deficits. Patients diagnosed with PSD were assigned to the patient group, while those with normal sleep assessments were assigned to the control group.

For each patient, demographic data (age, gender, and body mass index (BMI)), comorbidities, history of smoking and alcohol use, disease severity or physical status (NYHA classification and ASA classification), perioperative indices (operation duration, recovery time, anesthetic agents, and blood loss), pain status (NRS-P), peripheral inflammation markers (NLR, MLR, PLR, SII, IL-6, and IL-10), and PSD status (NRS-S and AIS) were collected.

2.2 PSD diagnosis

All participants included in the study completed the AIS and NRS-S scales to assess sleep status preoperatively and 1 day postoperatively. The AIS score is a commonly used and recognized valid tool for sleep assessment. The scale consists of 8 questions, each of which is assigned a score based on severity, and has a total score of 24, with higher scores representing poorer sleep. The NRS-S score ranges from 0 to 10, with 0 indicating excellent or good sleep and 10 representing an inability to sleep throughout the night. PSD was defined as an NRS-S score $\geq$ 6 or an NRS-S score $\geq$ 6.

2.3 Data for peripheral inflammation

Peripheral blood cell counts were retrospectively obtained from patient medical records at three time points: preoperatively, on the day

the surgery was completed (POD0), and on postoperative day 1 (POD1). These counts were measured using a clinical blood cell analyzer (XE-2100, Sysmex, Japan) and included absolute counts of neutrophils (NEU), lymphocytes (LYM), monocytes (MON), and platelets (PLT). Various inflammatory indices were then calculated as follows: (1) NLR as NEU/LYM; (2) PLR as PLT/LYM; (3) MLR as MON/LYM; and (4) SII as PLT × NEU/LYM. Additionally, we collected data on peripheral inflammatory factors, including IL-6 and IL-10.

2.4 Statistical analysis

Statistical analysis was performed with SPSS, version 27.0 (Statistical Package for Social Sciences). The normal distribution of the variables was examined using the Kolmogorov–Smirnov test. Continuous data were presented as mean (SD) and compared using the unpaired or paired t-test, or one-way ANOVA if distributed normally. Data that were not normally distributed were reported as median (IQR) and analyzed using the Mann–Whitney test. Categorical variables were reported as number (%) and compared using χ^2 or Fisher exact test, as appropriate. Correlation analysis was performed by Spearman's correlation analysis. Receiver operating characteristic (ROC) curves were plotted separately for each index of peripheral inflammation, and the diagnostic efficacy was assessed by comparing the area under the curve (AUC). Binary logistic regression models were implemented to evaluate associations between peripheral inflammatory marker levels and PSD risk, with PSD status as the dependent variable and inflammatory biomarkers as independent variables. Subsequent analyses further adjusted for covariate interactions between biomarkers and age, gender, preoperative AIS and NRS-S scores, and recovery length. All association estimates were quantified as odds ratios (ORs) with corresponding 95% confidence intervals (CIs). Two-sided $p < 0.05$ was considered to be statistically significant.

3 Results

3.1 Patients' characteristics

A total of 293 patients were assessed for eligibility, with 137 patients excluded based on the exclusion criteria (Figure 1). A final sample of 156 patients was enrolled in the study, including 81 (52%) males and 75 (48%) females, with a mean age of 72.5 years. Two cohorts were created to identify risk factors related to peripheral inflammation that may influence PSD before and after surgery. In Cohort I (Table 1), patients were divided into those with preoperative PSD (pre-PSD; $n = 36$, 23%) and those without pre-PSD ($n = 120$, 77%). In Cohort II (Table 2), patients were divided based on postoperative PSD status, with 75 (48%) in the post-PSD group and 81 (52%) in the non-post-PSD group. We compared age, gender, BMI, smoking status, alcohol use, coronary heart disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD),

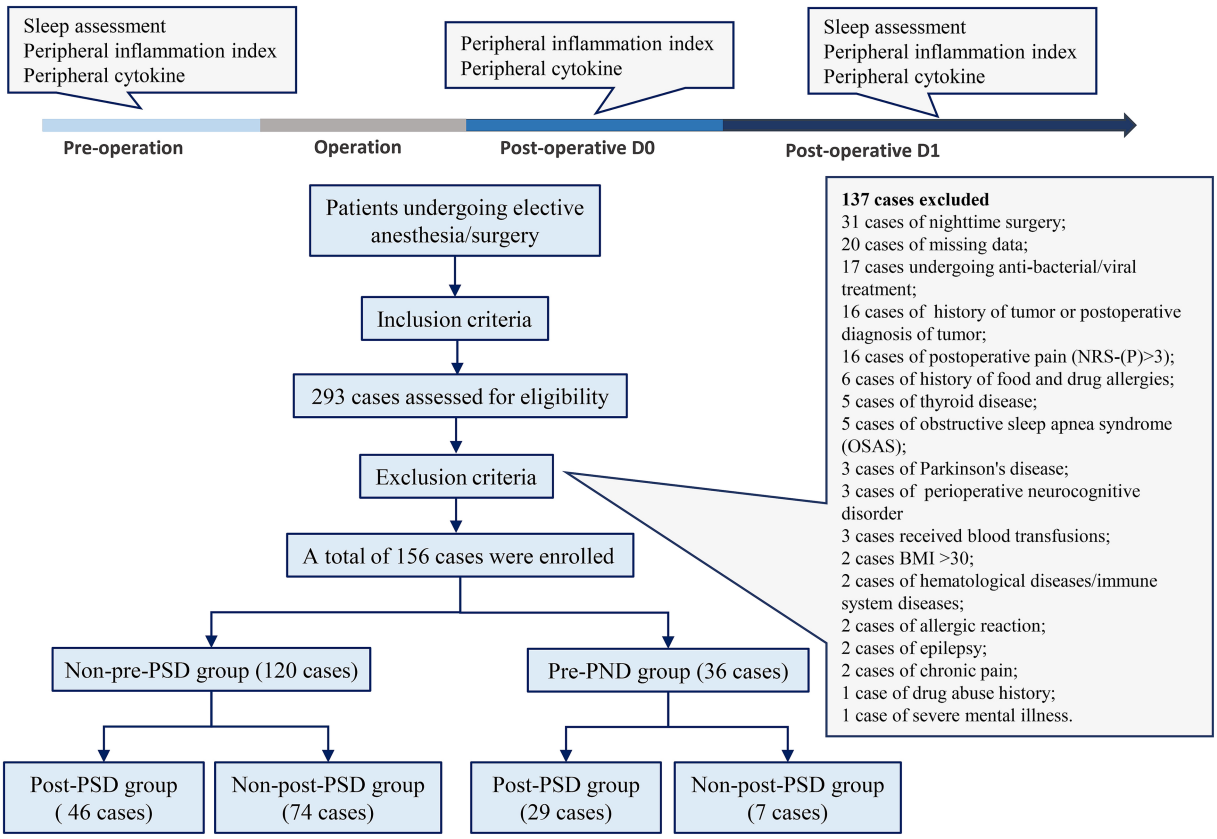

FIGURE 1
Participant flowchart.

TABLE 1 Comparison of baseline characteristics between the non-pre-PSD and the pre-PSD groups.

Baseline data	Non-pre-PSD (n = 120)	pre-PSD (n = 36)	p-value
Age (y), median (IQR)	72 (68–77)	71 (66–75)	0.46
Gender (male), No. (%)	67 (56)	18 (50)	0.57
BMI, median (IQR)	18.5 (16.4–20.3)	19 (16.7–20.2)	0.19
ASA classification			
I, No. (%)	25 (21)	6 (17)	0.85
II, No. (%)	71 (59)	22 (61)	
III, No. (%)	24 (20)	8 (22)	
Hypertension, No. (%)	32 (27)	13 (36)	0.30
Diabetes mellitus, No. (%)	8 (7)	5 (14)	0.18
Coronary heart disease, No. (%)	13 (11)	6 (17)	0.39
COPD, No. (%)	7 (6)	3 (8)	0.70
NYHA classification			
I, No. (%)	98 (82)	25 (69)	0.16
II, No. (%)	22 (18)	11 (31)	
Drinking, No. (%)	28 (23)	7 (19)	0.82
Smoking, No. (%)	29 (24)	10 (28)	0.67
Pre-NRS-P, median (IQR)	1 (0–1)	1 (0–1)	0.23
Pre-AIS, median (IQR)	3 (3–4)	6 (6–7)	<0.001
Pre-NRS-S, median (IQR)	3 (2–4)	6 (5–6)	<0.001

AIS, Athens Insomnia Scale; ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; NRS-P, numeric rating scale-pain; NRS-S, numeric rating scale-sleep; NYHA, New York Heart Association; PSD, perioperative sleep disturbance. Data presented as median (IQR) were compared using the Mann–Whitney test. Data reported as the number of patients (%) were compared using the χ^2 test or Fisher exact test.

thyroid disease, and physical condition between the groups to ensure comparability. The post-PSD and non-post-PSD groups differed in recovery time as well as preoperative AIS and NRS-S scores (Table 2).

3.2 High levels of preoperative peripheral inflammation are associated with the development of both pre-/post-PSD

We initially analyzed preoperative sleep quality and peripheral inflammation in elderly patients undergoing elective laparoscopic hepatobiliary surgery. Our findings indicated that levels of peripheral inflammatory markers, including NLR, SII, IL-6, and IL-10, were significantly higher in patients with pre-PSD compared to those with normal sleep patterns (non-pre-PSD) (Figures 2A–D). Correlation analysis further revealed significant linear relationships between preoperative NLR, SII, IL-6, and IL-10 levels and preoperative sleep scores assessed by the AIS and NRS-S (Figures 2E–H). Results of the unadjusted analyses and multivariable models are presented in Table 3. Models were created to adjust the associations between the biomarkers and outcomes for age and gender based on previous studies as deemed clinically relevant (1, 16). After adjustment, the preoperative level of NLR, SII, IL-6, and IL-10 were all associated with pre-PSD in separate models. Subsequently, we constructed ROC curves to evaluate the diagnostic efficacy of these markers for pre-PSD. Among these, preoperative SII showed the highest diagnostic value (AUC = 0.82), followed by NLR, IL-6, and IL-10, with AUCs of 0.64, 0.63, and 0.76, respectively (Figures 2I–L). The combined diagnostic efficacy of all four markers achieved an 0.86 (Figure 2M). These findings suggest a significant association between preoperative peripheral inflammatory status and sleep disturbances.

Since the incidence of post-PSD was significantly higher in patients with pre-PSD than in those with normal preoperative sleep (80% in the pre-PSD group vs. 38% in the non-pre-PSD group, $p < 0.0001$), this suggests that postoperative sleep is substantially influenced by preoperative sleep conditions (Figure 3A). To further examine this relationship, we divided preoperative peripheral inflammation levels into two categories, using the median as a cutoff, and assessed their effects on postoperative sleep. The results indicated that postoperative sleep scores were higher (reflecting poorer sleep) in patients with elevated preoperative levels (≥ median) of NLR, SII, IL-6, and IL-10 (Figures 3B,C). Additionally, the AUC values for preoperative NLR, SII, IL-6, and IL-10 in predicting post-PSD were 0.69, 0.65, 0.55, and 0.59, respectively, with a combined diagnostic/predictive AUC of 0.7 (Figures 3D–H).

The differences in peripheral MLR and PLR between patients with pre-PSD and those with normal sleep were not statistically significant, with AUC values for pre- and post-PSD ranging from 0.51 to 0.58 (Supplementary Figure S1). Given that the inflammatory index is derived from blood cell components, we compared levels of NEU, LYM, MON, and PLT between the pre-PSD and non-pre-PSD groups. The results indicated that, aside from NEU levels, there were no significant differences in these blood cell components between the two groups (Supplementary Figure S1).

TABLE 2 Comparison of baseline characteristics between the non-post-PSD and the post-PSD groups.

Baseline data	Non-post-PSD (*n* = 81)	Post-PSD (*n* = 75)	*p*-value
Age (y), median (IQR)	72 (66–76)	72 (68–77)	0.60
Gender (male), No. (%)	45 (56)	40 (53)	0.87
BMI, median (IQR)	19.5 (16.9–22.9)	18.3 (16.3–21.5)	0.08
ASA classification			
I, No. (%)	17 (21)	14 (19)	0.80
II, No. (%)	49 (60)	44 (58)	
III, No. (%)	15 (19)	17 (23)	
Hypertension, No. (%)	25 (31)	20 (27)	0.60
Diabetes mellitus, No. (%)	5 (6)	8 (11)	0.39
Coronary heart disease, No. (%)	11 (14)	8 (11)	0.81
COPD, No. (%)	6 (7)	4 (5)	0.75
NYHA classification			
I, No. (%)	65 (80)	58 (77)	0.70
II, No. (%)	16 (20)	17 (23)	
Drinking, No. (%)	16 (20)	19 (25)	0.45
Smoking, No. (%)	22 (27)	17 (23)	0.58
Preoperative variables			
Pre-NRS-P, median (IQR)	0 (0–1)	1 (0–1)	0.27
Pre-PSD, No. (%)	7 (8.6)	29 (38.7)	<0.001
Pre-AIS, median (IQR)	3 (3–4)	3 (3–6)	0.007
Pre-NRS-S, median (IQR)	3 (2–4)	4 (2–6)	0.03
Intraoperative variables			
Operation duration (min), median (IQR)	90 (70–120)	105 (85–125)	0.13
Recovery length (min), median (IQR)	22 (18–30)	26 (21–32)	0.02
Bleeding (mL), median (IQR)	20 (20–50)	20 (2–100)	0.88
Porpofol (mg/kg), median (IQR)	3.69 (2.83, 4.75)	4.05 (3.22, 4.84)	0.14
Sufentanil (ug/kg), mean (SD)	0.67 (0.20)	0.71 (0.20)	0.14
Remifentanil (ug/kg), median (IQR)	7.64 (5.56, 10.38)	7.30 (5.52, 8.67)	0.17
Vecuronium bromide (mg/kg), median (IQR)	0.19 (0.14, 0.24)	0.18 (0.15, 0.21)	0.73
Postoperative variables			
Analgesic remedy, No. (%)	14 (17)	12 (16)	0.99
Pod0-NRS-P, median (IQR)	2 (2–2)	2 (2–2)	0.12
Pod1-NRS-P, median (IQR)	1 (1–2)	1 (1–2)	0.22
Post-AIS, median (IQR)	5 (4–5)	9 (7–14)	<0.001
Post-NRS-S, median (IQR)	5 (4–5)	7 (6–8)	<0.001

AIS, Athens Insomnia Scale; ASA, American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; NRS-P, numeric rating scale-pain; NRS-S, numeric rating scale-sleep; NYHA, New York Heart Association; PSD, perioperative sleep disturbance. Data presented as median (IQR) were compared using the Mann–Whitney test. Data reported as the number of patients (%) were compared using the χ^2 test or Fisher exact test.

3.3 Peripheral inflammatory features at POD0 have no significant predictive potential for post-PSD

Only elevated levels (≥ median) of peripheral IL-6 on POD0 were associated with significant differences in postoperative AIS scores (Supplementary Figure S2). The AUC values for the predictive efficacy of NLR, SII, MLR, PLR, IL-6, and IL-10 in discriminating post-PSD were 0.55, 0.52, 0.53, 0.54, 0.56, and 0.52, respectively (Supplementary Figure S2). These findings suggest that peripheral inflammation on POD0 has limited discriminatory ability for post-PSD.

3.4 Post-PSD patients are accompanied by persistent activation of peripheral inflammation

This study included 81 elderly surgical patients with normal postoperative sleep (non-post-PSD) and 75 patients with

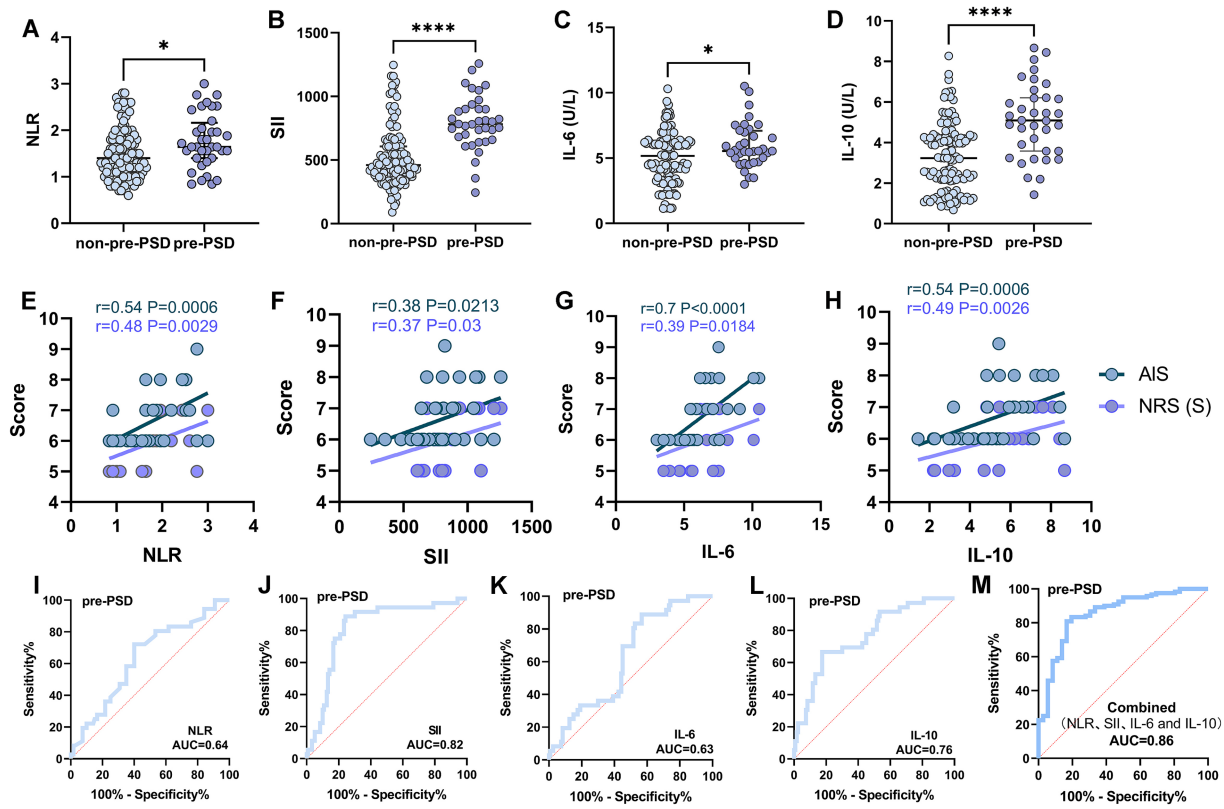

FIGURE 2
Comparison and correlation analysis of peripheral inflammatory parameters in patients with non-pre-PSD and pre-PSD. **(A–D)** Comparison of peripheral blood NLR **(A)**, SII **(B)**, IL-6 **(C)**, and IL-10 **(D)** levels between non-pre-PSD and pre-PSD patients; **(E–H)** Correlation of preoperative NLR **(E)**, SII **(F)**, IL-6 **(G)**, and IL-10 **(H)** levels with sleep status in pre-PSD patients (n = 36); **(I–L)** ROC curves illustrating the discriminatory efficacy of preoperative NLR **(I)**, SII **(J)**, IL-6 **(K)**, and IL-10 **(L)** between pre-PSD and non-pre-PSD groups; **(M)** Evaluation of the discriminatory ability of combined preoperative NLR, SII, IL-6, and IL-10 on the pre-PSD and non-pre-PSD patients. *p < 0.05; ****p < 0.0001.

TABLE 3 **Preoperative NLR, SII, IL-6, and IL-10 were associated with the risk of pre-PSD.**

Items	Presence of pre-PSD			
	Unadjusted		Adjusted for age and sex	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
NLR	2.18 (1.15, 4.21)	0.018	2.17 (1.13, 4.25)	0.022
SII	1.04 (1.03, 1.06)	<0.001	1.05 (1.03, 1.07)	<0.001
IL-6	1.29 (1.07, 1.60)	0.012	1.30 (1.07, 1.60)	0.011
IL-10	1.76 (1.40, 2.28)	<0.001	1.80 (1.42, 2.34)	<0.001

OR, odds ratio; 95% CI, 95% confidence interval.

post-PSD. Peripheral inflammation data for these patients were collected preoperatively, as well as on POD0 and POD1, to observe dynamic changes in inflammation associated with the development of PSD. Compared to the non-post-PSD group, post-PSD patients exhibited significantly higher NLR and SII levels and lower IL-10 levels at POD1, with no significant difference observed in IL-6 levels between the two groups (Figures 4A–D). In the crude models, increased postoperative level of NLR and SII, lower level of IL-10, were associated with an increase incidence of post-PSD. This association persisted after adjustment for age, gender, pre-AIS, pre-NRS-S, and recovery time (Table 4). The AUC values for postoperative NLR, SII, IL-6, and IL-10 in predicting post-PSD were 0.74, 0.62, 0.54, and 0.63, respectively (Figures 4E–H), with a combined AUC of 0.74 for all four indices (Figure 4I). No significant differences were found in MLR or PLR levels between the two groups on POD1 (Supplementary Figure S3).

A significant elevation in inflammatory markers was observed in all patients on POD0 compared to the preoperative period. Analysis of the non-post-PSD group revealed a substantial decrease in NLR and SII levels at POD1 compared to POD0, while IL-6 and IL-10 levels remained largely unchanged (Figures 4A–D). In contrast, in post-PSD patients, NLR, SII, and IL-6 levels at POD1 showed no significant difference from POD0, while IL-10 levels were significantly lower at POD1 (Figures 4A–D). These findings indicate distinct patterns of

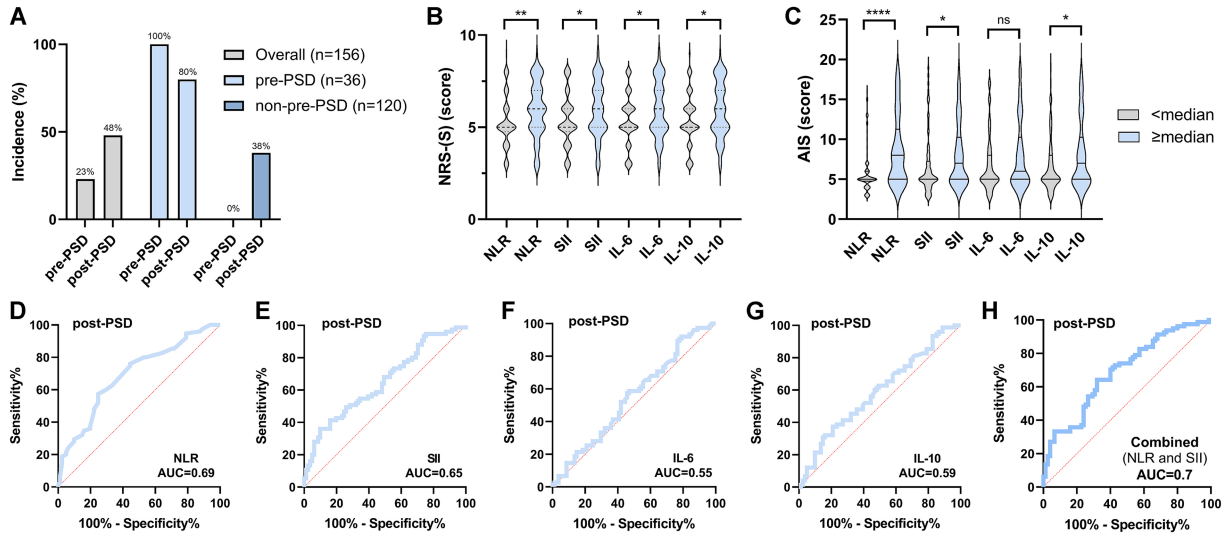

FIGURE 3
Preoperative sleep condition and peripheral inflammatory status significantly affect postoperative sleep. **(A)** Comparison of the incidence of post-PSD between patients in the pre-PSD and non-pre-PSD groups; **(B)** Effect of preoperative high/low levels of NLR, SII, IL-6, and IL-10 on postoperative NRS-S scores; **(C)** Effect of preoperative high/low levels of NLR, SII, IL-6, and IL-10 on postoperative AIS scores; **(D–G)** ROC curves of preoperative peripheral blood NLR **(D)**, SII **(E)**, IL-6 **(F)**, and IL-10 **(G)** differentiating between post-PSD and non-post-PSD patients; **(H)** Evaluation of the discriminatory ability of combined preoperative NLR, SII, IL-6, and IL-10 on the post-PSD and non-post-PSD patients. ns, not significant; *$p < 0.05$; **$p < 0.01$; ****$p < 0.0001$.

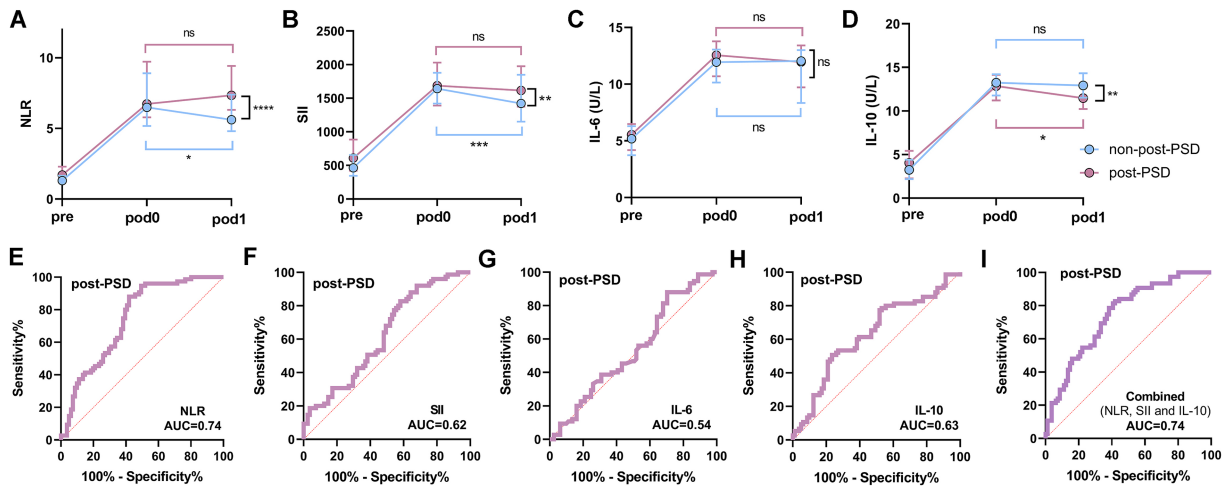

FIGURE 4
Dynamic analysis of perioperative peripheral inflammatory status in post-PSD and non-post-PSD patients. **(A–D)** Comparison of peripheral blood NLR **(A)**, SII **(B)**, IL-6 **(C)**, and IL-10 **(D)** levels between post-PSD and non-post-PSD patients at different periods; **(E–H)** ROC curves of postoperative (POD1) peripheral blood NLR **(E)**, SII **(F)**, IL-6 **(G)**, and IL-10 **(H)** differentiating between post-PSD and non-post-PSD patients; **(I)** Evaluation of the discriminatory ability of combined postoperative NLR, SII, IL-6, and IL-10 on the post-PSD and non-post-PSD patients. ns, not significant; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

peripheral inflammatory changes between the two groups in the postoperative period, with post-PSD patients experiencing sustained peripheral inflammation from POD0 to POD1, suggesting an imbalance in the body's proinflammatory and anti-inflammatory responses.

Given that NLR and SII are calculated based on NEU, LYM, and PLT counts, we further analyzed these blood cell levels in both groups. The results showed that NEU levels were significantly higher in post-PSD patients than in non-post-PSD patients at POD1, while LYM levels were significantly lower, with no significant differences observed in PLT or MON levels between the two groups (Supplementary Figure S4). In both non-post-PSD and post-PSD groups, NEU and LYM levels at POD1 were not significantly different from POD0 (Supplementary Figure S5). Interestingly, we found that surgery/anesthesia resulted in a significant increase in peripheral NEU levels and a significant decrease in LYM counts in both groups (Supplementary Figure S5). These findings suggest that the dynamic changes in NEU and LYM levels induced by surgery and anesthesia

TABLE 4 Postoperative NLR, SII, and IL-10 were associated with the risk of pre-PSD.

Items	Presence of post-PSD			
	Unadjusted		Adjusted for age, sex, pre-AIS, pre-NRS-S, and recovery length	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
NLR	1.23 (1.08, 1.44)	0.007	1.23 (1.07, 1.45)	0.01
SII	1.01 (1.00, 1.02)	0.005	1.01 (1.00, 1.02)	0.009
IL-6	1.08 (0.97, 1.21)	0.17	1.04 (0.92, 1.17)	0.55
IL-10	0.84 (0.72, 0.96)	0.02	0.83 (0.71, 0.95)	0.01

OR, odds ratio; 95% CI, 95% confidence interval.

contribute to the alterations in NLR and SII and may be associated with the development of post-PSD.

4 Discussion

This study provides evidence of a correlation between peripheral inflammatory status and PSD in elderly surgical patients. Our findings revealed that elevated preoperative peripheral blood levels of NLR, SII, IL-6, and IL-10 were associated with increased pre-PSD incidence, and post-PSD occurrence correlated with higher NLR/SII and lower IL-10 levels. Specifically, those with poorer preoperative sleep showed significantly heightened peripheral inflammatory activation. Additionally, the results suggest that preoperative sleep disturbances are more likely to persist into the postoperative period. Based on these findings, we stratified patients by preoperative inflammatory marker levels to assess the effects of high vs. low preoperative peripheral inflammation on postoperative sleep outcomes. Patients with elevated preoperative peripheral inflammation demonstrated poorer postoperative sleep scores, suggesting that perioperative sleep status in elderly surgical patients is influenced by preoperative or long-term sleep conditions, potentially mediated by peripheral inflammation.

We also found that while peripheral inflammation levels at POD0 had little discriminatory power for postoperative PSD, all patients experienced a significant inflammatory response likely due to anesthesia- and surgery-induced stress and tissue injury. During the perioperative period, patients are exposed to a complex array of stressors, which may obscure the relationship between peripheral inflammation and PSD. Among elderly patients who developed PSD postoperatively, peripheral inflammation levels were elevated relative to those without PSD, although IL-6 levels did not differ significantly. Notably, postoperative PSD patients had lower peripheral IL-10 levels, which is interesting as higher preoperative IL-10 levels were positively associated with PSD pathogenesis. In the postoperative phase, IL-10 levels were significantly elevated in all patients compared with preoperative levels. Given IL-10's role as an anti-inflammatory mediator, contributing to the initiation of anti-inflammatory responses and the maintenance of immune-inflammatory homeostasis (17). These findings may reflect the body's attempt to restore balance in preoperative PSD patients. Importantly, postoperative PSD patients had relatively lower IL-10 levels than non-PSD patients, suggesting a reduced anti-inflammatory capacity that could exacerbate inflammation, potentially contributing to PSD pathogenesis.

In this study, NLR and SII were screened as significant factors associated with PSD due to remarkable level differences. Higher levels of both were associated with the occurrence of PSD both preoperatively and at POD1. Both NLR and SII reflect the peripheral systemic inflammatory immune state of the body, and several studies have provided evidence of the value of NLR and SII for the diagnosis/prognosis of related diseases. For example, NLR predicts in-hospital mortality/survival in patients with extensive burns after hospital admission and in patients with sepsis (18, 19). Similarly, in the general population, SII is significantly associated with all-cause cardiovascular disease causation (20). To clarify the reasons leading to elevated levels of NLR and SII, we analyzed the differences in preoperative and postoperative NEU and LYM, as well as PLT levels in different cohorts of patients. We found that peripheral NEU levels were significantly higher in older patients with preoperative sleep disturbances than in patients with normal sleep, whereas LYM and PLT levels were similar in both groups, so higher NLR and SII values may be associated with higher NEU levels. Notably, in contrast to the significant increase in NEU after surgery compared with a preoperative period, peripheral LYM levels were reduced in both groups at POD0 and POD1. Active neutrophil proliferation *in vivo* due to surgical and tissue trauma has been demonstrated in several studies (21, 22), and there is also evidence of functional inhibition and reduction in the number of peripheral LYMs induced by anesthesia/surgical exposure, as well as accelerated programmed death processes (23–27), which is in line with the reduction in the number of LYMs observed in this study.

The mechanisms underlying the association between peripheral inflammatory alterations and perioperative sleep homeostasis in elderly populations represent a critically important issue, with three key aspects warranting in-depth exploration: First, can fluctuations in peripheral inflammation affect sleep? Second, can sleep disturbances induce peripheral inflammatory activation? Third, are elderly individuals more susceptible to sleep dysregulation under peripheral inflammatory states? Experimental animal studies have indeed identified bidirectional sleep-immune interactions (28–30). On the one hand, inflammatory cytokines exhibit circadian rhythmicity, and their daytime elevation during illness or irregular sleep patterns disrupt sleep architecture (28). Previous research has shown that rodents exposed to lipopolysaccharide (LPS)-induced inflammation display altered sleep architecture, including dysregulation in the ratio of REM to non-REM sleep, increased EEG delta activity in non-REM sleep, and impaired sleep continuity (31–34). Additionally, sleep deprivation in mice is linked to compromised immune function, resulting in increased susceptibility to infectious and inflammatory diseases (35). Prolonged sleep deprivation in mammals has been associated with the accumulation of circulating neutrophils and a cytokine storm-like syndrome (36, 37). These findings suggest a

bidirectional relationship between peripheral inflammation and sleep status. In elderly patients, age-related immunosenescence (characterized by elevated baseline inflammation and impaired anti-inflammatory capacity) (38) and compromised BBB integrity (39, 40) create synergistic vulnerabilities. Peripherally activated inflammatory responses can disrupt functional brain network connectivity, while excessive peripheral inflammation may induce neuroinflammation. Pro-inflammatory mediators released by activated glial cells can lead to synaptic dysfunction, accelerated programmed neuronal death, and a range of neurocognitive complications (39, 41). These findings collectively suggest that elderly surgical patients may not only exhibit increased susceptibility to sleep disturbances due to compromised peripheral inflammatory homeostasis but also experience exacerbated systemic immune-inflammatory responses secondary to abnormal sleep patterns, thereby establishing a self-reinforcing pathophysiological loop.

There are limitations to this study. We retrospectively collected perioperative data from elderly patients undergoing hepatobiliary surgery. Whereas both sleep and peripheral immune status are influenced by a variety of factors, we tried to control for effects by excluding factors such as pain, Parkinson's disease, and chronic inflammation, but as an observational study, the ability to infer causality is limited. Retrospective study designs introduce the risk of bias and unmeasured sources of confounding by other factors that cannot be fully mitigated by the use of exclusion strategies. We stratified the level of peripheral inflammation preoperatively and postoperatively to explore the sleep of people with different levels of peripheral inflammation, respectively. This analysis was considered exploratory because we did not compare baseline data for the stratified populations, and the sample size for stratification was determined based on the population of participants already included in this study, which did not ensure adequate test efficacy. Other limitations are that the sample size of this study was small, partly because we had limited access to cases with documented sleep assessments. In addition, this study did not include the inclusion of sleep architecture data. Our subsequent research agenda will focus on conducting prospective studies with expanded sample sizes and broader inclusion of peripheral inflammatory biomarkers, coupled with prolonged observation windows and integration of multidimensional sleep assessment methodologies (including polysomnography and actigraphy), to systematically investigate the impact of peripheral inflammation on specific sleep architecture features such as sleep duration, arousal frequency, REM sleep, and NREM sleep characteristics.

5 Conclusion

This retrospective study investigated the correlation between postoperative sleep disturbances (PSD) and perioperative peripheral inflammatory dynamics in elderly patients undergoing laparoscopic hepatobiliary surgery. Key findings revealed that elevated preoperative/postoperative NLR and SII, coupled with reduced postoperative IL-10 levels, were significantly associated with increased PSD incidence. These discoveries provide novel insights for early identification of high-risk PSD populations and establish new pathways for elucidating the pathogenic mechanisms underlying PSD development.

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 First Hospital Affiliated to Hunan Normal University. 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

LW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. XZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. YZh: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. YZo: Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. TH: Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. QH: Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. JL: Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. BP: Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. GK: Data curation, Formal analysis, Funding acquisition, Methodology, Validation, Writing – review & editing. ST: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. WC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by grants partly from the Clinical Medical Technology Innovation Guidance Project of Hunan Province (no. 2021SK50907) and the Perioperative Enhanced Recovery Anesthesia Clinical Medical Research Center of Hunan Province (no. 2018SK7001).

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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2025.1537780/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Clinical Trial
PUBLISHED 22 April 2025
DOI 10.3389/fmed.2025.1573150

OPEN ACCESS

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RECEIVED 08 February 2025
ACCEPTED 02 April 2025
PUBLISHED 22 April 2025

CITATION
Luo Y, Qin S, Liu M, Shen Q, An R and Jiang Y (2025) Individualized positive end-expiratory pressure guided by driving pressure in robot-assisted laparoscopic radical prostatectomy: a prospective, randomized controlled clinical trial. *Front. Med.* 12:1573150. doi: 10.3389/fmed.2025.1573150

Individualized positive end-expiratory pressure guided by driving pressure in robot-assisted laparoscopic radical prostatectomy: a prospective, randomized controlled clinical trial

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Background: Despite the widespread use of lung-protective ventilation in general anesthesia, the optimal positive end-expiratory pressure (PEEP) remains uncertain. This study aimed to investigate the effects of driving pressure-guided individualized PEEP in patients undergoing robot-assisted laparoscopic radical prostatectomy.

Methods: Forty-two male patients undergoing robot-assisted laparoscopic radical prostatectomy were randomized to receive conventional fixed PEEP of 5 cmH_2O (n = 21, $PEEP_5$) or driving pressure-guided individualized PEEP (n = 21, $PEEP_{IND}$). The primary outcome was the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2). The secondary outcomes included respiratory mechanics, hemodynamics, optic nerve sheath diameter (ONSD), and the incidence of postoperative delirium (POD) and postoperative pulmonary complications (PPCs) within a 7-day period.

Results: In comparison with the $PEEP_5$ group, the $PEEP_{IND}$ group showed significantly higher ($p < 0.001$) PEEP values during pneumoperitoneum in the Trendelenburg position (mean [standard deviation], 11.29 cmH_2O [1.01 cmH_2O]) and after deflation and repositioning to the supine position (mean [standard deviation], 7.05 cmH_2O [1.20 cmH_2O]). The PaO_2/FiO_2 values in the $PEEP_{IND}$ group were significantly higher than those in the $PEEP_5$ group 120 min after pneumoperitoneum in the Trendelenburg position (p = 0.023) and at the end of the operation (p = 0.028). The groups showed no differences in ONSD, hemodynamics, and incidence of POD and PPCs ($p > 0.05$).

Conclusion: In comparison with a fixed PEEP of 5 cmH_2O, driving pressure-guided individualized PEEP improves intraoperative respiratory mechanics and oxygenation without causing deterioration in hemodynamics, further escalation in intracranial pressure, or an increase in the incidence of POD. Nevertheless, this procedure requires meticulous monitoring. Unfortunately, individualized PEEP did not result in a reduction in the incidence of PPCs in this study.

Clinical Trial Registration: http://www.chictr.org.cn, ChiCTR2400081338.

KEYWORDS

positive end-expiratory pressure, driving pressure, pulmonary gas exchange, lung protection ventilation, intracranial hypertension, postoperative delirium, radical prostatectomy

1 Introduction

Robot-assisted laparoscopic radical prostatectomy has become an increasingly popular procedure among surgeons due to several advantages, including minimal surgical trauma and blood loss, preservation of nerve structures, and facilitation of faster postoperative recovery (1). However, it is important to note that pneumoperitoneum and the steep Trendelenburg position, which are essential for achieving adequate surgical exposure, can elevate intra-abdominal pressure. This, in turn, can exacerbate atelectasis during general anesthesia, leading to detrimental effects on respiratory mechanics (2). Positive end-expiratory pressure (PEEP) plays a critical role in preventing small-airway collapse, maintaining alveolar patency, reducing atelectasis, and improving lung function (3). However, conventional fixed PEEP of 5 cmH_2O is often insufficient to prevent alveolar collapse under conditions of elevated intra-abdominal pressure and diaphragmatic displacement (4, 5), necessitating higher PEEP levels in certain scenarios. Studies suggested that PEEP up to 15 cmH_2O may be required to mitigate airway collapse and ventilation heterogeneity induced by the Trendelenburg position (6, 7). However, excessive PEEP carries risks of lung hyperinflation, inflammatory mediator release, and hemodynamic compromise (7, 8). Given the significant inter-individual variability in optimal PEEP levels, a standardized "one-size-fits-all" approach is suboptimal (9). Therefore, individualized PEEP ($PEEP_{IND}$), tailored to patient-specific factors, pneumoperitoneum pressure, and body position, may provide superior lung protection compared to fixed PEEP strategies.

Although various methods can be used for titrating individualized PEEP (4, 9–12), driving pressure-guided individualized PEEP titration can be performed without any special equipment other than the anesthesia machine. Studies have demonstrated that the incidence of postoperative pulmonary complications (PPCs) can be reduced exclusively by modifying ventilatory parameters with the objective of reducing driving pressure (13, 14). Consequently, a ventilation strategy involving individualized titration of PEEP guided by a minimum driving pressure has the potential to optimize intraoperative respiratory mechanics, improve oxygenation, reduce PPCs, and promote recovery. Kim et al. (15) found that the driving pressure-guided PEEP group showed improved intraoperative oxygenation, but did not show a reduction in the incidence of PPCs. However, in clinical practice, we found that in decremental PEEP trials guided by driving pressure, the minimum driving pressure corresponded to a range of PEEP values rather than a specific point, which had not been explicitly stated in previous studies. Therefore, the present study defined the minimum PEEP value within the specified range corresponding to the lowest driving pressure as the individualized PEEP ($PEEP_{IND}$) and investigated whether it could improve oxygenation and postoperative recovery.

Pneumoperitoneum and the Trendelenburg position have been observed to cause a series of physiological changes in patients, including alterations to the respiratory and cardiovascular systems as well as an increased intracranial pressure (ICP) (16, 17). An elevated ICP could result in delayed emergence from general anesthesia, postoperative delirium (POD), and a decline in cognitive function (18–20). Non-invasive ocular sonography is a well-established method of evaluating ICP (21–23). The issue of whether supplying patients with individualized PEEP will lead to further disruption of hemodynamics and the exacerbation of the rise in intracranial pressure, potentially leading to POD, remains to be evaluated.

2 Patients and methods

This single center randomized controlled trial was approved by the ethics committee of Chongqing University Cancer Hospital and registered at http://www.chictr.org.cn (registration No.: ChiCTR2400081338) on 28/02/2024. This study was conducted from March 2024 to November 2024, and informed consent was obtained from all patients before enrolment.

2.1 Participants

2.1.1 Inclusion criteria

The study population consisted of patients scheduled to undergo robot-assisted laparoscopic radical prostatectomy who were aged ≥18 years and had BMI < 30 and >18.5 kg/m^2, American Society of Anesthesiologists physical status I-III, and a moderate or high risk of PPCs based on a Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score ≥ 26.

2.1.2 Exclusion criteria

Patients were excluded from the study if they had experienced heart failure (New York Heart Association classification III or greater), had a history of severe cardiopulmonary diseases, atrial fibrillation, neuromuscular dysfunction, increased ICP or glaucoma, preoperative mini-mental state examination score < 24, undergone conversion to open approach, or showed life-threatening complications due to intraoperative hemorrhage.

2.1.3 Randomization and blinding

The randomization sequence was generated using a computer program by an investigator not involved in the study. A total of 58

Abbreviations: ASA, American Society of Anesthesiologists physical status; ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ANOVA, Analysis of variance; BMI, Body mass index; CI, Cardiac index; ICP, Intracranial pressure; MAP, Mean arterial pressure; ONSD, Optic nerve sheath diameter; PaO2/FiO2, The ratio of arterial oxygen partial pressure to fractional inspired oxygen; PEEP, Positive end-expiratory pressure; PEEP5, Positive end-expiratory pressure of 5 cmH2O; PEEPIND, Individualized positive end-expiratory pressure; POD, Postoperative delirium; PPCs, Postoperative pulmonary complications; PaCO2, Arterial partial pressure of carbon dioxide; RM, Recruitment maneuver; SVV, Stroke volume variation.

patients who underwent robot-assisted laparoscopic radical prostatectomy were recruited, and 42 patients were eventually enrolled and randomized into two groups: a conventional group that received fixed PEEP of 5 cm H_2O ($PEEP_5$ group, $n = 21$) and an individualized PEEP group in which PEEP was guided by the minimum driving pressure ($PEEP_{IND}$ group, $n = 21$). The random allocation sequence was sealed in an opaque envelope and released to the attending anaesthesiologist immediately before the trial. The surgeons, patients, and independent investigators who performed the data collection and analysis were all blinded to group allocation, but the attending anaesthesiologist was not blinded to study group allocation. The flow chart of the study is shown in Figure 1.

2.2 Study protocol

After admission to the operating theater, the patient underwent routine monitoring of peripheral pulse oximetry, electrocardiography, non-invasive blood pressure, and heart rate data, and a peripheral venous catheter was inserted to allow fluid infusion. In addition, an arterial cannula was inserted and connected to Most-care (Vytech health, PROJECT ENGINEERING, Italy) for continuous monitoring of blood pressure, cardiac index, and stroke volume variation and for arterial blood gas sampling.

After induction of anesthesia and endotracheal intubation, patients were mechanically ventilated (WATO EX—65 Pro, Mindray, China) in a volume-controlled mode with PEEP of 5 cmH_2O. Other settings included a tidal volume of 6–8 mL/kg of predicted body weight (50 + 0.91 × [height (cm) – 152.4]), 20% inspiratory pause, inspiratory oxygen fraction of 0.4, inspiratory to expiratory (I: E) ratio of 1:2, and a respiration rate adjusted for an end-tidal carbon dioxide partial pressure in the range of 35–45 mmHg. Patients received volume expansion to maintain the stroke volume variation (SVV) to less than 13% prior to the recruitment maneuver (RM). In both groups, the first RM was performed after intubation. After the first RM, the PEEP was decreased to 5 cmH_2O in the $PEEP_5$ group and then maintained throughout the surgery. In the $PEEP_{IND}$ group, a decremental PEEP-titration trial (volume-controlled ventilation mode as mentioned above) was then initiated immediately at the end of the first RM. During this trial, the minimum driving pressure was documented by reducing PEEP in 2-cmH_2O decrements from 20 cmH_2O to 4 cmH_2O. The minimal PEEP corresponding to the minimum driving pressure was defined as the $PEEP_{IND}$. Following PEEP titration, a second RM was performed immediately in the $PEEP_{IND}$ group. Subsequent mechanical ventilation was then conducted with $PEEP_{IND}\_1$ (defined as $PEEP_{IND}$ level determined in supine position).

For patients in the $PEEP_{IND}$ group, the third RM was initiated after establishing a pneumoperitoneum of 12 mmHg in the 25° Trendelenburg position. At the end of the RM, an additional PEEP-titration trial for $PEEP_{IND}\_2$ was initiated, which was immediately followed by a fourth RM. The patient was then mechanically ventilated with $PEEP_{IND}\_2$ until the pneumoperitoneum was deflated and the patient was repositioned in the supine position. $PEEP_{IND}\_2$ was then adjusted to $PEEP_{IND}\_1$ for mechanical ventilation until the end to prevent further lung hyperinflation. The tidal volume was maintained unchanged until extubation in both groups. All RMs were uniformly performed in pressure-controlled ventilation mode, with

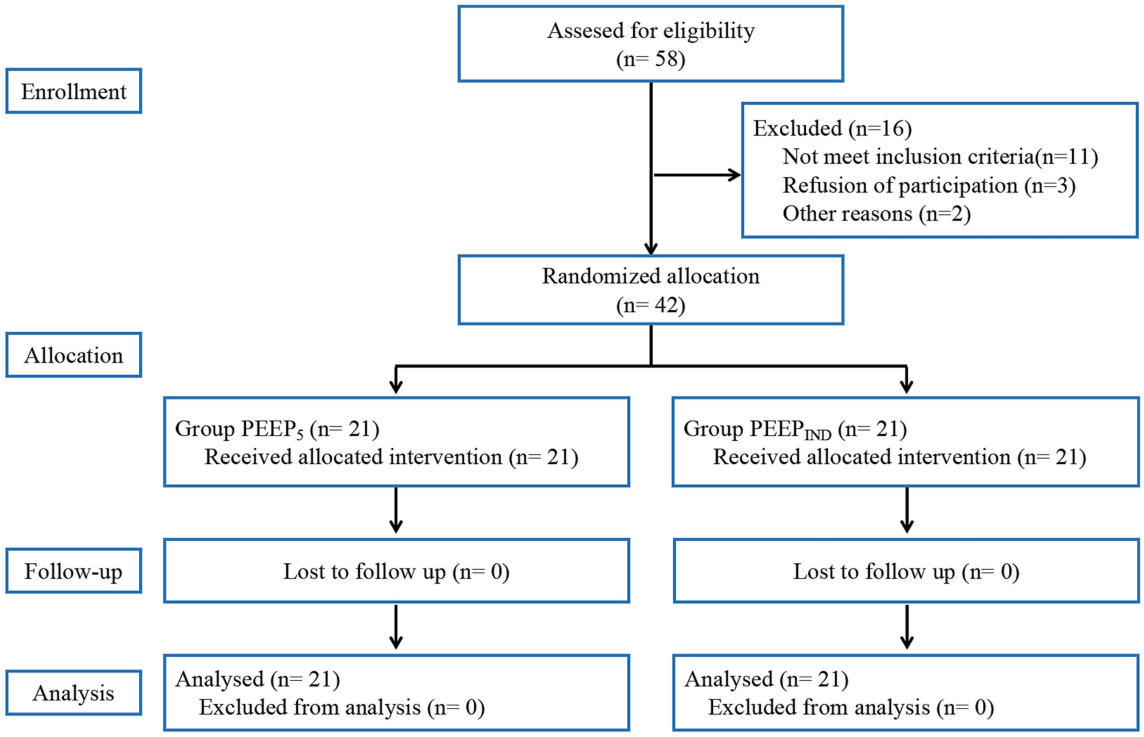

FIGURE 1
Flow chart of the study. $PEEP_5$, positive end-expiratory pressure of 5 cmH_2O; $PEEP_{IND}$, individualized positive end-expiratory pressure.

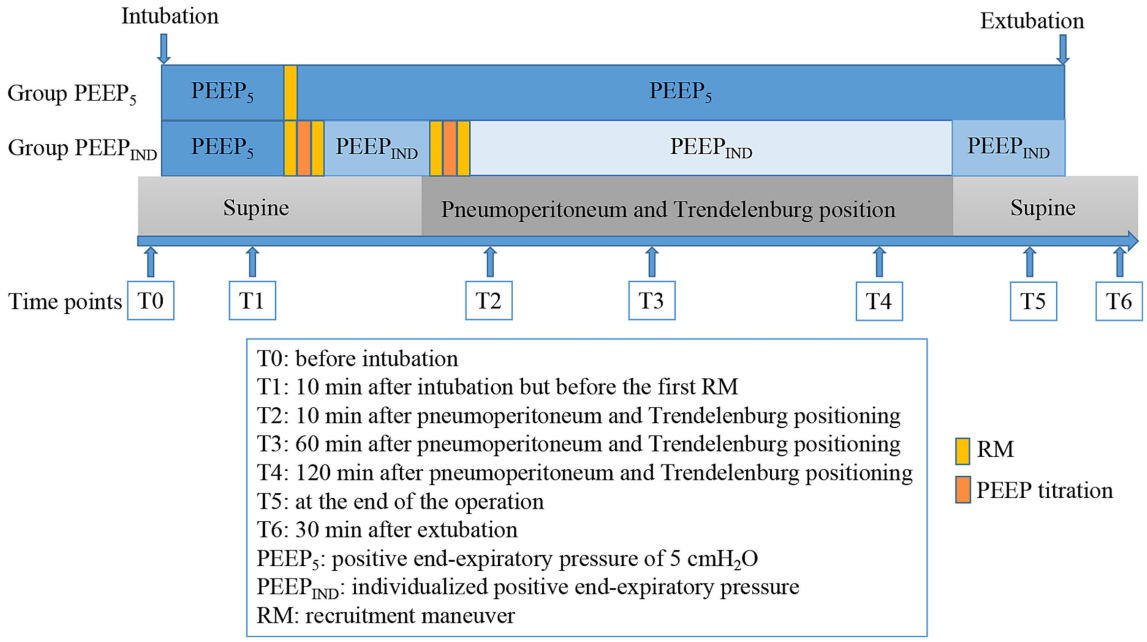

FIGURE 2
Timeline of the study protocol and interventions for both groups.

a gradient of 20 cmH_2O in airway pressure and PEEP. Specifically, PEEP was initiated at 5 cmH_2O and gradually increased by 5 cmH_2O every three respiratory cycles, up to a maximum of 20 cmH_2O. Simultaneously, the airway pressure was increased stepwise to 30, 35, and 40 cmH_2O, and maintained at 40 cmH_2O for six respiratory cycles. The entire recruitment process was completed within 90 s (7). The study protocol timeline and interventions are shown in Figure 2.

Total intravenous anesthesia was adopted in this study. Propofol (2–3 μg/mL) and remifentanil (2–4 ng/mL) in target-controlled infusion mode were applied for the maintenance of general anesthesia; sufentanil 5–10 μg was administered when necessary; and muscle relaxants were administered in a stepwise fashion under the guidance of a neuromuscular monitor. The bispectral index was maintained at 40–55, and the nasopharyngeal temperature was maintained at 36°C to 37°C during anesthesia. In the event of hypotension (systolic blood pressure < 90 mmHg) or bradycardia (HR < 50 bpm), vasoactive drugs were administered intravenously as appropriate. Intraoperative data were collected, including variables such as duration of surgery and anesthesia, duration of pneumoperitoneum and Trendelenburg position, volume of fluid infusion, bleeding and urine output, and dosage of vasoactive drugs.

2.3 Outcome measures

The following time points were designated for collection of data: before intubation (T0); 10 min after intubation but before the first RM (T1); 10 min after pneumoperitoneum and Trendelenburg positioning (T2); 60 min after pneumoperitoneum and Trendelenburg positioning (T3); 120 min after pneumoperitoneum and Trendelenburg positioning (T4); at the end of the operation (T5); and 30 min after extubation (T6). The time points for data collection are shown in Figure 2.

2.3.1 Primary outcome

The primary outcome was the PaO_2/FiO_2 ratio. Arterial blood gas samples for analysis of PaO_2/FiO_2 were collected at T0, T1, T4, T5, and T6.

2.3.2 Secondary outcomes

Data pertaining to pulmonary variables (airway peak pressure, airway plateau pressure, respiratory system compliance, driving pressure, PEEP) and hemodynamic data (mean arterial pressure, cardiac index, and stroke volume variation) were collected at T1, T2, T3, T4, and T5. The driving pressure is defined as the tidal volume divided by the respiratory system compliance and can be readily calculated as the plateau pressure minus the PEEP (24). Arterial blood gas samples for analysis of arterial partial pressure of carbon dioxide ($PaCO_2$) were collected at T0, T1, T4, T5, and T6.

Optic nerve sheath diameter (ONSD) was measured by an investigator trained in ocular sonography who was blinded to the group assignment. ONSD was measured 3 mm behind the sphere at three time points (T1, T4, and T5) using a high-frequency linear-array ultrasound probe (UMT −500; Mindray, China). This process was repeated for both eyes, with three measurements taken for each. The average value was obtained as the patient's ONSD.

The occurrence of complications within 7 days after surgery was meticulously documented. These complications were defined as follows: hypoxemia (SpO_2 < 90%), the necessity for postoperative oxygen therapy on day 2 or later, initial ventilatory support for a period exceeding 24 h, re-intubation and mechanical ventilation, pneumonia, pneumothorax, pulmonary failure, and POD. The

Confusion Assessment Method was used to assess POD twice a day with a 6-h interval from day 1 to 7 after surgery.

2.4 Statistical analysis

The sample-size calculation was based on detecting differences of 100 mmHg in PaO_2/FiO_2 between the two ventilation strategies, with an SD of 90 mm Hg in each arm (4). A total sample size of 38 participants was needed to achieve a study power of 90% with a 5% alpha error. Allowing for a 10% rate of incomplete follow-up or dropout, at least 42 patients were required in this study.

Statistical analysis was performed using SPSS software (version 25.0, IBM Corp, Armonk, NY). The Shapiro–Wilk test was used to assess the normality of the distributions. Continuous data were analyzed using the independent Student *t* test or the Manne-Whitney U test. Pearson's χ^2 test or Fisher's exact test was used to compare categorical data where appropriate. Two-way analysis of variance (ANOVA) followed by the Bonferroni *post-hoc* test was used for repeated-measures data. A value of $p < 0.05$ was considered statistically significant.

3 Results

3.1 Demographic and clinical characteristics

The two groups showed no significant differences in demographic and clinical characteristics (Table 1).

TABLE 1 The demographic and clinical characteristics of patients.

Baseline characteristics	Group $PEEP_5$	Group $PEEP_{IND}$	*P* value
Age (y)	67.00 ± 6.88	66.48 ± 6.21	0.797
Predicted body weight (kg)	66.64 ± 6.98	67.81 ± 8.04	0.618
Body mass index (kg/m^2)	24.97 ± 2.48	25.18 ± 3.10	0.805
ASA physical status			0.525
II	9 (42.9)	7 (33.3)	
III	12 (57.1)	14 (66.7)	
ARISCAT score	26 (8)	26 (4)	0.636
Pre-existing medical condition			
Smoking			0.931
Never	7 (33.3)	6 (28.6)	
Former	7 (33.3)	8 (38.1)	
Current	7 (33.3)	7 (33.3)	
Hypertension	7 (33.3)	11 (52.4)	0.212
Diabetes	3 (14.3)	5 (23.8)	0.697
Coronary heart disease	3 (14.3)	4 (19.0)	1.000
Sleep apnea	2 (9.9)	2 (9.9)	1.000
Intraoperative characteristic			
Anesthesia duration (min)	311.10 ± 79.74	311.24 ± 80.29	0.995
Surgery duration (min)	265.86 ± 79.63	260.81 ± 65.56	0.824
Pneumoperitoneum duration (min)	223.29 ± 67.38	218.81 ± 67.92	0.831
Infusion volume (mL)	2665.48 ± 716.30	2498.81 ± 676.13	0.443
Bleeding (mL)	97.62 ± 66.09	88.57 ± 44.64	0.606
intraoperative output (mL)	714.29 ± 266.52	764.29 ± 232.99	0.521
Ephedrine (mg)	7.19 ± 5.98	6.33 ± 4.95	0.616
Norepinephrine (μg)	720.78 ± 450.86	602.17 ± 283.82	0.314

Data are presented as mean ± standard deviation, median (inter-quartile range), or n (%). $PEEP_5$, positive end-expiratory pressure of 5 cmH_2O; $PEEP_{IND}$, individualized positive end-expiratory pressure; ARISCAT, Assess Respiratory Risk in Surgical Patients in Catalonia; ASA, American Society of Anesthesiologists.

3.2 Primary outcome—PaO_2/FiO_2

A two-way repeated-measures ANOVA was performed to evaluate the PaO_2/FiO_2 at five designated time points. The findings demonstrated no difference in PaO_2/FiO_2 between the two groups neither before nor after intubation ($p > 0.05$). PaO_2/FiO_2 was significantly higher 120 min after pneumoperitoneum in the Trendelenburg position ($p = 0.023$) and at the end of the operation ($p = 0.028$) in the $PEEP_{IND}$ group than in the $PEEP_5$ group. However, no intergroup difference was found in the PaO_2/FiO_2 30 min after extubation ($p > 0.05$) (Figure 3). The $PaCO_2$ showed no significant difference between the two groups ($p > 0.05$) (Figure 3).

3.3 Secondary outcomes

3.3.1 Respiratory mechanics

In comparison with the $PEEP_5$ group, the $PEEP_{IND}$ group showed significantly higher ($p < 0.001$) PEEP values during pneumoperitoneum in the Trendelenburg position (mean [standard deviation], 11.29 cmH_2O [1.01 cmH_2O]) and after deflation and repositioning to the supine position (mean [standard deviation], 7.05 cmH_2O [1.20 cmH_2O]), with mean differences (95% confidence interval [CI]) were 6.29 cmH_2O (5.84–6.73) and 2.05 cm H_2O (1.52–2.58), respectively. The results revealed a significantly lower driving pressure in the $PEEP_{IND}$ group than that in the $PEEP_5$ group. The mean differences in driving pressure were 3.67 cmH_2O (95% CI, 1.63–5.71), 3.91 cmH_2O (95% CI, 2.01–5.80), 4.19 cmH_2O (95% CI, 2.20–6.19), and 1.39 cmH_2O (95% CI, 0.12–2.65) at T2, T3, T4, and T5, respectively ($PEEP_5$ vs. $PEEP_{IND}$, $p = 0.001$, $p = 0.000$, $p = 0.000$, and $p = 0.033$, respectively) (Figure 4).

During pneumoperitoneum in the Trendelenburg position, peak airway pressure ($p = 0.000$) and plateau pressure ($p = 0.000$) were significantly higher in both groups, while lung compliance showed a reduction ($p = 0.000$). After deflation of the pneumoperitoneum and transition to the supine position, these parameters returned to baseline levels in the $PEEP_5$ group ($p > 0.05$). In contrast, in the $PEEP_{IND}$ group, peak airway and plateau pressures returned to baseline levels, while lung compliance showed an enhancement ($p = 0.000$). Compared with the $PEEP_5$ group, the $PEEP_{IND}$ group exhibited higher peak airway pressure ($p = 0.025$) and plateau pressure ($p = 0.029$) but superior lung compliance ($p = 0.009$) (Figure 4).

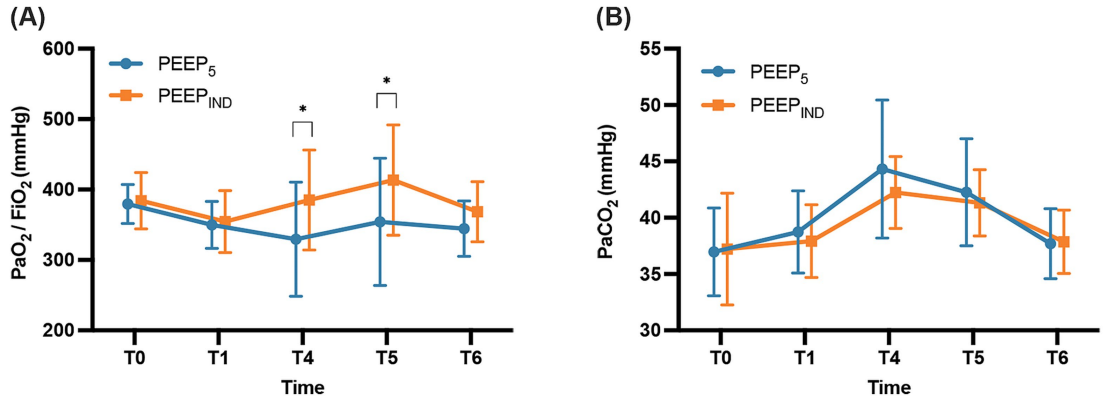

FIGURE 3
Arterial blood gas parameters at five time points. **(A)** PaO_2/FiO_2 ratio. **(B)** $PaCO_2$. T0, before intubation; T1, 10 min after intubation but before the first RM; T4, 120 min after pneumoperitoneum and Trendelenburg positioning; T5, at the end of the operation; T6, 30 min after extubation. *$p < 0.05$.

TABLE 2 Comparisons of intraoperative hemodynamics between the two groups.

Variable	Group	T1	*P* value	T2	*P* value	T3	*P* value	T4	*P* value	T5	*P* value
MAP (mmHg)	$PEEP_5$	81.19 ± 7.63	0.859	88.67 ± 10.49	0.881	80.52 ± 5.48	0.128	79.52 ± 7.01	0.322	83.19 ± 6.45	0.902
	$PEEP_{IND}$	81.62 ± 7.91		88.19 ± 9.90		83.67 ± 7.47		81.52 ± 5.87		82.90 ± 8.39	
CI ($L \cdot min^{-1} \cdot m^{-2}$)	$PEEP_5$	3.14 ± 0.24	0.401	2.87 ± 0.35	0.795	2.72 ± 0.19	0.271	2.63 ± 0.21	0.409	2.86 ± 0.25	0.536
	$PEEP_{IND}$	3.07 ± 0.30		2.90 ± 0.41		2.82 ± 0.33		2.71 ± 0.41		2.91 ± 0.29	
SVV (%)	$PEEP_5$	10.15 ± 2.00	0.594	9.29 ± 1.89	0.610	9.22 ± 2.92	0.413	9.95 ± 2.92	0.188	10.97 ± 3.10	0.512
	$PEEP_{IND}$	10.52 ± 2.41		8.99 ± 2.05		8.59 ± 1.91		8.92 ± 1.97		10.39 ± 2.53	

Data are presented as mean ± standard deviation. MAP, mean arterial pressure; CI, cardiac index; SVV, stroke volume variation; T1, 10 min after intubation but before the first recruitment maneuver; T2, 10 min after pneumoperitoneum and Trendelenburg positioning; T3, 60 min after pneumoperitoneum and Trendelenburg positioning; T4, 120 min after pneumoperitoneum and Trendelenburg positioning; T5, at the end of the operation.

3.3.2 ONSD

In this study, the results showed that the group*time interaction had no statistically significant effect on ONSD. Therefore, the main effects of the group and time factors on ONSD were analyzed separately. There was no significant difference in ONSD in both groups ($F = 0.299$, $p = 0.591$). The time factor had a statistically significant impact on ONSD ($F = 36.329$, $p = 0.000$). After pairwise comparison, a significant difference was observed between T1 and T4 ($p = 0.000$) with an MD of 0.020 (95% CI: 0.013–0.026) and between T4 and T5 ($p = 0.000$) with an MD of 0.014 (95% CI: 0.007–0.021). However, no significant differences were observed between T1 and T5 ($p > 0.05$) (Figure 4).

3.3.3 Hemodynamics

Symptoms of hypotension were observed in almost all patients during the RM in supine position, even though the SVV% before the RM was less than 13. After completion of the RM, the blood pressure and cardiac index returned to normal. In contrast, no patient experienced hypotension when undergoing the RM in the Trendelenburg position. No statistically significant differences were detected in the hemodynamic measurements between the groups, which included mean arterial pressure, cardiac index, and stroke volume variation ($p > 0.05$) (Table 2). The two groups also showed no differences in the dosage of vasoactive drugs ($p > 0.05$) (Table 1).

3.3.4 Postoperative complication

In this study, four patients developed hypoxemia after extubation, two each in the $PEEP_5$ and $PEEP_{IND}$ groups, with no significant difference between the two groups ($p > 0.05$). In both groups, none of the patients required postoperative oxygen therapy on day 2 or later, received initial ventilatory support for a period longer than 24 h, required re-intubation and mechanical ventilation, or developed pneumonia or pneumothorax. Five patients developed POD, two in the $PEEP_5$ group and three in the $PEEP_{IND}$ group, with no significant difference between the two groups ($PEEP_5$ vs. $PEEP_{IND}$, n (%), 2[9.5] vs. 3[14.3], $p > 0.05$).

4 Discussion

The present study demonstrated that the implementation of individualized PEEP guided by driving pressure can yield enhanced intraoperative oxygenation in comparison with administration of fixed PEEP of 5 cmH_2O. This finding is consistent with the conclusions of previous studies (4, 15, 25). RM can facilitate the reopening of atrophied alveoli, and PEEP has been shown to maintain this reopened state, thereby improving oxygenation. In the present study, a RM was performed after intubation in both groups to offset the pulmonary atelectasis that occurred during the intubation process. However, after pneumoperitoneum and Trendelenburg positioning, the oxygenation

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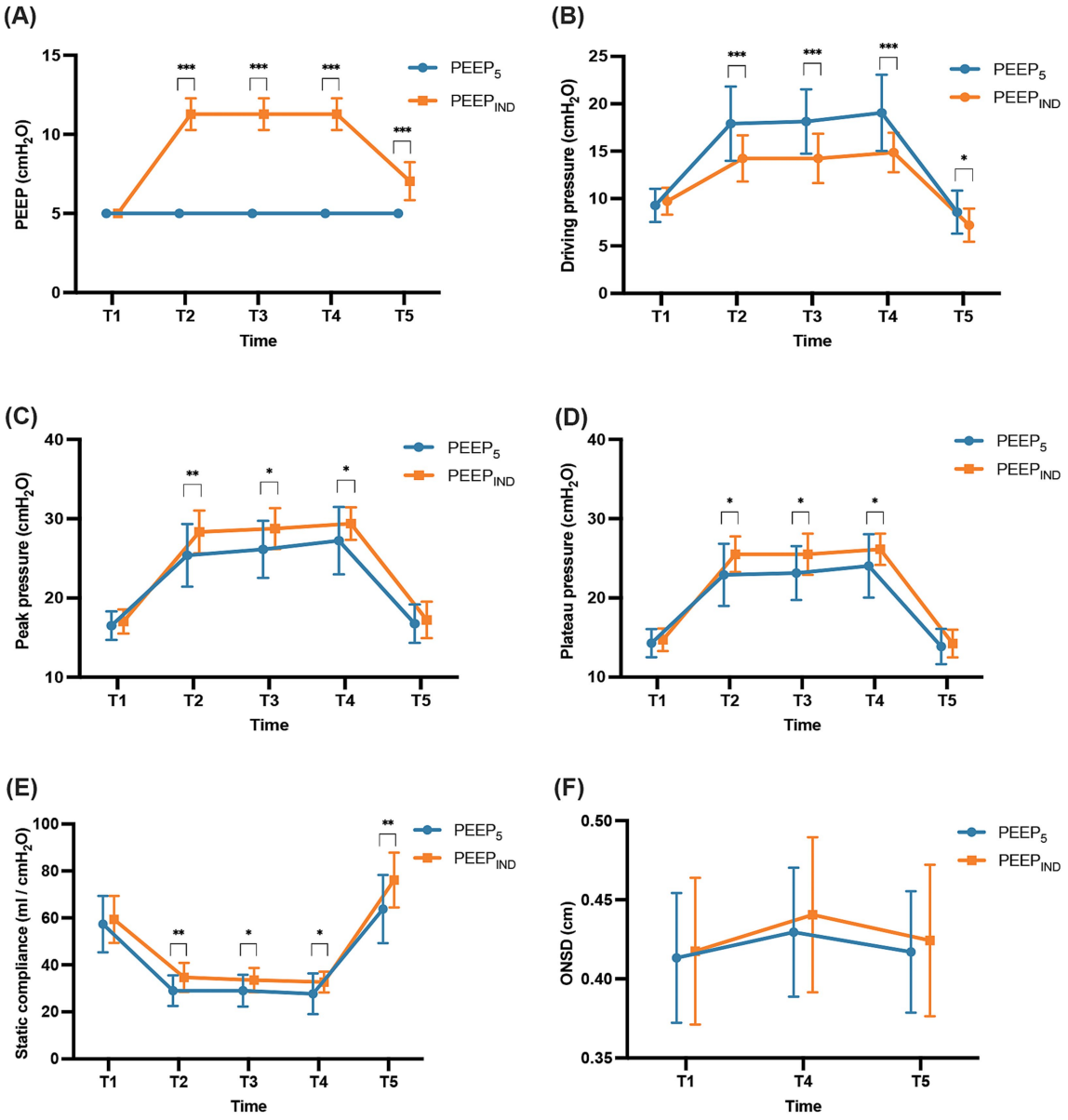

FIGURE 4
Intraoperative respiratory mechanics and ONSD. **(A)** PEEP, **(B)** driving pressure, **(C)** peak inspiratory pressure, **(D)** plateau pressure, **(E)** static compliance, **(F)** ONSD. T1, 10 min after intubation but before the first RM; T2, 10 min after pneumoperitoneum and Trendelenburg positioning; T3, 60 min after pneumoperitoneum and Trendelenburg positioning; T4, 120 min after pneumoperitoneum and Trendelenburg positioning; T5, at the end of the operation. ONSD, optic nerve sheath diameter. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

index was lower in the $PEEP_5$ group than in the $PEEP_{IND}$ group. This suggests that a fixed PEEP of 5 cmH_2O was inadequate to counteract alveolar atrophy resulting from changes in position and intra-abdominal pressure and that individualization of PEEP enhances ventilation-perfusion matching, thereby improving oxygenation. Similarly, our results also failed to demonstrate a sustained beneficial effect on oxygenation after extubating, suggesting that the advantages of individualized PEEP may be limited to the intraoperative period. Girrbach et al. (4) found that in normal–weight patients, RM and $PEEP_{IND}$ primarily improved intraoperative lung function, while atelectasis from mechanical ventilation, Trendelenburg positioning, and capnoperitoneum resolved after extubation in patients with PEEP of 5 cmH_2O. This may further explain the loss of oxygenation advantage following extubation. Based on these findings, further investigation into the two groups undergoing periodic RMs is warranted, particularly their differential impacts on oxygenation and hemodynamics across different surgical positions.

The study employed volume-controlled ventilation, the most common mode in general anesthesia, which maintained consistent tidal volume despite fluctuations in intra-abdominal pressure and changes in patient positioning. In this study, peak and plateau airway pressures increased but compliance decreased in both groups during pneumoperitoneum in Trendelenburg positioning. In the $PEEP_{IND}$ group, peak and plateau pressure levels were higher due to the $PEEP_{IND}$ levels exceeding 5 cmH_2O. Notably, the mean individualized PEEP in this study was lower than that observed in previous studies (4, 15), as we defined

$PEEP_{IND}$ as the minimal PEEP within the range corresponding to the lowest driving pressure. Despite this, driving pressure was lower in the $PEEP_{IND}$ group than in the $PEEP_5$ group, leading to improved pulmonary compliance. The reduction in driving pressure enhanced pulmonary mechanics, which may in turn have contributed to better oxygenation.

Cardiocirculatory depression during RM remains a primary anesthetic consideration, particularly in volume-depleted patients. In our study, despite performing RM after volume resuscitation, transient hypotension developed in most supine-positioned patients but resolved promptly post-maneuver. Importantly, no hypotensive episodes occurred during pneumoperitoneum in Trendelenburg position, attributable to augmented venous return. These findings emphasize the necessity of pre-RM volume optimization and vigilant hemodynamic monitoring. Furthermore, our study revealed similar hemodynamic profiles between $PEEP_{IND}$ and $PEEP_5$ groups, with comparable vasopressor needs, consistent with Girrbach et al. and Ma et al.'s findings (4, 5), demonstrating its safety for circulatory function. A multicenter study suggested that patients receiving a higher PEEP with the RM were more likely to experience hemodynamic instability (26), which was not consistent with the findings of our study. This discrepancy may be explained by the higher proportion of supine-positioned RM in high-PEEP patients in the previous study.

ICP elevation during pneumoperitoneum in the steep Trendelenburg position (16, 17, 21, 27) may result from increased intra-abdominal pressure and cephalad diaphragmatic displacement imparing cerebral venous drainage. Therefore, the application of individualized PEEP raises concerns about potential further ICP elevation. Studies reported that the application of 5 or even 8 cmH_2O of PEEP did not increase the ONSD in comparison with that observed using zero PEEP during pneumoperitoneum in steep Trendelenburg positioning (28, 29). In the present study, both groups exhibited increased ONSD during pneumoperitoneum with steep Trendelenburg positioning. However, the implementation of $PEEP_{IND}$, adapted to the surgical procedure, did not result in a further increase in ONSD when compared with $PEEP_5$. In this study, the end-expiratory carbon dioxide concentration was maintained within the normal range as far as possible. As mentioned above, the two groups showed no notable differences in $PaCO_2$, ensuring that the impact of carbon dioxide on cerebral blood flow was minimized to the greatest extent possible. This study found no significant differences in POD incidence between groups, suggesting that $PEEP_{IND}$ may be safely performed in robot-assisted laparoscopic prostatectomy patients without preexisting intracranial hypertension. However, given the limited sample size, this conclusion should be interpreted cautiously, and larger multicenter studies are needed to validate these findings.

While multiple studies have established the correlation between driving pressure and PPCs (19, 20, 30), others have reported no significant reduction in PPCs with driving pressure optimization (15, 31). Aligning with the latter, our study found no significant PPCs reduction in PPCs within 7 days after surgery with driving pressure-guided PEEP, potentially due to the transient intraoperative oxygenation improvement. However, these null findings should be interpreted cautiously given our limited sample size, which may have underpowered the detection of clinically relevant differences in PPC rates.

Our study had some limitations. First, the sample size, calculated based on the primary outcome (PaO_2/FiO_2 ratio), may be underpowered to detect clinically meaningful differences in postoperative complications (POD and PPCs). Importantly, the systematic assessment of these secondary outcomes provides complementary data to our intraoperative monitoring parameters. These findings should be interpreted with caution and require confirmation in larger, multicenter trials. Second, in the present study, the minimal PEEP value within the specified range that corresponded to the lowest driving pressure was defined as the individualized PEEP. However, more research is required to determine whether the maximum PEEP value within the specified range will yield analogous results. Third, despite the fact that patients were enrolled in the study on the basis of a moderate or high risk of PPCs, as determined by their ARISCAT risk score, the actual risk score was lower than expected.

5 Conclusion

In conclusion, driving pressure-guided individualized PEEP improves intraoperative respiratory mechanics and oxygenation without compromising hemodynamic stability or increasing intracranial pressure in patients undergoing robot-assisted laparoscopic radical prostatectomy. While these findings demonstrate its intraoperative safety profile, the limited sample size precludes definitive conclusions regarding POD and PPCs. These null findings require cautious interpretation and warrant validation through larger multicenter trials.

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 ethics committee of Chongqing University Cancer 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.

Author contributions

YL: Data curation, Investigation, Writing – original draft. SQ: Data curation, Investigation, Writing – original draft. ML: Data curation, Writing – original draft. QS: Formal analysis, Writing – original draft. RA: Methodology, Project administration, Supervision, Writing – review & editing. YJ: Conceptualization, Methodology, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This research was supported by the Chongqing Shapingba District Joint Medical Research Project of Science and Health (2023SQKWLH019) and Chongqing Medical

Scientific Research Project (Joint project of Chongqing Health Commission and Science and Technology Bureau, NO. 2024MSXM128).

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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1573150/full#supplementary-material

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frontiers | Frontiers in Neuroscience

TYPE Review
PUBLISHED 28 April 2025
DOI 10.3389/fnins.2025.1543421

OPEN ACCESS

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RECEIVED 11 December 2024
ACCEPTED 07 April 2025
PUBLISHED 28 April 2025

CITATION
Ma D, Li L, Liu W and Xu J (2025) The impact of postoperative pain interventions on circadian rhythm disruptions: mechanisms and clinical implications.
Front. Neurosci. 19:1543421.
doi: 10.3389/fnins.2025.1543421

The impact of postoperative pain interventions on circadian rhythm disruptions: mechanisms and clinical implications

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Postoperative pain is a prevalent clinical issue that significantly impacts patient recovery, making its management crucial for rehabilitation. Recent studies have shown that postoperative pain not only affects the physiological state of patients but may also disrupt their circadian rhythms, leading to decreased sleep quality and physiological dysfunctions. This review aims to explore the effects of postoperative pain interventions on circadian rhythm disturbances, analyze the underlying mechanisms, and summarize the effective strategies currently used in clinical practice. Through a comprehensive analysis of the relevant literature, we will highlight the importance of pain management during the recovery process and emphasize its potential role in regulating circadian rhythms. Pharmacological treatments like NSAIDs and melatonin have shown efficacy in regulating circadian rhythms and improving sleep quality in postoperative patients. Multimodal analgesia combining pharmacological and non-pharmacological methods (e.g., CBT, acupuncture) can optimize pain relief while minimizing side effects. However, further research is needed to clarify the bidirectional relationship between pain perception and circadian rhythms and translate these findings into clinical practice.

KEYWORDS

pain, postoperative, pain management, circadian rhythm, sleep disorders, physiological process

1 Introduction

Postoperative pain represents a significant challenge for patients after surgery, greatly affecting their comfort and recovery process. Managing this pain effectively is crucial, as it not only enhances patient satisfaction but also contributes to better recovery outcomes. Recent studies have highlighted the intricate relationship between postoperative pain and circadian rhythms, suggesting that pain can disrupt the body's natural biological clock, which in turn negatively affects sleep quality and various physiological functions (Zee et al., 2013; Guo et al., 2023; Jiang et al., 2024). This review aims to explore how interventions aimed at managing postoperative pain influence circadian rhythms, while also clarifying the underlying mechanisms and clinical implications of this relationship. After surgery, patients often experience changes in their sleep patterns and circadian rhythms, both of which are essential for maintaining homeostasis and overall health. Disruptions in these rhythms can worsen pain perception, creating a harmful cycle that hinders recovery (Barnadas Solé et al., 2021; Li et al., 2023; Šmon et al., 2023). This review aims to systematically evaluate how postoperative pain interventions modulate circadian rhythm disruptions, analyze underlying mechanisms, and summarize evidence-based strategies for clinical implementation.

A multi-center, prospective cohort study revealed that 53.9% of surgical patients experienced severe postoperative pain (Numerical Rating Scale ≥7) within the critical 0–24 h postoperative window. This nociceptive burden was significantly associated with impairments in mood, ambulation, deep breathing, and sleep quality, alongside increased incidence of vertigo, nausea, and fatigue ($p < 0.05$) (Emrich et al., 2023). Notably, this statistical pattern has shown no significant improvement across three decades of observational research, underscoring the urgent need for innovative analgesic strategies (Wu et al., 2024). For instance, research shows that patients with severe postoperative pain frequently report poor sleep quality, which can lead to increased pain sensitivity and longer recovery times (Büyükyilmaz et al., 2011; Wylde et al., 2011). The connection between pain and circadian rhythms is complex, involving various biological systems such as hormonal regulation, immune responses, and neurophysiological mechanisms (Santos et al., 2020; Bumgarner et al., 2021; Zhu et al., 2024). A thorough understanding of these interactions is vital for developing effective pain management strategies that not only aim to relieve pain but also support the restoration of circadian rhythms and improve overall health (Kaur and Shyu, 2018; Seiger et al., 2024).

The onset of chronic postoperative pain can result in a range of ongoing complications, often presenting as chronic pain syndromes that may be influenced by disruptions in circadian rhythms (Liu et al., 2021; Suarez-Roca et al., 2024). Consequently, it is essential for healthcare providers to implement a multimodal approach to pain management that takes into account the circadian factors affecting both pain perception and recovery (Al-Waeli et al., 2020; Tanaka et al., 2021; Daguet et al., 2022).

While previous research has touched on the relationship between postoperative pain and circadian rhythms, there is a lack of comprehensive analysis and practical guidance for clinicians. While previous studies have linked postoperative pain to circadian dysfunction, few reviews have synthesized the bidirectional relationship or translated findings into actionable clinical guidelines. This review aims to explore the various interventions available for managing postoperative pain, their impact on circadian rhythms, and the potential to enhance patient outcomes through focused pain management strategies.

1.1 Physiological mechanisms of postoperative pain

The physiological mechanisms underlying postoperative pain involve a complex interplay between the peripheral and central nervous systems in the transmission and processing of nociceptive signals. This process begins when peripheral nociceptors identify harmful stimuli, converting them into electrical impulses that travel along afferent nerve fibers to the spinal cord. Within the spinal cord, the relay of pain signals is facilitated by several receptors, including transient receptor potential (TRP) channels and purinergic receptors, which are vital in modulating pain perception (Khan et al., 2019; Yang L. et al., 2023). Upon reaching the dorsal horn of the spinal cord, these signals undergo additional processing, during which excitatory neurotransmitters such as glutamate and substance P are released, further amplifying the pain response (Han et al., 2021).

The phenomenon of central sensitization can occur when the spinal cord becomes more responsive to stimuli, leading to increased sensitivity to pain and the potential development of chronic pain (Lai et al., 2024). This is particularly relevant in postoperative situations, where surgical injuries can sensitize the nervous system, resulting in heightened pain experiences after surgery. Research has shown that hypersensitivity to pain before surgery can predict the severity of postoperative pain, highlighting the importance of assessing pain sensitivity prior to surgical procedures (Del Tedesco et al., 2023; Lai et al., 2024). Understanding how pain signals are transmitted and processed is crucial for developing effective pain management strategies in postoperative care.

The central nervous system (CNS) plays a key role in how pain is perceived and modulated, especially during recovery after surgery. Pain signals processed in the spinal cord are sent to various brain regions, including the thalamus and cortex, where emotional and cognitive aspects of pain are integrated. The brain not only interprets these signals but also modulates them through descending pathways that can either enhance or diminish pain perception (Zhang et al., 2023).

In the context of postoperative recovery, acute pain can trigger neuroinflammatory responses that heighten pain perception and may lead to cognitive deficits, especially in older adults (Zhao et al., 2021). This neuroinflammatory response is driven by the release of pro-inflammatory cytokines, which can sensitize neurons and change synaptic plasticity, resulting in persistent pain. Furthermore, neurotrophic factors like brain-derived neurotrophic factor (BDNF) are essential for pain modulation and recovery following surgical procedures (Rajamanickam et al., 2024). Understanding the CNS's response to pain is crucial for developing targeted therapies that can mitigate postoperative pain and its associated complications, ultimately improving patient outcomes in surgical settings.

1.2 Biological basis of circadian rhythm

Circadian rhythms are innate biological mechanisms that function on a roughly 24 h cycle, playing a crucial role in regulating various physiological processes across different organisms (Ikonomov et al., 1998; Wang et al., 2021). At the heart of these rhythms is the circadian clock, primarily located in the suprachiasmatic nucleus (SCN) of the hypothalamus in mammals, which serves as the main pacemaker (Schwartz et al., 1980; Liang et al., 2025). This nucleus is essential for synchronizing peripheral oscillators found in nearly all tissues, ensuring that the organism's physiological functions align with external environmental signals, especially the cycles of light and darkness. The molecular basis of the circadian clock involves a complex network of genes and proteins that interact in feedback loops to regulate the expression of clock-related genes. For instance, acute surgical injury triggers a cascade of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which disrupt circadian clock gene expression in both the suprachiasmatic nucleus (SCN) and peripheral tissues (Paladino et al., 2014). These cytokines downregulate the transcription of core clock genes BMAL1 and CLOCK, while upregulating PER2 and CRY1 in a time-dependent manner, leading to desynchronization between the central and peripheral circadian oscillators (Guo et al., 2015). For instance, TNF-α-mediated inflammation directly impairs SCN

function by altering glutamate receptor signaling, thereby blunting the SCN's response to light–dark cues (Paladino et al., 2014). Recent studies have highlighted the importance of post-translational modifications in the stability and function of these clock proteins, emphasizing the dynamic nature of circadian regulation and its evolutionary conservation across various species (Philpott et al., 2022; Sharma and Partch, 2024).

Circadian rhythms significantly influence a range of physiological states, including metabolism, sleep–wake cycles, hormonal secretion, and immune responses (Cable et al., 2021; Liu et al., 2022). Disruptions to these rhythms, often seen in scenarios like shift work or chronic jet lag, can lead to negative health outcomes, such as metabolic disorders, cardiovascular problems, and mood disturbances. For example, research indicates that misalignment of circadian rhythms can negatively impact glucose metabolism and insulin secretion, thereby heightening the risk of developing type 2 diabetes (Ashraf et al., 2019). Circadian rhythms play a crucial role in regulating the gastrointestinal system, and when these rhythms are disrupted, it can lead to functional gastrointestinal disorders (Fowler et al., 2022). Research shows that these rhythms also have a significant impact on mental health, with disturbances exacerbating conditions like bipolar disorder and depression (Jermann et al., 2020). Additionally, the timing of medication intake, known as chronotherapy, is increasingly recognized as essential for enhancing therapeutic effectiveness, as the metabolism and effectiveness of drugs can be greatly influenced by the body's circadian rhythms (Lassi et al., 2021). Understanding the biological underpinnings of circadian rhythms is therefore vital for developing strategies to mitigate the health consequences of circadian disruption and to promote overall well-being.

The PER3 VNTR polymorphism changes how pain is regulated throughout the day. Carriers of the PER3(5/5) genotype show reduced pain inhibition in the afternoon compared to those with the PER3(4/4) genotype. This reduction is linked to sharper decreases in serum BDNF and S100B levels during the day (Carvalho et al., 2019). This finding is consistent with data from myocardial infarction that indicate PER3(5/5) genotypes are linked to pain that occurs primarily in the morning, along with increased inflammatory markers (Lipkova et al., 2014).

1.3 Postoperative pain and circadian rhythm relationship

The bidirectional interaction between postoperative pain and circadian rhythms is increasingly recognized as a critical determinant of recovery outcomes. Postoperative pain is not just a physiological response to surgical injury; it also follows a circadian rhythm dictated by the body's internal biological clock. Studies indicate that the severity of pain and inflammatory responses fluctuate throughout the day in line with these rhythms, which are regulated by clock genes (Rodríguez-Palma et al., 2025). For example, research has shown that administering non-steroidal anti-inflammatory drugs (NSAIDs) during the active phase of the circadian cycle can lead to better pain management and recovery compared to giving them during the inactive phase (Al-Waeli et al., 2020). This is because the body's natural healing processes, including the release of anti-inflammatory cytokines, are more effective at specific times of the day. Therefore, pain management strategies should consider the timing of medication to align with these biological rhythms for optimal results (Al-Waeli et al., 2020; Tamimi et al., 2022).

Circadian rhythm disorders can manifest in various clinical symptoms, especially during surgical interventions. Patients may face sleep disturbances, heightened sensitivity to pain, and increased anxiety and delirium, all of which can impede recovery. For instance, studies have shown that surgeries performed at night can lead to poorer postoperative outcomes due to misalignment with circadian rhythms, adversely affecting sleep quality and raising the incidence of postoperative delirium (Cicekci et al., 2024; Jiang et al., 2024). Moreover, the impact of circadian rhythm disruptions on pain perception is significant, as certain pain conditions (Junker and Wirz, 2010; Knezevic et al., 2023), like fibromyalgia, exhibit specific fluctuations in pain intensity throughout the day (Korszun, 2000). Healthcare professionals should consider the timing of surgical procedures and pain relief methods to align with patients' circadian rhythms, as this synchronization is essential for improving recovery outcomes and minimizing complications (Knezevic et al., 2023; McEachern et al., 2024). Effectively managing postoperative pain while taking circadian factors into account can significantly enhance patient experiences and overall recovery paths.

Melatonin disruption plays a critical role in the interplay between pain and circadian dysfunction. Chronic pain not only significantly disrupts circadian rhythms but also creates a harmful cycle that intensifies both pain and sleep-related issues (Chen et al., 2016; Kaur and Shyu, 2018; Fujimoto et al., 2024). Specifically, postoperative pain can inhibit the synthesis of melatonin by reducing the activity of arylalkylamine N-acetyltransferase (AANAT), the key enzyme in melatonin production. As melatonin levels drop, patients often experience poor sleep quality and heightened pain perception, given that melatonin has direct analgesic effects through the modulation of spinal cord glutamate release via MT1/MT2 receptors.

This relationship is further evidenced by the temporal variations in pain perception. Research indicates circadian-dependent fluctuations in nociceptive thresholds, with increased sensitivity noted in the late evening and decreased sensitivity in the early morning (Kubynin and Ignatov, 1996). Patients undergoing abdominal surgery, for instance, report significantly higher pain intensity at night, which aligns with diminished melatonin secretion and elevated pro-inflammatory cytokines such as IL-6. This chronic state of sleep fragmentation due to pain exacerbates the production of pro-inflammatory cytokines, perpetuating circadian misalignment.

Moreover, the body's response to pain can disrupt hormonal balance, particularly affecting melatonin production, which is essential for maintaining circadian rhythms (Gögenur et al., 2007). The resulting sleep disturbances not only impede recovery but also elevate the risk of postoperative complications. Effective pain management is thus crucial to prevent disruptions in circadian rhythms and facilitate a more efficient recovery process (Tan et al., 2019; Al-Waeli et al., 2020). Chronic pain significantly disrupts circadian rhythms, creating a harmful cycle that exacerbates both pain and sleep-related issues. The body's response to pain can interfere with hormonal balance, particularly affecting melatonin production, which is crucial for regulating circadian rhythms. When pain leads to sleep disturbances, it can impede recovery and increase the risk of postoperative complications. Research shows that patients experiencing acute postoperative pain often report sleep issues, which may worsen pain perception and elevate anxiety levels (Al-Waeli et al.,

2020; Yang J. et al., 2023). This relationship highlights the importance of effective pain management to prevent disruptions in circadian rhythms, ultimately facilitating a more efficient recovery process (Vij et al., 2018; Yin et al., 2022). Additionally, understanding how pain affects circadian rhythms could lead to innovative treatments, such as using melatonin or other chronobiotic substances to mitigate these negative effects (Cicekci et al., 2024; Jiang et al., 2024) (Figure 1).

1.4 Pain intervention strategies and methods

Pharmacological treatments play a crucial role in pain management, providing a wide array of medications to address various pain types, including acute, chronic, and procedural discomfort. Recent advancements in pharmacotherapy have focused on refining existing medications and developing new agents that specifically target pain pathways. For instance, NSAIDs and opioids are commonly used, but their use is often tempered by concerns regarding side effects and the potential for addiction, especially with opioids (Boblewska and Dybowski, 2023). Consequently, there is a growing interest in alternative pharmacological options, such as innovative analgesics that interact with different receptors, including cannabinoids and certain antidepressants that have shown effectiveness in treating neuropathic pain (Hurley-Wallace et al., 2021). Additionally, the integration of pharmacogenetics into pain management strategies is starting to personalize treatment approaches, allowing for more tailored therapies based on individual genetic profiles that influence drug metabolism and effectiveness (Watanabe et al., 2024).

Recent investigations have highlighted the importance of multimodal analgesia, which combines pharmacological agents with non-pharmacological methods to optimize pain relief while minimizing side effects. For example, using NSAIDs together with acetaminophen or adding therapies like gabapentinoids has shown to provide better pain management than using a single treatment alone (Boblewska and Dybowski, 2023). Additionally, the trend of drug repurposing has gained traction, particularly during the COVID-19 pandemic, as existing medications are being explored for new roles in pain management (Khadka et al., 2020). In summary, as pharmacological strategies evolve, the focus remains on improving effectiveness, reducing adverse effects, and integrating these therapies into a comprehensive pain management approach.

Non-pharmacological approaches have gained widespread recognition in pain management as critical complements or alternatives to pharmacological therapies (Wei et al., 2022). These methods-including cognitive behavioral therapy (CBT), physical therapy, acupuncture, and mindfulness-based interventions-have demonstrated efficacy in alleviating pain and improving overall quality of life (Garland et al., 2019; Klausen et al., 2019; Yang et al.,

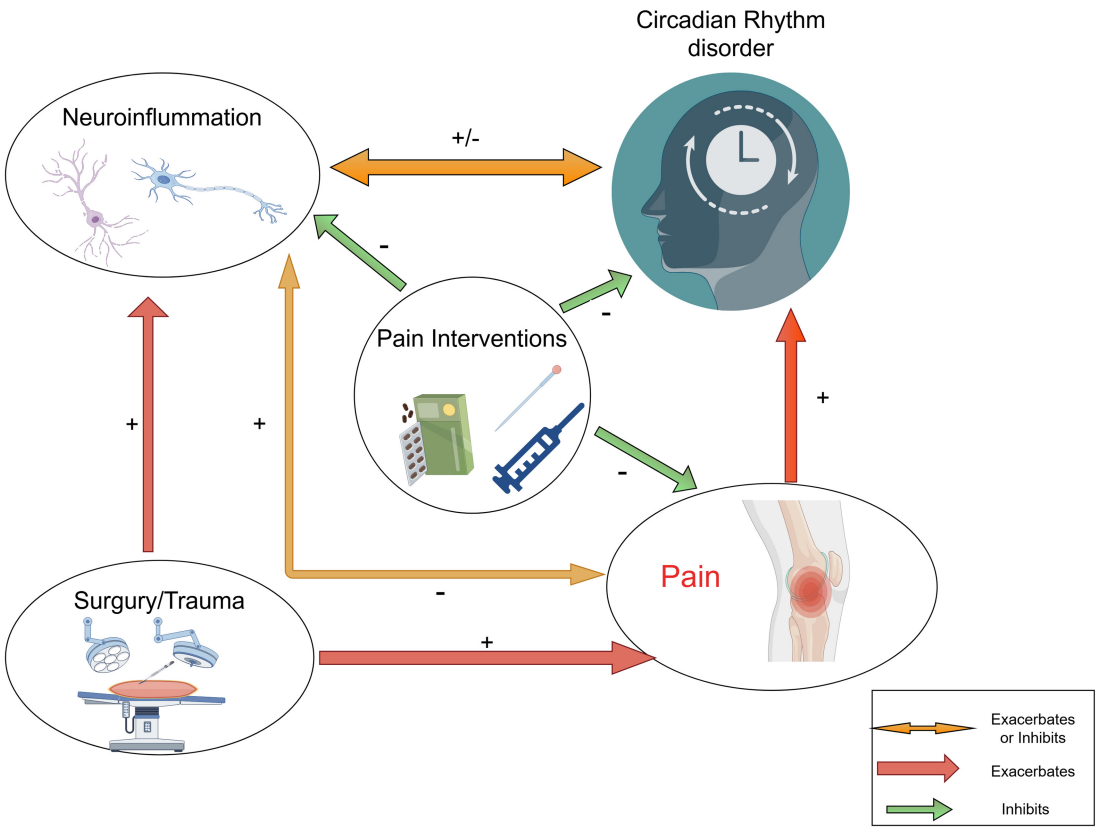

FIGURE 1
Interactions between circadian rhythms disorder, neuroinflammation and pain interventions. The figure illustrates the links between pain, neuroinflammation (including glial cells and neurons), and circadian rhythms. Further study is needed to understand the mechanisms regulating circadian pain.

2021). For instance, CBT has shown significant effectiveness in chronic pain management by addressing psychological aspects of pain, enhancing coping strategies, and reducing pain-related disability (Thorn and Kuhajda, 2006; Smith et al., 2019; Urits et al., 2019, p. 51). Similarly, physical therapies such as physiotherapy and exercise have been validated for pain relief, particularly in musculoskeletal disorders, where they improve functionality and decrease reliance on medications (Fortún-Rabadán et al., 2021; Hurley-Wallace et al., 2021).

These integrative approaches not only optimize pain management but also enhance patients' overall quality of life. Acupuncture is a significant non-drug approach that has gained recognition for its ability to relieve pain. Systematic reviews indicate that acupuncture can significantly reduce pain intensity, particularly in conditions like osteoarthritis and chronic lower back pain (Brinkhaus et al., 2003; Xu et al., 2013; Chang et al., 2022). Mechanistically, acupuncture modulates the hypothalamic–pituitary–adrenal axis, reducing cortisol levels and promoting melatonin synthesis (Li et al., 2021). Additionally, integrative methods that combine various non-drug techniques, such as mindfulness meditation and yoga, have shown promise in relieving pain and enhancing psychological well-being. This suggests that a comprehensive approach to pain management could yield the best results (Wolkin, 2015; Zeidan et al., 2015; Johnston et al., 2023).

Postoperative pain management involves a variety of techniques targeting different mechanisms within the pain pathway, ranging from local anesthetics to systemic medications like opioids and NSAIDs. These strategies aim to alleviate pain by either blocking pain signals at their origin, reducing inflammation, or modulating the central nervous system's perception of pain. An overview of the schematic diagram of pain management and drug mechanism of action, is depicted in Figure 2.

2 Potential areas and challenges for future research

Future research should focus on areas like personalized medicine, digital health monitoring, and the discovery of new biomarkers. The increasing use of smartwatches and other digital health technologies calls for effective integration of these tools into pain management, representing a key area for further exploration (Xie et al., 2021; Imeraj et al., 2022). However, future research must tackle challenges such as addressing ethical issues in current clinical trials, variability in patient selection, and barriers to data sharing (Morain et al., 2022; Møller et al., 2024). Progress in these areas will advance medical research, improve clinical treatment outcomes, and ultimately enhance patients' quality of life.

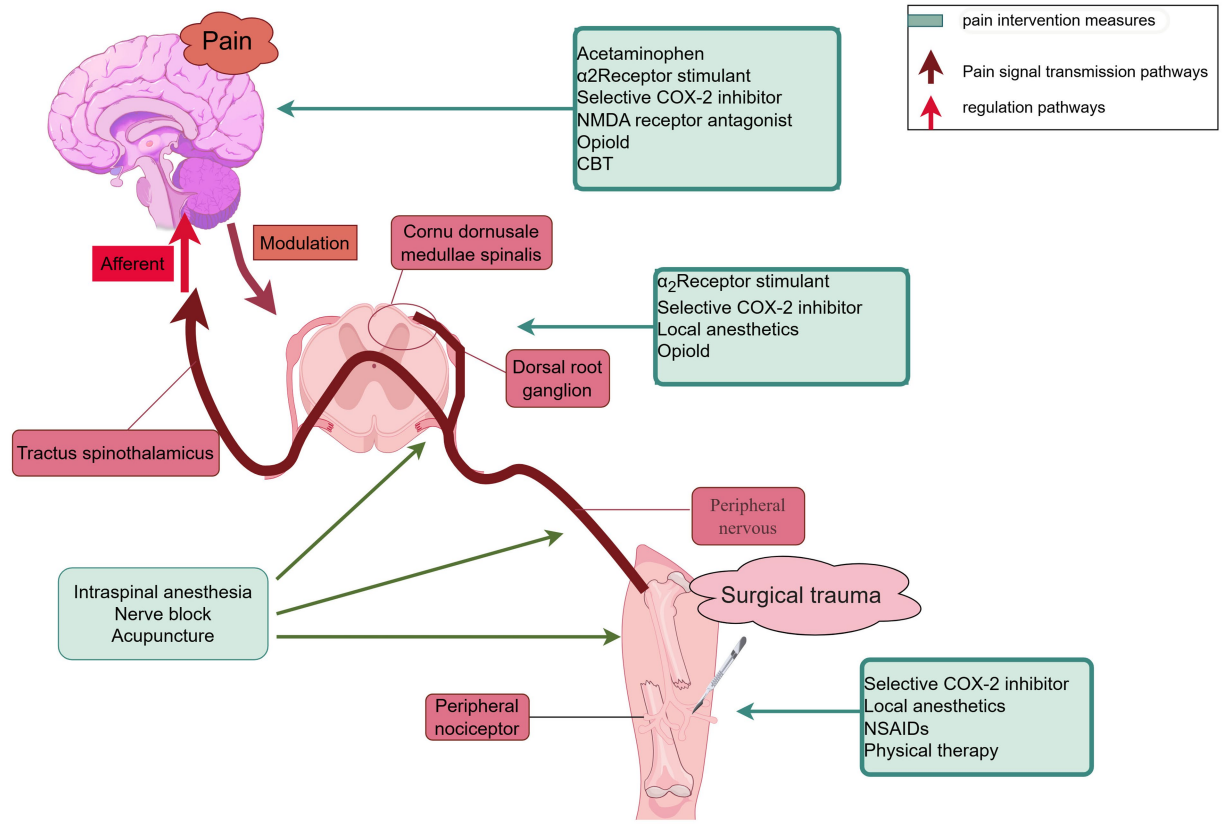

FIGURE 2
Schematic diagram of pain management and drug mechanism of action. The figure illustrates the basic principles and interrelationships of different pain management methods, helping to understand how to improve pain management effects through these interventions. NSAIDs, non-steroidal anti-inflammatory drugs; CBT, cognitive-behavioral therapy.

The circadian rhythms play a crucial role in enhancing patient comfort and optimizing recovery outcomes. This systematic review emphasizes the increasing recognition of effective pain management strategies as essential for postoperative recovery and overall quality of life. The interplay between pain and circadian rhythms is complex, influenced by biological, psychological, and social factors, necessitating a multifaceted approach to pain management that considers these diverse perspectives. While traditional analgesic methods have been thoroughly examined, there is an urgent need to explore innovative strategies, including multimodal analgesia and non-pharmacological interventions, to assess their effectiveness and potential integration into clinical settings. Future research should focus on the bidirectional relationship between pain perception and circadian rhythms, investigating how disruptions in circadian cycles can exacerbate pain and vice versa. Gaining insights into these interactions could lead to the creation of tailored pain management strategies that align with patients' biological rhythms, ultimately enhancing recovery outcomes. Additionally, fostering interdisciplinary collaboration among healthcare providers, researchers, and patients is crucial for advancing this field. Engaging patients in their pain management choices can empower them and potentially lead to better treatment outcomes.

Evidence highlights a two-way relationship between postsurgical pain and disruptions in circadian rhythms, which are influenced by neuroinflammatory pathways and neuroendocrine imbalances. To improve treatment outcomes, clinicians should consider timing analgesic medications in accordance with the body's natural circadian rhythms. This involves scheduling nonsteroidal anti-inflammatory drug (NSAID) doses to coincide with periods of heightened pro-inflammatory cytokine activity, as determined by circadian biomarker profiling. Such a chronotherapeutic strategy could enhance the effectiveness of pain relief while reducing the risk of developing tolerance by aligning treatment with biological rhythms. Current guidelines suggest using a multimodal approach that combines α_2-adrenergic agonists with complementary therapies, such as electroacupuncture, to effectively manage pain signaling and correct circadian misalignment. Melatonin, which plays dual roles in pain relief and circadian regulation, can help reduce postoperative pain and restore normal sleep–wake cycles, particularly in patients with substantial circadian misalignment. A thorough assessment of circadian rhythms should include both subjective evaluations, like validated sleep questionnaires, and objective measurements, such as actigraphy to track rest-activity cycles, to accurately gauge circadian health.

Author contributions

DM: Conceptualization, Funding acquisition, Supervision, Visualization, Writing – original draft, Writing – review & editing. LL: Formal analysis, Methodology, Software, Writing – review & editing. WL: Formal analysis, Visualization, Writing – review & editing. JX: Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This study was supported by Science and Technology program of Jinhua Science and Technology Bureau (2021-4-179) and Foundation of Zhejiang Provincial Education Department (Y202146994).

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.

Generative AI statement

The authors declare that Gen AI was used in the creation of this manuscript. Generative AI tools were used to assist in language editing and formatting of the manuscript. Specifically, e.g., Deep Seek and Kimi was employed to refine sentence structure, grammar, and clarity. All content generated by AI was thoroughly reviewed, revised, and verified by the authors to ensure accuracy, consistency with the study's objectives, and alignment with academic integrity standards. The authors retain full responsibility for the final content and conclusions presented in this manuscript.

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frontiers | Frontiers in Medicine

TYPE Systematic Review
PUBLISHED 28 April 2025
DOI 10.3389/fmed.2025.1567794

OPEN ACCESS

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RECEIVED 28 January 2025
ACCEPTED 02 April 2025
PUBLISHED 28 April 2025

CITATION
Wang Y, Gou Z-h, Wang G-m, Ye L-h, Chen L and Wang Q (2025) Association of remimazolam with delirium and cognitive function in elderly patients undergoing general anesthesia or procedural sedation: a meta-analysis of randomized controlled trials. *Front. Med.* 12:1567794.
doi: 10.3389/fmed.2025.1567794

Association of remimazolam with delirium and cognitive function in elderly patients undergoing general anesthesia or procedural sedation: a meta-analysis of randomized controlled trials

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Background: Remimazolam is an ultra-short-acting benzodiazepine with sedative effects, but its impact on postoperative delirium (POD) and cognitive function in elderly patients remains unclear. This study aimed to compare the incidence of POD and cognitive function between remimazolam and other sedatives in elderly patients undergoing general anesthesia or procedural sedation.

Methods: This study included randomized controlled trials (RCTs) comparing remimazolam with other sedatives in elderly patients undergoing general anesthesia or procedural sedation. A comprehensive search was conducted in Ovid MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and the China National Knowledge Infrastructure (CNKI) from inception to January 2, 2025, without language restrictions. Data were pooled quantitatively using a random-effects model. The primary outcomes were the incidence of POD and cognitive function.

Results: A total of 1,808 elderly patients from 11 RCTs were included. Compared with other sedatives, remimazolam did not increase the incidence of POD (OR: 0.62, 95% CI [0.23, 1.68], $p = 0.35$, $I^2 = 73\%$), but improve cognitive function, as measured by Mini-Mental State Examination scores, the seventh postoperative day (MD: 0.53, 95% CI [0.16, 0.91], $p = 0.005$, $I^2 = 28$). Additionally, remimazolam significantly reduced the incidence of hypotension (OR: 0.27, 95% CI [0.21, 0.35], $p < 0.001$, $I^2 = 0\%$) and respiratory depression (OR: 0.35, 95% CI [0.17, 0.69], $p = 0.003$, $I^2 = 0\%$) compared to other sedatives. However, no significant differences were observed between remimazolam and other sedatives for postoperative nausea and vomiting (OR: 1.31, 95% CI [0.91, 1.89], $p = 0.15$, $I^2 = 0\%$) or hypoxemia (OR: 0.69, 95% CI [0.35, 1.34], $p = 0.28$, $I^2 = 0\%$).

Conclusion: Overall, the use of remimazolam in the elderly population appears to pose fewer risks than other sedatives. It does not increase the incidence of postoperative delirium following general anesthesia or sedation, but it improves postoperative cognitive function and provides more stable hemodynamics. However, further well-designed RCTs with long-term follow-up are needed to establish a standardized medication regimen and optimal dosage tailored to elderly patients.

Systematic review registration: https://www.crd.york.ac.uk/PROSPERO/myprospero, registration number (CRD4202563620).

KEYWORDS

delirium, cognitive function, elderly, remimazolam, postoperative

1 Introduction

Postoperative delirium is a common, acute, and transient neurological syndrome that primarily affects elderly individuals (1, 2). It is typically characterized by impaired concentration, altered levels of consciousness, drowsiness, agitation, and aggressive behavior. Elderly patients who experience postoperative delirium are more likely to suffer from perioperative complications, such as accidental removal of wound drainage tubes, wound infections, deep vein thrombosis, and even death (3). These complications not only hinder the recovery process but also increase medical costs and pose significant challenges to the healthcare system in an aging population (4).

With aging, there's an increase in the nervous system's responsiveness and alterations in neurotransmitters. The disruption of GABA receptors by benzodiazepines more readily results in consciousness issues among elderly patients (5). Traditional benzodiazepines, known for their extended half-life, may often retain their sedative and cognitive-suppressant properties post-surgery, especially when combined with reduced liver and kidney function in older patients. Additionally, certain benzodiazepines have anticholinergic effects, potentially exacerbating cognitive impairments during therapy (6). Naturally, older patients frequently experience various fundamental health issues, and the interplay among different medications, which can potentially impact cognitive function, is also an aspect that must not be ignored. Based on its pharmacological properties and previous clinical studies (7, 8), individuals tend to consider conventional benzodiazepines as a separate risk factor for postoperative delirium (9), especially in the elderly. Such drugs may result in reduced vigilance, psychomotor impairment, and anterograde amnesia, potentially impairing cognitive function (10). During the perioperative phase, their use should be advised with careful consideration for elderly patients. Recent studies indicate that benzodiazepines are not a primary cause of postoperative delirium (11), and they are still widely used in the perioperative period. Nevertheless, the potential harm of traditional benzodiazepines to elderly patients should not be overlooked, highlighting the urgent need for new, safer sedative drugs with fewer side effects.

Remimazolam is an ultra-short-acting benzodiazepine that induces sedation by binding to central gamma-aminobutyric acid type A receptors (GABA_A). It is increasingly used in various surgical procedures due to its rapid metabolism, short half-life, minimal circulatory effects, and the availability of a specific antagonist (12). Some studies suggest that remimazolam may reduce neuronal inflammation and the incidence of postoperative delirium and cognitive dysfunction (13, 14). However, recent retrospective studies and systematic reviews have found no significant correlation between remimazolam and postoperative delirium in adults (15, 16). In particular, for elderly patients, the association remains unclear due to limited sample sizes and other confounding factors.

To better understand the effects of remimazolam on postoperative delirium and cognitive changes in elderly patients and to enhance its safety in this population, we conducted this comprehensive meta-analysis.

2 Methods

2.1 Protocol and guidance

This meta-analysis was performed following the established methods recommended by the Cochrane Collaboration. The article adheres to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Additionally, the study protocol was prospectively registered on PROSPERO (ID: CRD42025636200).

2.2 Criteria for considering studies for this review

Eligible studies were selected based on the following PICOS (participants, interventions, comparators, outcomes, and study design) criteria:

(1) Population: Elderly patients (age ≥65) undergoing general anesthesia or procedural sedation.
(2) Intervention: Use of remimazolam as the primary hypnotic or as an adjunct.
(3) Comparison of intervention: Other hypnotics or sedatives.
(4) Outcome: At least one of the primary outcomes, including the incidence of postoperative delirium or cognitive function. Secondary outcomes included hypotension, postoperative nausea and vomiting, hypoxemia, and respiratory depression.
(5) Study design: Randomized controlled trials.

The studies were excluded based on the following criteria: (1) patients with pre-existing delirium or dementia; (2) patients diagnosed with other neurocognitive or psychiatric disorders; (3) patients with known benzodiazepine allergies; (4) use of other benzodiazepines in perioperative management; or (5) use of remimazolam for the postoperative treatment of delirium or agitation.

2.3 Information sources and search strategy

A medical librarian (YW) developed comprehensive search strategies for Ovid MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and the China National Knowledge

Infrastructure (CNKI) from their inception through January 2, 2025. Additionally, the World Health Organization International Clinical Trials Registry Platform was searched for completed but unpublished studies. References from key articles were also screened to identify any additional relevant studies. No restrictions were applied regarding language or publication status. The search terms included "remimazolam," "hypnotics," "sedatives," "elder," "older," and "randomized controlled trial," used individually or in combination. The detailed search strategies are presented in Supplementary Table 1.

2.4 Study selection

Two researchers (Z-hG and G-mW) independently assessed the eligibility of studies based on the titles and abstracts retrieved from the electronic search. The full texts of the studies that met the initial criteria were then reviewed independently and in duplicate by both researchers. Disagreements were resolved through consultation with a third researcher (QW).

2.5 Data extraction

Two researchers (YW and L-hY) independently extracted data on study characteristics and outcomes from the full-text articles using pretested forms. Disagreements were resolved through consultation with a third researcher (QW).

2.6 Assessment of risk of bias and quality of evidence

For each randomized controlled trial (RCT), two researchers (YW and LC) independently assessed the risk of bias using the Cochrane Risk of Bias Tool (RoB 2). The assessment addressed the following domains: random sequence generation, blinding of participants and personnel, allocation concealment, blinding of outcome assessment, selective reporting, incomplete outcome data, and other potential sources of bias. Each domain was categorized as having a low, unclear, or high risk of bias.

The certainty of the evidence regarding the effects of remimazolam in elderly patients undergoing general anesthesia or procedural sedation was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This evaluation took into account the risks of bias, inconsistency, imprecision, indirectness, and publication bias in accordance with the detailed GRADE guidelines.

2.7 Data synthesis

Statistical analyses were conducted using RevMan (version 5.4, The Cochrane Collaboration) and the meta package in R (version 4.4.2, R Project for Statistical Computing). Pooled treatment effects across studies were estimated using a random-effects model. For dichotomous outcomes, odds ratios (ORs) with 95% confidence intervals (CIs) were computed, while for continuous outcomes, mean differences (MDs) with 95% CIs were reported. Statistical significance was evaluated using two-sided tests, with a p-value of < 0.05 deemed significant.

Heterogeneity was assessed visually using forest plots and quantified with I^2 values, categorized as low (0–40%), moderate (40–75%), or high (>75%). Publication bias was not evaluated statistically due to the inclusion of fewer than 10 studies for each outcome.

2.8 Subgroup analysis and sensitivity analysis

Subgroup analyses were conducted to identify potential sources of heterogeneity. The prespecified subgroup factors included: (1) type of anesthesia (general anesthesia vs. procedural sedation), (2) American Society of Anesthesiologists (ASA) status, (3) sex distribution (male proportion <50% vs. ≥50%), (4) sample size, and (5) type of surgery (minor, intermediate, and major surgeries). These factors were selected based on their known influence on patients' responses to anesthesia and recovery, and were considered crucial for evaluating the robustness and reliability of the synthesized results.

Additionally, a leave-one-out sensitivity analysis was performed to assess small-study effects and determine whether any individual study significantly influenced the robustness of the pooled effect size. Furthermore, additional sensitivity analyses for the primary outcomes were conducted using fixed-effect models. Given the heterogeneity of the comparator group, further sensitivity analyses for the primary outcomes were carried out by including only RCTs that compared remimazolam with propofol.

3 Results

3.1 Study selection and study characteristics

Figure 1 displays the PRISMA flow diagram for the meta-analysis. A total of 540 potentially eligible publications were initially identified. After removing 241 duplicates, 299 articles were screened based on titles and abstracts, leading to the exclusion of 80 articles. Following a full-text review, 108 studies were further excluded, leaving 11 trials to be included in the final analysis.

The main characteristics of the included studies are summarized in Table 1, which involved a total of 1,808 elderly participants. Sample sizes ranged from 59 to 400 patients. Six studies (17–22) involved patients receiving general anesthesia, while the remaining five studies (23–27) focused on sedation. Propofol was the most commonly used non-benzodiazepine hypnotic in the control group. Postoperative delirium was assessed using the Confusion Assessment Method (CAM) (17, 18, 23), and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (21). Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) scores in all studies, with Liao et al. (19) additionally employing the Montreal Cognitive Assessment (MoCA). The majority of participants were classified as American Society of Anesthesiologists (ASA) status I or II.

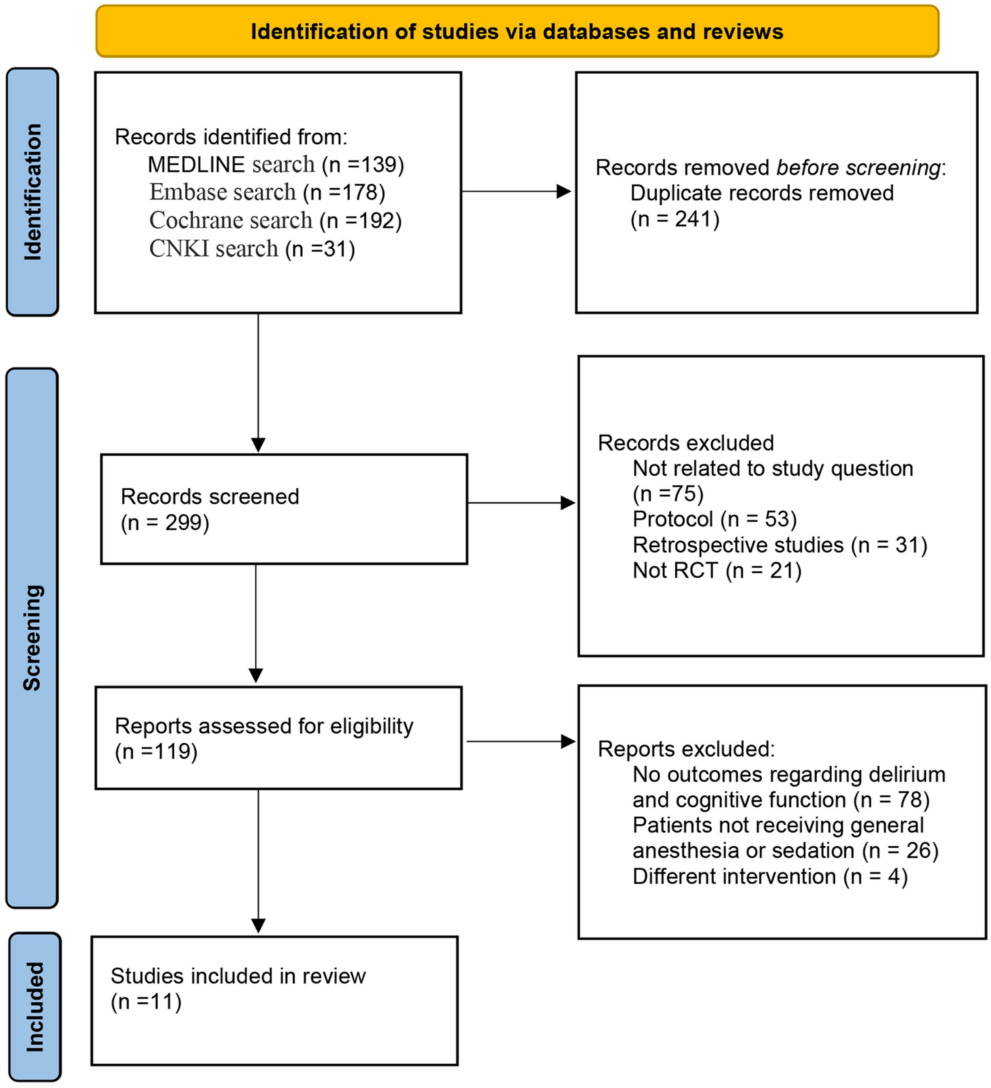

FIGURE 1
PRISMA flow diagram of study selection.

3.2 Risk of bias and quality of evidence

The risk-of-bias assessments are presented in Figure 2. Most domains in the included studies showed a low risk of bias; however, attention is warranted for deviations from intended interventions and outcome measurements, as several studies exhibited a high risk of bias.

The GRADE summary findings for all outcomes are presented in Supplementary Table 2. The quality of evidence for postoperative delirium and cognitive function on postoperative day 7 was rated as moderate. Publication bias was not assessed due to the limited number of studies (<10) included for each outcome.

3.3 Postoperative delirium

Eight trials involving 1,561 patients reported data on postoperative delirium. The time window and frequency of delirium assessments in these trials are detailed in Supplementary Table 3. The overall incidence of postoperative delirium was 4.9% in the remimazolam group, compared to 6.3% in the other sedatives group. The pooled effect size showed that remimazolam administration did not significantly increase the incidence of postoperative delirium (OR: 0.62, 95% CI [0.23, 1.68], $p = 0.35$, $I^2 = 73\%$; Figure 3).

In a subgroup analysis of three studies involving elderly patients undergoing general anesthesia, there was no significant difference in the incidence of delirium between remimazolam and other sedatives (OR: 1.00, 95% CI [0.52, 1.93], $p = 0.23$, $I^2 = 31\%$; Figure 3). However, remimazolam was significantly associated with a lower risk of postoperative delirium compared to other sedatives following procedural sedation (OR: 0.21, 95% CI [0.06, 0.67], $p = 0.02$, $I^2 = 73\%$; Figure 3). The interaction between anesthesia type (general anesthesia vs. procedural sedation) and remimazolam on postoperative delirium was statistically significant (p for interaction = 0.02).

Other subgroup analyses of postoperative delirium revealed no significant interactions with variables such as ASA status (I-III vs. III-IV) (The interaction term was not applicable), sex (The interaction

TABLE 1 Baseline characteristics of randomized controlled trials.

References	Number of patients	Intervention	Age (years)	Male (%)	Surgery/ procedure	Type of surgery	ASA	Anesthesia
Liu et al. (17)	100	Remimazolam	71.62 ± 5.47	22 (44)	Radical resection of colon cancer	Major	I-III	GA
		Propofol	71.40 ± 5.50	21 (42)				
Duan et al. (34)	106	Remimazolam	77.4 ± 6.1	24 (45)	Hip fracture surgery	Intermediate	II-III	Sedation
		Propofol	75.3 ± 7.7	25 (47)				
Chen et al. (24)	240	Remimazolam+ Sufentanil	71.9 ± 5.0	66 (54)	Gastroscopy	Minor	III-IV	Sedation
		Propofol+ Sufentanil	71.7 ± 5.1	62 (52.5)				
Yang et al. (18)	300	Remimazolam	68 [65 to 71]	61 (41.5)	Orthopedic surgery	Intermediate	I-III	GA
		Propofol	68 [65 to 71]	56 (36.6)				
Liu et al. (25)	216	Remimazolam	67.6 ± 5.7	51 (47.7)	Gastrointestinal endoscopy	Minor	I-III	Sedation
		Propofol	67.5 ± 4.9	51 (46.8)				
Liao et al. (19)	104	Remimazolam+Propofol+Remi	70.12 ± 3.57	21 (61.8)	Laparoscopic radical resection of gastric cancer	Major	NR	GA
		Dex + Propofol+Remi	69.69 ± 2.52	21 (60)				
		Propofol+Remi	71.26 ± 3.58	20 (57.1)				
Kuang et al. (20)	84	Remimazolam	65.4 ± 3.9	19 (45.2)	Thoracoscopic lobectomy	Major	I-II	GA
		Propofol	65.2 ± 4.4	20 (47.6)				
Jeon et al. (21)	122	Remimazolam	70.9 ± 4.3	38 (63.3)	Laparoscopic cholecystectomy and TURBT	Minor	I-III	GA
		Propofol	71.5 ± 4.3	40 (64.5)				
Zhang et al. (22)	59	Remimazolam	74.31 ± 10.6	11 (36.6)	Hip replacement	Major	II-III	GA
		Propofol	75.04 ± 9.98	12 (41.3)				
Lu at al. (26)	400	Remimazolam	70.6 ± 4.7	78 (39.0)	Gastrointestinal endoscopy	Minor	I-II	Sedation
		Propofol	70.1 ± 4.5	83 (46.5)				
Guo et al. (27)	77	Remimazolam	70.4 ± 3.9	25 (64.1)	Gastrointestinal endoscopy	Minor	I-II	Sedation
		Propofol	69.1 ± 4.0	22 (57.9)				

Dex, Demedetomidine; Remi, remifentanil; ASA, American Society of Anesthesiologists; GA, general anesthesia; TURBT, transurethral resection of bladder tumor.

FIGURE 2
Risk-of-bias results of include studies.

term was not applicable), sample size (<200 vs. ≥200) (p for interaction = 0.07), or type of surgery (p for interaction = 0.87); (Supplementary Figure 1).

A sensitivity analysis demonstrated that the pooled OR remained consistent after sequentially omitting individual studies, confirming the robustness of the findings (Supplementary Figure 2). Furthermore,

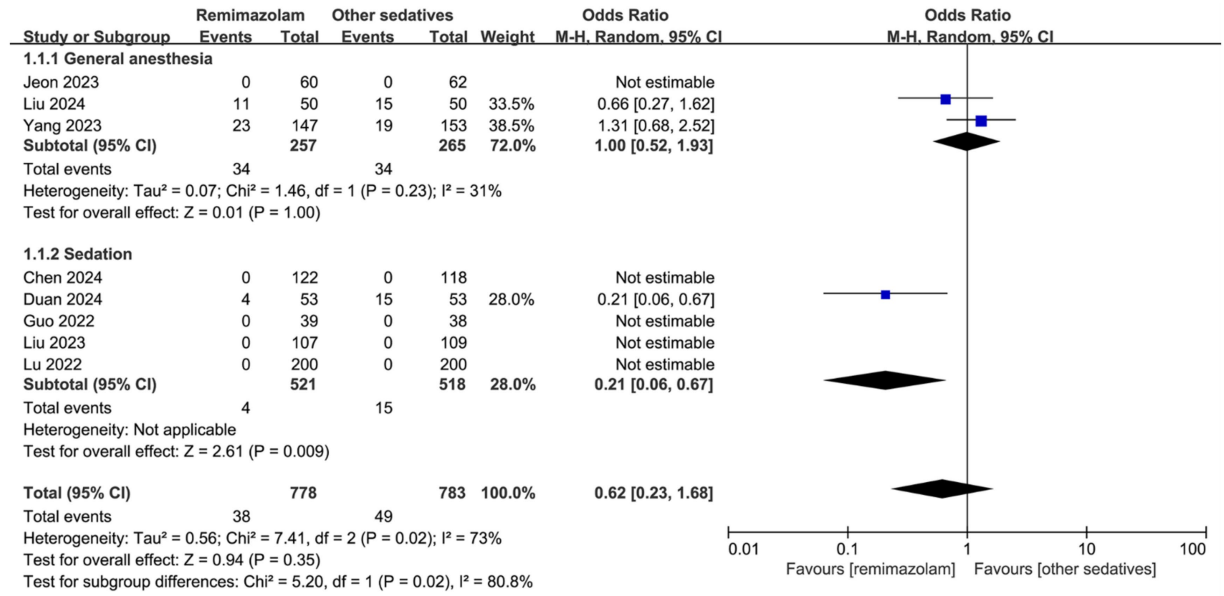

FIGURE 3
Forest plot for the incidence of postoperative delirium. CI, confidence interval.

the incidence of delirium did not differ significantly between remimazolam and other sedatives, as assessed using fixed-effect models (OR: 0.75, 95% CI [0.47, 1.20], $p = 0.23$, $I^2 = 73\%$). Similarly, no significant difference was observed in the incidence of delirium between remimazolam and propofol (OR: 0.62, 95% CI [0.23, 1.68], $p = 0.35$, $I^2 = 73\%$).

3.4 Postoperative cognitive function

Four trials involving 353 patients reported data on postoperative cognitive function. Overall, there was no significant difference in postoperative cognitive function, as measured by MMSE scores on the first postoperative day, between remimazolam and other sedatives (MD: 2.18, 95% CI [−1.25, 5.61], $p = 0.21$, $I^2 = 94\%$; Figure 4). However, among patients undergoing general anesthesia, remimazolam demonstrated a significant advantage over other sedatives (MD: 3.90, 95% CI [2.94, 4.86], $p < 0.001$, Figure 4).

By the seventh postoperative day, cognitive function was significantly higher in the remimazolam group compared to the other sedatives group. Specifically, for patients receiving general anesthesia, remimazolam maintained its superiority (MD: 0.53, 95% CI [0.16, 0.91], $p = 0.005$, $I^2 = 28\%$; Figure 4). However, this association was not observed in patients receiving procedural sedation (MD: 0.80, 95% CI [−0.70, 2.30]; Figure 4).

Subgroup analyses of cognitive function on the seventh postoperative day revealed no significant interactions with variables such as type of anesthesia (p for interaction = 0.73), ASA status (I-II vs. II-III) (p for interaction = 0.32), sex (p for interaction = 0.73), sample size (<100 vs. ≥100) (p for interaction = 0.75), or type of surgery (p for interaction = 0.73); (Supplementary Figure 3).

A leave-one-out sensitivity analysis of cognitive function on the seventh postoperative day showed that remimazolam did not demonstrate superiority over other sedatives after excluding the trial by Kuang et al. However, the pooled MD remained consistent when each of the other trials was sequentially omitted, supporting the robustness of the results (Supplementary Figure 4). Additionally, cognitive function remained significantly higher in the remimazolam group compared to the other sedatives group on the seventh postoperative day, as assessed using fixed-effect models (MD: 0.53, 95% CI [0.31, 0.76], $p < 0.001$, $I^2 = 7\%$). Similarly, cognitive function was significantly higher in the remimazolam group compared to the propofol group on the seventh postoperative day (MD: 0.56, 95% CI [0.32, 0.81], $p < 0.001$, $I^2 = 0\%$).

3.5 Secondary outcomes

The incidence of hypotension during surgery is shown in Figure 5. Overall, remimazolam significantly reduced the incidence of hypotension compared to other sedatives (OR: 0.27, 95% CI [0.21, 0.35], $p < 0.001$, $I^2 = 0\%$; Figure 5). This effect was consistent in both the general anesthesia subgroup (OR: 0.29, 95% CI [0.20, 0.43], $p < 0.001$, $I^2 = 0\%$; Figure 5) and the sedation subgroup (OR: 0.26, 95% CI [0.19, 0.36], $p < 0.001$, $I^2 = 0\%$; Figure 5).

Other outcomes, including postoperative nausea and vomiting, hypoxemia, and respiratory depression, are presented in Supplementary Figure 5. Specifically, the definitions of respiratory depression used in the included RCTs were detailed in Supplementary Table 4. No significant differences were found between remimazolam and other sedatives for postoperative nausea and vomiting (OR: 1.31, 95% CI [0.91, 1.89], $p = 0.15$, $I^2 = 0\%$) or hypoxemia (OR: 0.69, 95% CI [0.35, 1.34], $p = 0.28$, $I^2 = 0\%$). However, remimazolam was associated with a significantly lower incidence of respiratory depression compared to other sedatives (OR: 0.35, 95% CI [0.17, 0.69], $p = 0.003$, $I^2 = 0\%$).

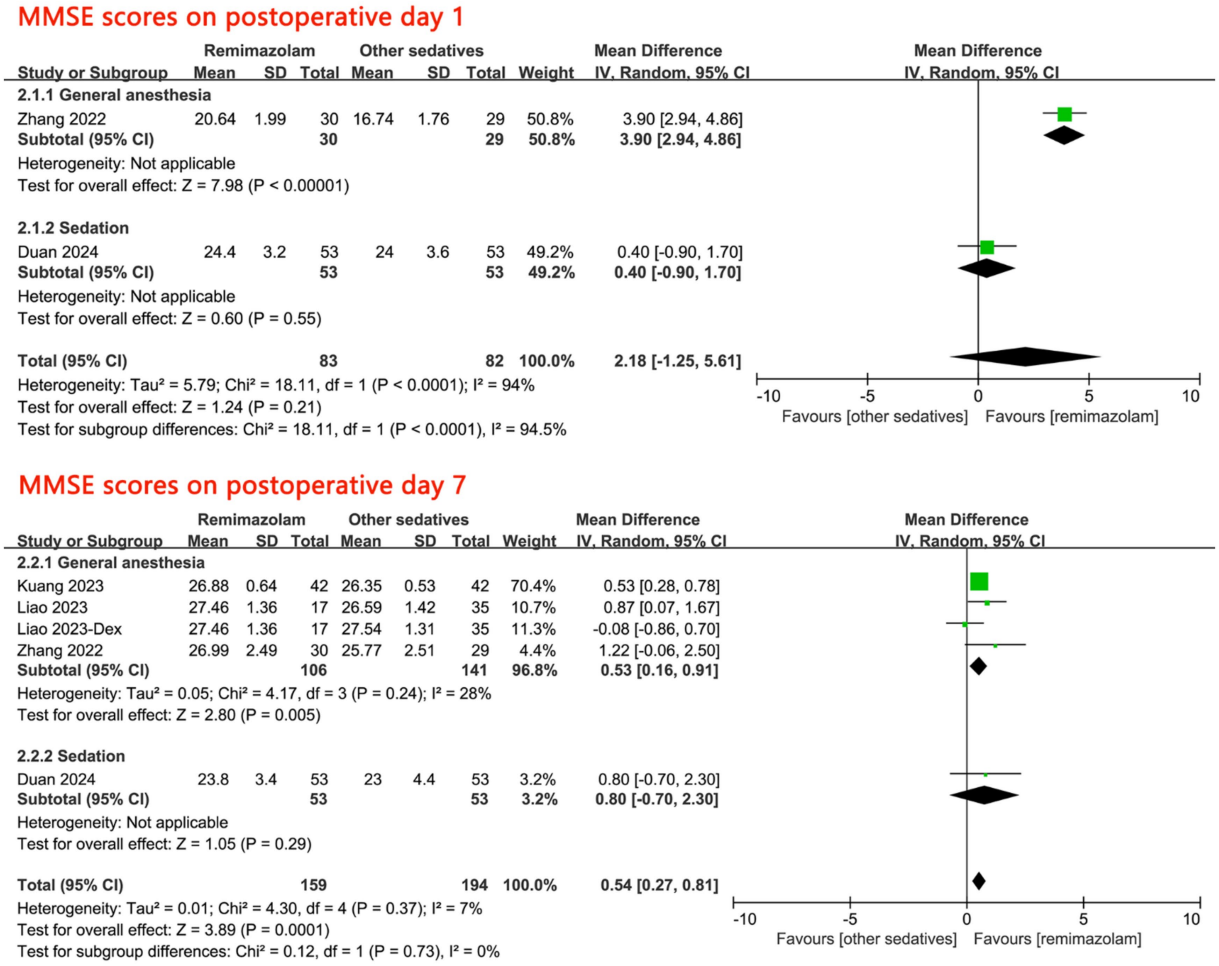

FIGURE 4
Forest plot for postoperative cognitive function. MMSE, Mini-Mental State Examination; Dex, Demedetomidine; CI, confidence interval.

4 Discussion

Our meta-analysis included 11 randomized controlled trials (RCTs), and the results indicated that while remimazolam does not significantly reduce the incidence of postoperative delirium in this population, it notably improves cognitive function by the seventh postoperative day. Additionally, remimazolam was associated with a reduced risk of intraoperative hypotension and respiratory complications during surgery. These benefits seem to contribute to maintaining a steadier blood oxygen flow to the brain throughout the perioperative phase, which may adjust the prolonged cognitive condition of older patients. These advantages collectively highlight its potential as a safer anesthetic.

Relative to other populations, elderly patients tend to suffer more from delirium and consciousness issues post-surgery, often due to pathological and physiological alterations like reduced central nervous system activity. However, earlier research focusing on remimazolam and POD lacks a comprehensive examination and discussion of this particular group. Given the increasing use of remimazolam in medical practice in recent years and the acceleration of population aging, it is necessary to closely monitor the potential impact of remimazolam on elderly patients. Consequently, our research focused on elderly patients, aiming to bridge the research gap by assessing remimazolam's impact on cognitive function and the occurrence of delirium post-surgery.

The American Geriatrics Society has highlighted the increased risk of delirium in older adults associated with anticholinergic drugs, extended-release benzodiazepines, and opioids like ketamine, advising caution in their use (28, 29). However, the widespread use of benzodiazepines and opioids in surgical settings continues across various patient groups, largely due to their unique pharmacological benefits and irreplaceability, particularly for sedation and the treatment of anxiety in elderly patients. In our study, the use of remimazolam in elderly patients did not result in statistically significant differences in the incidence of delirium. However, there was moderate heterogeneity (73%) in the incidence of delirium. We observed a statistically significant interaction between anesthesia type (general anesthesia vs. procedural sedation) and remimazolam on postoperative delirium (P for interaction = 0.02). But the interaction suggests that the effect of remimazolam on the incidence of postoperative delirium may vary depending on the type of anesthesia used. However, the finding that remimazolam reduces the incidence of postoperative delirium in procedural sedation is based on a single small study (n = 106), and further research is needed to confirm these results.

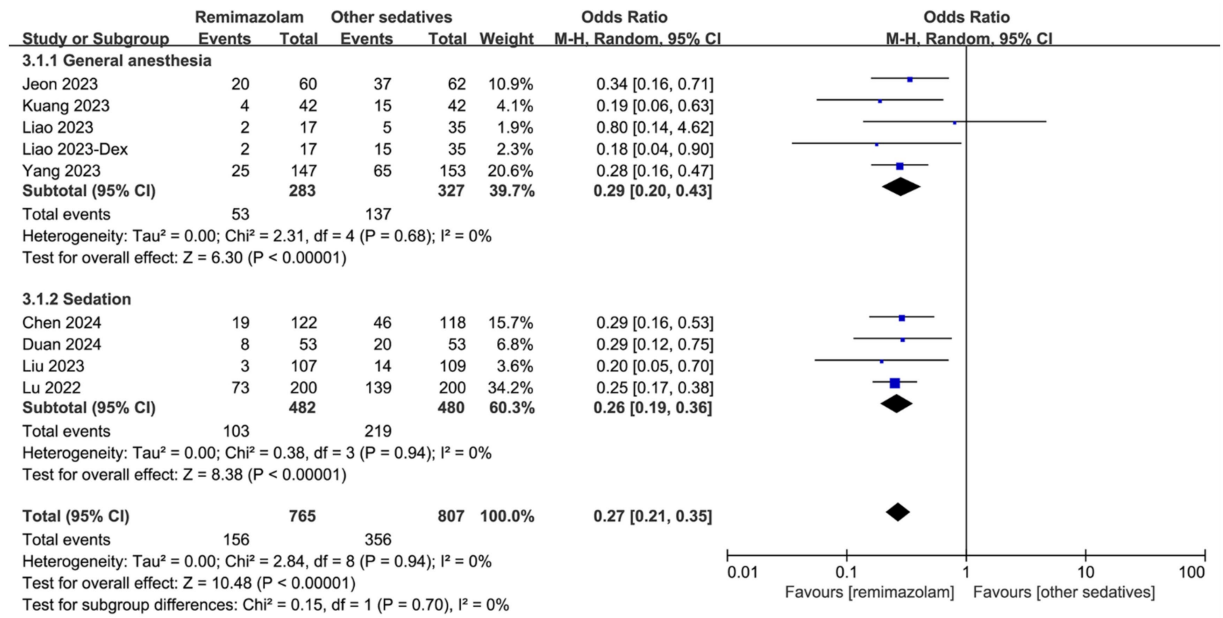

FIGURE 5
Forest plot for the incidence of hypotension during surgery. Dex, Demedetomidine; CI, confidence interval.

Although some studies suggested that remimazolam may alleviate delirium symptoms in elderly patients following surgery (23, 30), our analysis and other scientific research (15, 16, 31) conducted in adults consistently indicate that remimazolam does not offer a significant advantage in reducing postoperative delirium. Subgroup analysis revealed no intrinsic link between the type of anesthesia, gender, and postoperative cognitive function. However, elderly patients who underwent general anesthesia had a significantly higher likelihood of developing postoperative delirium compared to those who received sedation. This implies that the variety and total amount of anesthesia medications play crucial roles that must not be overlooked when developing POD in elderly patients. Up until now, the precise impact of remimazolam on postoperative delirium and cognitive function in elderly patients has remained largely undefined. Despite our discovery that remimazolam enhances cognitive abilities on the seventh day post-surgery, the lack of long-term consciousness-state monitoring data necessitates further extensive research to understand its precise effects on the consciousness state in older patients.

Remimazolam, an innovative ultra-short-acting benzodiazepine, does not significantly increase the risk of POD in elderly patients compared to sedatives like propofol. We believe this may be attributed to several key factors outlined below: first, remimazolam is rapidly metabolized by tissue esterases into inactive carboxylic acid metabolites, thus preventing the accumulation of active metabolites. And its elimination half-life after a single injection is less than 1 h, meaning that even elderly patients with liver or kidney dysfunction can minimize its persistent depressive effects on the nervous system (32). Second, its observed properties in multiple studies, including promoting the recovery of cellular immune function (33), antioxidant (34), and anti-inflammatory (35) properties, as seen in fundamental experimental studies, appear to offer neuroprotective benefits. Furthermore, the reduced regulation of blood circulation in the brain in the elderly significantly contributes to the development of POD. Compared to other sedatives, remimazolam ensures steadier blood flow to the brain during surgical procedures, enhancing neuroprotection. Moreover, the safety of remimazolam is further enhanced by flumazenil, a specific antagonist that rapidly reverses its neuroinhibitory effects (36). These make remimazolam a potentially safer option for the elderly population.

Our analysis indicates that, compared to other anesthetics, remimazolam provides more stable organ blood flow during surgery in elderly patients and reduces the risk of respiratory depression. These factors may play a critical role in preserving cognitive function after surgery (16, 31). While no statistically significant differences were observed between remimazolam and non-benzodiazepine drugs in cognitive function on the first postoperative day, patients treated with remimazolam demonstrated significantly better cognitive function by day 7. The results indicated that remimazolam might be preferred as a sedative in clinical settings for older patients, particularly for those at elevated risk of POD, including individuals susceptible to respiratory depression, obesity, frailty, hemodynamic instability, prolonged sedative use, or concurrent neurological conditions. Patients in this category often favor sedatives that barely affect breathing or blood flow.

Our systematic review and meta-analysis has several limitations. First, the limited sample size (11 RCTs) may affect the reliability and robustness of the findings. Second, most studies were conducted in China, limiting generalizability due to variations in medical practices, regions, and ethnicities. Broader research across diverse populations is needed. Third, the lack of standardized definitions and tools for assessing postoperative delirium may impact the accuracy of the results. For example, in the postoperative cognitive function assessment, the MMSE scale is mostly used, but it has the disadvantage of low sensitivity to mild cognitive impairment. Future research might explore employing evaluation instruments that are more attuned to the needs of older patients, like the Montreal Cognitive Assessment.

Fourth, the variation in the time window and frequency of postoperative delirium assessments across the included trials may influence the evaluation of remimazolam's impact on postoperative delirium. Fifth, the definitions used in the included RCTs showed slight variations, which may potentially affect the evaluation of remimazolam's impact on respiratory depression. Additionally, the limited sample size highlights the need for further research on this topic. Lastly, variations in remimazolam regimens, including dosage and duration, contribute to heterogeneity. These factors warrant caution when interpreting the results.

5 Conclusion

Overall, the use of remimazolam in the elderly population appears to pose fewer risks than other sedatives. It does not increase the incidence of postoperative delirium following general anesthesia or sedation, but it improves postoperative cognitive function and provides more stable hemodynamics. This could render it a safer medication option for fragile, severely sick older patients. Nonetheless, due to the limited existing experience and studies on remimazolam's application in older adults, there's a need for more meticulously planned randomized controlled trials (RCTs) and extended monitoring to formulate uniform medication protocols and ideal dosages for these patients.

Data availability statement

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

Author contributions

YW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. Z-hG: Data curation, Formal analysis, Methodology, Software, Writing – original draft. G-mW: Data curation, Formal analysis, Software, Writing – review & editing. L-hY: Data curation, Formal analysis, Writing – review & editing. LC: Data curation, Formal analysis, Writing – review & editing. QW: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research 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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1567794/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 09 May 2025
DOI 10.3389/fmed.2025.1580355

OPEN ACCESS

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RECEIVED 20 February 2025
ACCEPTED 15 April 2025
PUBLISHED 09 May 2025

CITATION
Gou Z-h, Su N, Li X-c, Ren D-p, Ren S-s, Wang L and Wang Y (2025) Integrated transcriptomic and immune profiling reveals crucial molecular pathways and hub genes associated with postoperative delirium in elderly patients.
Front. Med. 12:1580355.
doi: 10.3389/fmed.2025.1580355

Integrated transcriptomic and immune profiling reveals crucial molecular pathways and hub genes associated with postoperative delirium in elderly patients

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Background: Postoperative delirium (POD) manifests as severe mental disorientation, often experienced by elderly patients undergoing surgery, significantly hindering recovery and deteriorating the quality of life. Despite numerous clinical studies, the molecular mechanisms behind POD in elderly patients are still not well understood, requiring further investigation to identify potential biomarkers and therapeutic targets.

Methods: This study amalgamates Gene Set Variation Analysis (GSVA), Weighted Gene Co-expression Network Analysis (WGCNA), differential expression analysis, and immune infiltration assessments to identify molecular pathways and hub genes linked to the initiation of POD in the elderly. Gene expression data were sourced from the GSE163943 dataset in the Gene Expression Omnibus (GEO) database. A total of 18,894 protein-coding genes were extracted for analysis.

Results: We constructed a gene co-expression network using WGCNA and performed GSVA to investigate the link between POD and different types of cell death. The results indicated that POD is positively associated with pyroptosis and parthanatos, while negatively correlated with oxidative stress and disulfidptosis. Differential expression analysis revealed 145 differentially expressed genes (DEGs), including 83 downregulated and 62 upregulated genes. Analysis of functional enrichment revealed that DEGs were enriched in activities like neuron projection development, axonogenesis, and synapse organization, with KEGG pathway analysis identifying neuroactive ligand-receptor interaction and neurodegeneration pathways. Gene Set Enrichment Analysis (GSEA) further revealed the upregulation of the apoptosis pathway and the downregulation of neuroactive ligand-receptor interaction. Protein–protein interaction (PPI) network analysis identified 10 hub genes, including COL18A1, CD63, and LTF. Immune infiltration analysis indicated that the occurrence of POD is strongly associated with immune cell activation, particularly in T cells and macrophages.

Conclusion: Overall, this research primarily examines the intricate interplay between cell death processes and alterations in the immune microenvironment throughout the development of geriatric POD, pinpointing essential genes that provide vital theoretical support for further studies on geriatric POD. However, this discovery is only an initial one derived from analyzing the datasets.

Upcoming research ought to evaluate and scrutinize additional datasets and conduct essential experiments to guarantee the precision and widespread relevance of the analytical findings.

KEYWORDS

postoperative delirium, elderly, cell death, immune microenvironment, WGCNA, PPI

1 Introduction

Postoperative delirium (POD) is a common perioperative neurological complication in the elderly, characterized by acute neurocognitive impairment that occurs over a short period (1). As society ages, the adverse effects of POD on the quality of postoperative recovery, healthcare costs, and mortality rates are increasingly being recognized. Even with the growing focus on preventing and treating POD, along with extensive experimental and clinical studies (2, 3), the fundamental molecular mechanisms of its pathogenesis remain mostly a mystery, highlighting the need for further research to improve treatment outcomes.

With the emergence of bioinformatics technologies, such as high-throughput sequencing, transcriptome analysis, and weighted gene co-expression network analysis (WGCNA) (4), the field of pathophysiological research on POD has significantly expanded, providing more precise directions for research. Current theories suggest that different types of programmed cell death could intensify neuroinflammation and oxidative stress, thereby accelerating the onset of POD (5, 6). Additionally, immune dysfunction is also thought to be closely associated with the occurrence of POD. These research findings offer new perspectives—integrating transcriptome data with immune characteristic analysis may help us gain a deeper understanding of the interactions and effects between neuroinflammation and immune responses in the development of POD (7, 8).

Our aim is to elucidate the precise link between POD and the diverse patterns of cell death using advanced analytical techniques, such as GSVA and WGCNA. The study also employed several methods, including differential expression analysis, functional enrichment analysis (9), and protein–protein interaction (PPI) network analysis (10, 11), to identify the pathogenic molecular pathways and key genes associated with the development of POD. Finally, we performed immune infiltration analysis to explore the roles of various immune cells in the progression of POD. By employing various bioinformatics methods, our comprehensive molecular analysis of POD in the elderly led to the discovery of its key pathogenic genes and novel therapeutic targets, establishing a solid foundation for future studies and the development of more effective diagnostic and treatment approaches.

2 Materials and methods

2.1 Data acquisition and preprocessing

Gene expression data were obtained from the GSE163943 dataset in the Gene Expression Omnibus (GEO) database. This dataset includes peripheral blood samples from four elderly patients (aged > 75) who developed POD after orthopedic surgery, as well as four age- and sex-matched non-POD orthopedic surgery patients. The original study employed a rigorous case–control matching design to ensure that there were no statistically significant differences in baseline characteristics between the two groups, including age, sex, body mass index (BMI), surgery duration, coronary heart disease (CHD), cerebrovascular disease (CVD), hypertension, and diabetes (all $p > 0.05$). All sample collections followed standardized preoperative fasting, anesthesia protocols, and postoperative care standards to minimize confounding factors. Ultimately, a total of 18,894 protein-coding genes were extracted for further analysis.

The key regulatory genes for 14 types of programmed cell death (PCD) patterns come from various sources, including the KEGG database (12), GeneCards database (13), Molecular Characterization database, Reactome database (14), and review articles (15, 16). The final gene list for the 14 different PCD patterns is provided in Supplementary material 1. This includes genes related to various types of cell death pathways: alkaliptosis (17) (7 genes), apoptosis (18) (136 genes), autophagy (19) (151 genes), cuproptosis (20) (14 genes), disulfidptosis (21) (4 genes), entotic cell death (22, 23) (15 genes), ferroptosis (24) (64 genes), lysosome-dependent cell death (255 genes), necroptosis (25) (27 genes), netotic cell death (26) (17 genes), oxeiptosis (27, 28) (26 genes), parthanatos (29–31) (9 genes), pyroptosis (32, 33) (27 genes), and lactylation (34) (333 genes). A total of 1,216 PCD-related genes were collected.

2.2 GSVA and cell death pathway analysis

Investigating the link between POD and different types of cell death, GSVA was performed using predefined gene sets corresponding to various cell death mechanisms. A heatmap was generated to visualize the correlation between POD occurrence and the types of cell death.

2.3 WGCNA

A gene co-expression network was constructed using the WGCNA package in R. Sample hierarchical clustering was performed to assess clustering quality and detect potential outliers. The soft-threshold power was determined using the "sft$powerEstimate" function to ensure a scale-free network topology. To distinguish unique gene modules, a baseline of 30 units was established. An analysis of module eigengene (ME) correlations was performed to explore the link between gene modules and the incidence of POD.

2.4 Differential expression analysis

DEGs between POD and normal samples were identified using the "limma" package in R (35). The thresholds were set to $|\log2(\text{fold-change})| > 1$ and $p < 0.05$.

2.5 Functional enrichment analysis

GO and KEGG pathway enrichment analyses were performed using the "clusterProfiler" package in R (36). GO enrichment concentrated on biological processes, molecular functions, and cellular components, whereas KEGG analysis identified key signaling pathways linked to POD. Additionally, GSEA was conducted to determine upregulated and downregulated pathways with statistical significance.

2.6 PPI network construction

Genes overlapping between DEGs and key WGCNA modules were imported into the STRING database (37) to construct a PPI network. Cytoscape software was used for network visualization and analysis (38). The MCC algorithm in the CytoHubba plugin was applied to identify the top 10 hub genes.

2.7 Immune infiltration analysis

The CIBERSORT (39) and XCELL (40) algorithms were used to evaluate immune cell infiltration levels in both POD and normal samples. The study examined the relationships between the top 10 hub genes and immune cell populations. Furthermore, a correlation analysis between immune-related genes and the hub genes was performed to explore their potential roles in immune regulation.

2.8 Statistical analysis

All statistical analyses were performed using R software (version 4.2.2). Pearson correlation analysis was used to assess associations between gene modules and POD. A p-value < 0.05 was considered statistically significant in all analyses.

3 Results

3.1 GSVA analysis

For evaluating the association between different types of cell death and POD in elderly patients, we first performed GSVA scoring and generated a heatmap that shows the relationship between the occurrence of POD and various types of cell death (Figure 1A). A correlation analysis between POD and different types of cell death in the dataset revealed that POD occurrence was positively correlated with Pyroptosis and Parthanatos, and negatively correlated with Oxidative Stress and Disulfidptosis, with statistical significance (Figure 1B).

3.2 WGCNA network construction and module analysis

Analyzing the raw data statistically reveals no notable disparities in clinical factors like age, BMI, duration of surgery, and comorbidities between the POD and non-POD groups. Based on the balanced baseline characteristics of both groups, we constructed a gene co-expression network in the GSE163943 dataset using the WGCNA algorithm. Sample hierarchical clustering analysis revealed strong clustering among the eight samples, with no obvious outliers (Figure 1C). The soft threshold power was established to be 9 using the "sft$powerEstimate" function (Figure 1D).

Gene hierarchical clustering dendrograms were constructed based on gene correlations, with a minimum module size of 30, identifying 50 distinct gene modules. A dendrogram was generated based on the dissimilarity measurement (1-TOM) for all genes (Figure 1E). The MEwhite module displayed a strong positive correlation with POD ($r = 0.87$, $p = 0.005$), as well as a strong positive association with Pyroptosis and Parthanatos. The MEsienna3 module showed a strong negative correlation with POD ($r = -0.79$, $p = 0.02$) and a strong negative correlation with Pyroptosis. The MElightcyan1 module exhibited a strong negative correlation with POD ($r = -0.80$, $p = 0.02$) and with Necroptosis. The MEorangered4 module was strongly negatively correlated with POD ($r = -0.83$, $p = 0.01$) and with Pyroptosis and Neotic cell death. The MEbrown module showed a strong negative correlation with POD ($r = -0.80$, $p = 0.02$) and with Pyroptosis. The MEtan module showed a strong negative correlation with POD ($r = -0.76$, $p = 0.03$) and with Pyroptosis and Neotic cell death. The MEdarkorange2 module displayed a strong negative correlation with POD ($r = -0.72$, $p = 0.05$), a strong negative correlation with Neotic cell death, and a strong positive correlation with Lactylation. Finally, the MEplum2 module showed a strong positive correlation with POD ($r = 0.76$, $p = 0.03$).

By integrating WGCNA modules with GSVA scores, a heatmap was created to visualize the correlations between different modules and types of cell death (Figure 1F). Scatter plots (Figures 1G–N) demonstrate strong correlations between Gene Significance (GS) and Module Membership (MM) within the identified modules, with all p-values being statistically significant ($p < 0.05$).

3.3 Differential expression analysis and module intersections

The differential expression study of GSE163943 was performed with thresholds of $|\log2(\text{fold-change})| > 1$ and $p < 0.05$, identifying 145 DEGs, comprising 83 downregulated and 62 upregulated genes (Figure 2A). Modules with $|r| \geq 0.8$ overlapped with DEGs, identifying common genes across MEwhite (8 genes), MElightcyan1 (3 genes), MEorangered4 (9 genes), and MEbrown (64 genes) (Figure 2B). Similarly, modules with $|r| \geq 0.7$ identified common genes across MEsienna3 (2 genes), MEtan (17 genes), MEdarkorange2 (4 genes), and MEplum2 (2 genes) (Figure 2C).

3.4 Functional enrichment analysis

Enrichment analysis of the 145 DEGs showed that the GO terms were enriched in processes like regulation of neuron projection development, axonogenesis, synapse organization, neuron to neuron synapse, and glutamatergic synapse (Figure 2D). Analysis of the KEGG pathway revealed enrichment in pathways such as neuroactive ligand-receptor interaction, pathways of neurodegeneration (multiple

10.3389/fmed.2025.1580355

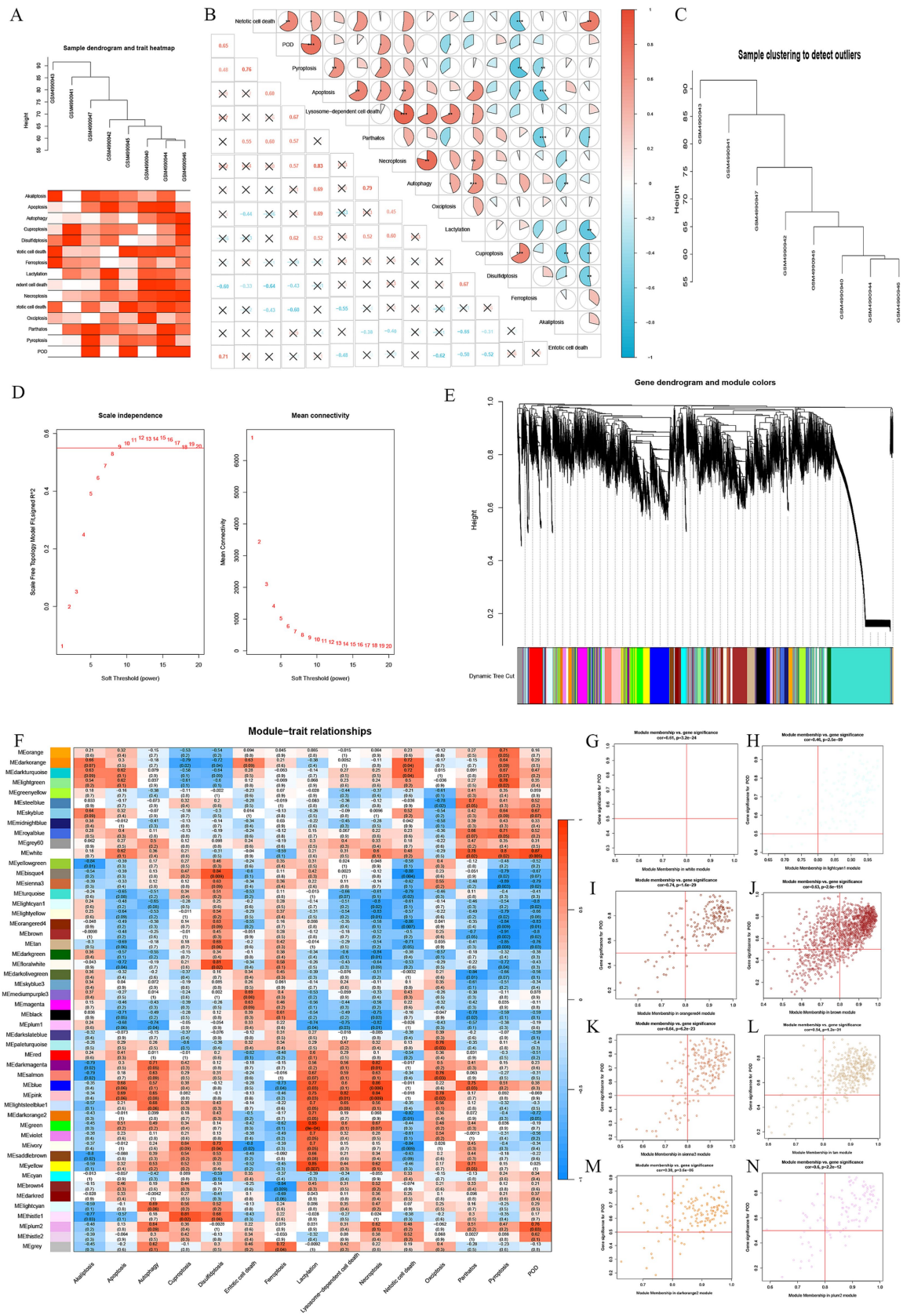

FIGURE 1
Association between POD and Cell Death pathways. **(A)** Heatmap of different types of cell death scores. **(B)** A heatmap depicts the relationship between various types of cell death and POD, with red indicating a positive correlation, blue indicating a negative one, and the completeness of the pie

(Continued)

FIGURE 1 (Continued)
chart representing the strength of the correlation. * represents $p < 0.05$, ** represents $p < 0.01$, *** represents $p < 0.001$. **(C)** Sample dispersion. **(D)** WGCNA soft threshold. **(E)** Gene dendrogram and module colors. **(F)** A heatmap illustrating the relationship between different gene modules from WGCNA and different types of cell death, where red represents positive correlation and blue represents negative correlation. **(G–N)** Scatter plots demonstrated strong correlations between the GS and MM within the identified modules.

diseases), calcium signaling pathway, PI3K-Akt signaling pathway, MAPK signaling pathway, circadian entrainment, and regulation of the actin cytoskeleton (Figure 2E). Furthermore, the KEGG analysis revealed enrichment in the GABAergic synapse pathway (Supplementary material 2).

GSEA indicated the upregulation of the apoptosis pathway and the downregulation of the neuroactive ligand-receptor interaction pathway, each showing statistical significance (Figures 2F,J). Additionally, there was a noticeable increase in oxidative phosphorylation, necroptosis, pathways of neurodegeneration (multiple diseases), Huntington disease, and Alzheimer disease pathways, while the GABAergic synapse pathway showed downregulation (Figures 2G–I,K–M).

3.5 PPI network analysis

The genes from the intersecting modules with the DEGs were combined, culminating in a total of 109 genes. Subsequently, these genes were integrated into the STRING website to construct a PPI network (Figure 3A). Results from the PPI (Supplementary material 3) were transferred to Cytoscape software, where the MCC algorithm was used to extract the top 10 genes. These genes were COL18A1, CD63, LTF, MCAM, CRP, KITLG, RPL13A, STAB1, RPL17-C18orf32, and ABCF3 (Figure 3B). A heatmap of the top 10 genes in the expression profile was generated, showing that RPL17-C18orf32, LTF, and MCAM were upregulated in the POD samples, while COL18A1, CD63, CRP, KITLG, RPL13A, STAB1, and ABCF3 were downregulated in the POD samples (Figure 3C).

3.6 Correlation between key genes and immune microenvironment

Investigating the relationship between the top 10 genes and the immune microenvironment involved conducting further analysis of immune infiltration. CIBERSORT results revealed that CD8 T cells, Monocytes, memory CD4 T cells resting, memory CD4 T cells activated, and M0 Macrophages had higher proportions in the samples (Figures 3D,E). In the correlation between the top 10 genes and CIBERSORT results, Plasma cells, M1 Macrophages, Dendritic cells activated, and Mast cells resting were closely related. RPL17-C18orf32, LTF, and MCAM showed a negative correlation with Plasma cells and M1 Macrophages, but a positive correlation with Dendritic cells activated and Mast cells resting. COL18A1, CD63, CRP, KITLG, RPL13A, STAB1, and ABCF3 demonstrated a positive correlation with Plasma cells and M1 Macrophages, but a negative correlation with Dendritic cells activated and Mast cells resting. Additionally, LTF, KITLG, and RPL17 − C18orf32 exhibited a strong correlation with various immune cells (Figure 3F).

The immune infiltration analysis of the samples using XCELL showed a significant correlation between the top 10 genes and the XCELL results. The following cell types were closely related: Astrocytes, Basophils, CD4 + Tcm, CD4 + Tem, CD8 + Tcm, CD8 + Tem, Chondrocytes, Dendritic cells (DC), Endothelial cells, immature Dendritic cells (iDC), lymphatic Endothelial cells (ly Endothelial cells), Macrophages M2, microvascular Endothelial cells (mv Endothelial cells), Myocytes, Neutrophils, plasmacytoid Dendritic cells (pDC), Platelets, Preadipocytes, pro B-cells, and Tregs. RPL17-C18orf32, LTF, and MCAM showed a positive correlation with Astrocytes, Basophils, CD8 + Tem, Chondrocytes, DC, iDC, mv Endothelial cells, Myocytes, Neutrophils, pDC, Preadipocytes, and a negative correlation with CD8 + Tcm, Endothelial cells, ly Endothelial cells, Platelets, and Tregs. COL18A1, CD63, CRP, KITLG, RPL13A, STAB1, and ABCF3 exhibited a negative correlation with Astrocytes, Basophils, CD8 + Tem, Chondrocytes, DC, iDC, mv Endothelial cells, Myocytes, Neutrophils, pDC, Preadipocytes, and a positive correlation with CD8 + Tcm, Endothelial cells, ly Endothelial cells, Platelets, and Tregs (Figure 3G).

For a deeper exploration of the relationship between the top 10 genes and immune targets, a correlation study was conducted between the 122 immune-related targets (Supplementary material 4) and the top 10 genes. A strong link was observed between several cytokines and chemokines, immune receptors and ligands, antigen presentation, major histocompatibility complex (MHC)-related genes, ligands, and activation molecules with the top 10 genes. Specifically, RPL17-C18orf32, LTF, and MCAM demonstrated a positive correlation with multiple cytokines and chemokines, while exhibiting a negative correlation with several MHC-related genes. Conversely, COL18A1, CD63, CRP, KITLG, RPL13A, STAB1, and ABCF3 exhibited an inverse relationship with multiple cytokines and chemokines, while displaying a positive correlation with several MHC-related genes (Figure 3H).

4 Discussion

POD significantly increases the risk of postoperative complications and mortality in elderly patients, exerting considerable strain on healthcare resources for both families and society (1, 41). However, there is still a lack of effective pharmacological treatments for POD. Consequently, an extensive study and assessment were carried out to explore the link between 14 distinct forms of programmed cell death (PCD) (17–34) and the emergence of POD in elderly patients, with the aim of discovering better treatments. Through the application of protein–protein interaction (PPI) network technology, we effectively pinpointed crucial genes implicated in POD development and their effects on the immune microenvironment, thereby establishing a robust theoretical foundation for seeking more effective POD treatment approaches.

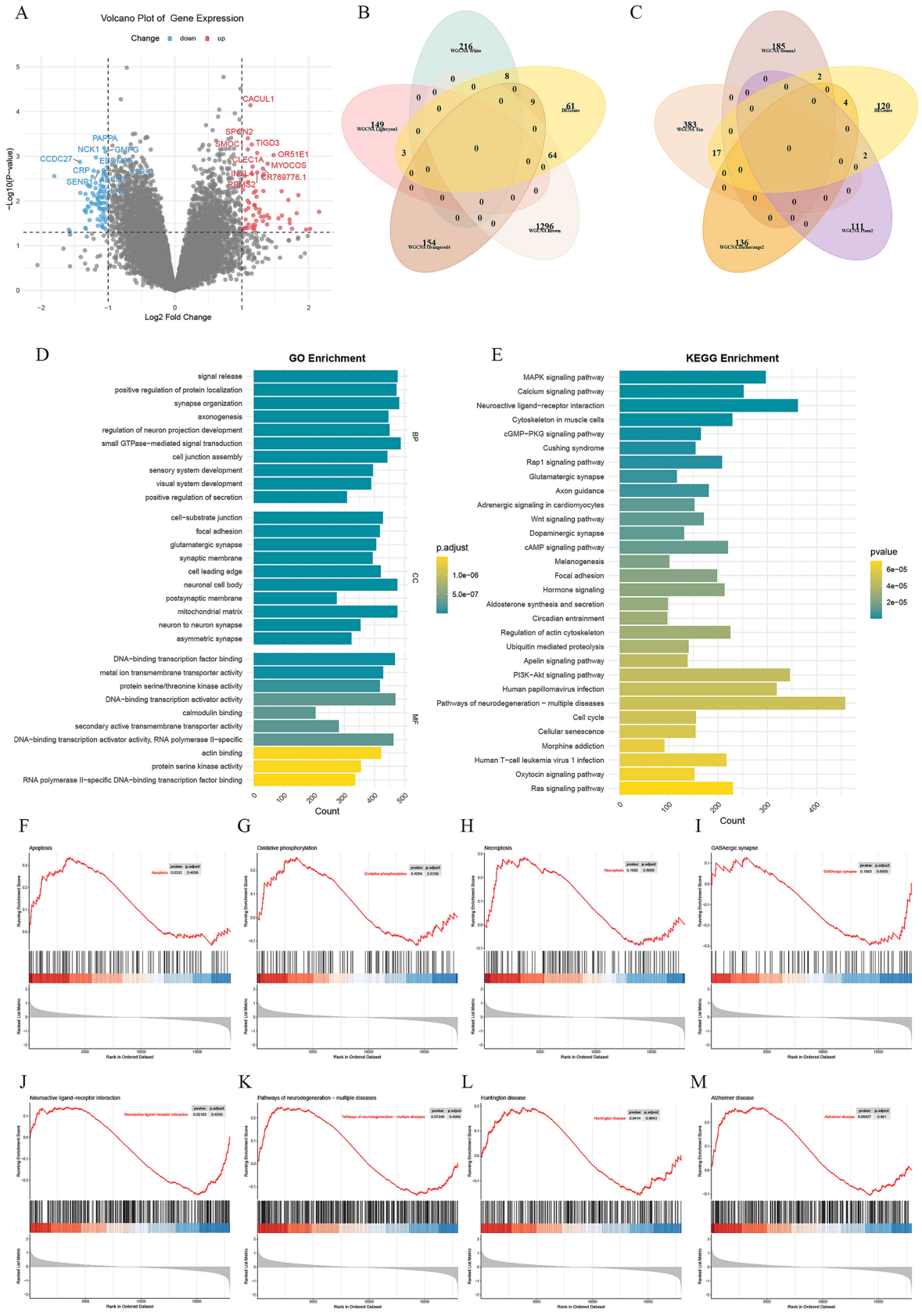

FIGURE 2
Differential expression analysis and functional enrichment analysis. **(A)** Volcano plot of differential analysis, where red represents upregulation and blue represents downregulation. **(B)** Modules with $|r| \geq 0.8$ overlapped with DEGs. **(C)** Modules with $|r| \geq 0.7$ overlapped with DEGs. **(D)** GO enrichment analysis. **(E)** KEGG enrichment analysis. **(F–M)** GSEA enrichment analysis.

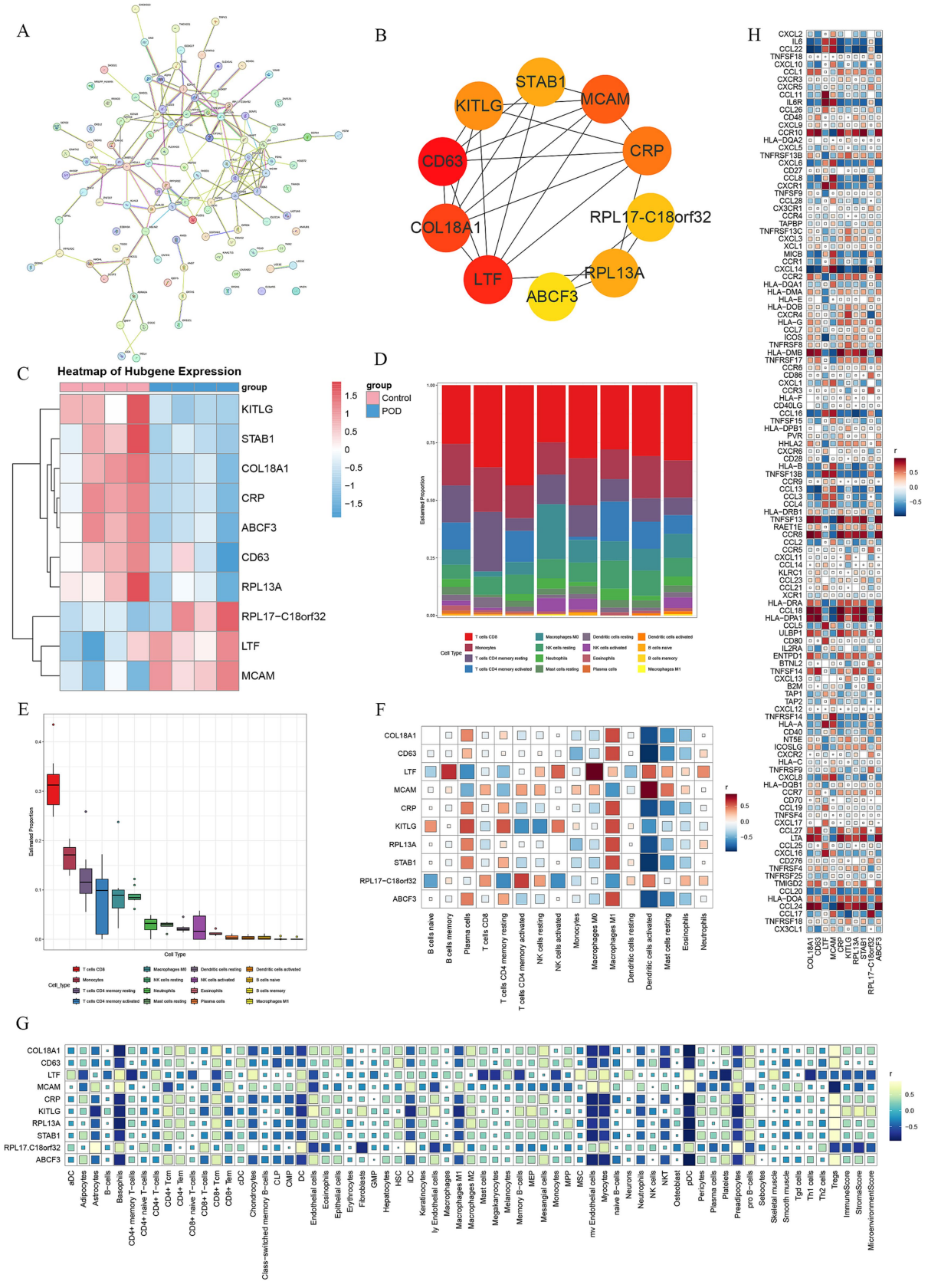

FIGURE 3
PPI network analysis and correlation between key genes and immune microenvironment. **(A)** PPI network diagram exported from the STRING website. **(B)** The top 10 genes were extracted using the MCC algorithm in Cytoscape software. **(C)** The heatmap displays the expression levels of the top 10

(Continued)

FIGURE 3 (Continued)
genes, with red indicating high expression and blue low expression. **(D)** CIBERSORT immune infiltration percentage bar plot. **(E)** CIBERSORT immune infiltration box plot. **(F)** The heatmap of the correlation between the top 10 genes and CIBERSORT immune infiltration, where red represents positive correlation and blue represents negative correlation. **(G)** A heatmap depicts the relationship between the leading 10 genes and xCell immune infiltration, with yellow-green indicating a positive link and cyan a negative one. **(H)** The heatmap of the correlation between the top 10 genes and 122 immune targets, where red represents positive correlation and blue represents negative correlation.

Each neuron requires a rich supply of blood oxygen, a stable immune system, and a balanced endocrine environment to ensure the normal transmission of neuronal signals and neurotransmitters, thus preserving brain function (42). However, in the perioperative phase, stressors such as surgical trauma, ischemia, or infection can modify the activity of crucial genes, potentially affecting the function of plasma cells, M1 macrophages, activated dendritic cells, and quiescent mast cells. This exacerbates the release of pro-inflammatory factors, such as IL-1β, IL-6, and TNF-α, which in turn regulate neuroinflammation, the balance of the blood–brain barrier (BBB), and imbalances in cellular metabolism by impacting pathways such as calcium, PI3K-Akt, and MAPK signaling, ultimately triggering POD in the elderly population (43, 44).

After screening, we identified 10 core genes closely associated with POD pathological changes, including RPL17-C18orf32, LTF, MCAM, COL18A1, CD63, CRP, KITLG, RPL13A, STAB1, and ABCF3. Within the POD specimens, there was a diminished expression of Col18a1, an essential element of the basement membrane. This decrease may be triggered by various mechanisms: firstly, diminished COL18A1 levels might interfere with the anchoring of proteins at endothelial cell junctions (like ZO-1 (45)), weakening the blood–brain barrier, thereby permitting external pro-inflammatory elements (such as IL-6, TNF-α) to infiltrate the central nervous system, intensifying inflammation in neural cells (46, 47); secondly, Col18A1 is responsible for coding the endostatin precursor protein, and its C-terminal non-collagenous domain (NC1) can emit endostatin with anti-angiogenic effects post-protease hydrolysis (48, 49). The downregulation of Col18A1 leads to a reduction in the levels of endothelial cell inhibitors, which in turn lessens the inhibition of MMP-9 activity (50) and promotes pathological restructuring of cerebral blood vessels (46, 51), thus intensifying ischemic harm in specific functional regions and brain malfunctions due to BBB permeability. In addition, Col18A1 reduces the binding region of its laminin, weakening the interaction between neurons and glial cells, which may result in neuronal dysfunction and a reduced ability to repair (52). Furthermore, some studies suggest that Col18A1 may affect cerebral blood supply by adjusting the release of neuroactive ligands or the sensitivity of receptors (53). These various changes act together, disrupting the protective function of the BBB, exacerbating neuroinflammation, and leading to the occurrence of POD.

The reduced expression of CD63 (lysosome-associated membrane protein) could indicate irregular immune interactions facilitated by extracellular vesicles (EVs). CD63-positive EVs typically carry anti-inflammatory molecules such as miR-124 (54, 55), capable of preventing the activation of pro-inflammatory M1-type microglia and A1-type astrocytes, thus safeguarding neurons by curbing neuroinflammation. Dysfunction of the GABAergic system is considered a key factor in the onset of delirium (56). A reduction in CD63 expression impacts lysosomal activity, potentially causing irregular regeneration of GABAergic synaptic vesicles and exacerbating the dysfunction of GABAergic synapses. Imbalance between excitatory neurotransmitters (such as glutamate) and inhibitory neurotransmitters (such as γ-aminobutyric acid, GABA) may have a negative impact on the consciousness level of elderly patients post-surgery. Given that benzodiazepines are widely and frequently used during the perioperative period for sedation and anesthetic induction, these medications enhance GABA_A receptors function and increase the efficacy of inhibitory neurotransmission (57). The interaction of these two elements can disturb synaptic balance, resulting in alterations in neural adaptability, which may potentially exacerbate cognitive impairments (58).

Neurons exhibit a high sensitivity to oxidative damage. The removal of RPL13A hinders the production of antioxidant enzymes (such as SOD), impacts the Nrf2/ARE pathway, worsens mitochondrial dysfunction, and elevates ROS levels (59, 60). An overabundance of peroxides triggers pathways like NF-κB, leading to the production of numerous inflammatory factors. The culmination of these reactions creates a harmful loop of inflammation and oxidative stress, which, in turn, impairs the synaptic plasticity of hippocampal neurons, negatively impacting cognitive abilities. The simultaneous downregulation of RPL13A and ABCF3 suggests a synergistic disruption of protein synthesis and metabolic homeostasis. A decline in RPL13A could result in issues with synaptic protein synthesis (61), and a decrease in ABCF3 expression might hinder the repair of damaged nerve cells, thus intensifying neurodegenerative changes.

It's important to highlight that our research revealed an inverse relationship between oxidative stress and POD, with an increase in LTF observed in POD samples. This is in opposition to the findings of numerous studies, which suggest that oxidative stress contributes to delirium (62, 63). The following processes may be responsible for this variance: (1) The biphasic effect of oxidative stress: Moderate reactive oxygen species (ROS) can enhance cellular antioxidant defenses by activating the Nrf2/ARE pathway, whereas excessive ROS may lead to neuronal damage (64, 65). (2) Time-dependent effects: The data we gathered for our study relied on transcriptomic analysis of peripheral blood samples taken within 24 h after surgery, potentially revealing the physiological signaling roles of ROS in the initial stress stage (like aiding in tissue healing), as opposed to the long-term pathological consequences of accumulation. (3) In elderly patients, a decrease in fundamental antioxidant abilities (like lower glutathione levels) can lead to moderate oxidative stress, potentially enhancing neuroprotection through the Hormesis effect (an adaptive response triggered by small amounts of harmful substances) (66). (4) Our research focuses on patients aged 75 years or older who are undergoing orthopedic surgery. The distinct metabolic alterations they exhibit with age, such as defects in mitochondrial autophagy, could lead to varying levels of oxidative

stress responses and roles compared to those in other groups, resulting in diverse outcomes (67).

Finally, we revealed the complex interaction between innate immunity and adaptive immunity in POD through immune microenvironment analysis. The positive correlation between COL18A1, CD63, plasma cells, and M1 macrophages may indicate an imbalance between anti-inflammatory reactions (like IL-10 release) (68, 69) and pro-inflammatory damage (like Tau phosphorylation) (70), potentially impacting cognitive abilities after surgery in older patients. Future research should incorporate multi-omics techniques (e.g., cerebrospinal fluid EVs miRNA sequencing) and gene knockout models under specific conditions (e.g., Cx3cr1-Cre mice) to explore the unique functions of these genes in BBB integrity, neuroimmune interference, and metabolic reprogramming, providing scientific evidence for targeted interventions.

Despite deriving numerous significant insights from our analysis, we must acknowledge certain limitations: First, the sample size of the dataset we used is relatively small ($n = 8$). Although the original study effectively controlled potential confounding factors such as age, gender, type of surgery, and comorbidities through a strict case–control matching design, the small sample size may lead to insufficient statistical power (such as the risk of false negatives), overfitting of gene expression variations, exaggerated false discovery rates, limited robustness in module detection, and reduced reliability of immune cell-related analysis results. Second, the analysis was limited to just one dataset (GSE163943), lacking experimental confirmation, potentially diminishing the precision and applicability of the findings and neglecting the intricate interconnections and characteristics of the data. Considering that there are relatively few datasets available for research related to POD in elderly patients, future studies might benefit from a second external group (like GSE174367) for comparative studies and additional clinical investigations. By enlarging the sample size and comparing it with cohorts from multiple centers, the precision and applicability of our current research findings can be further confirmed. Furthermore, the primary dataset collected for this research consists of peripheral blood samples. Although these blood samples are easier to obtain and the research findings can provide some guidance for POD treatment, the peripheral blood transcriptome may not fully capture the specific changes in the central nervous system. Therefore, future studies may need to incorporate cerebrospinal fluid proteomics or single-cell sequencing techniques to gain a deeper understanding of the mechanisms of neuroimmune interactions.

Even with some constraints, our research offers new data and guidance to support the advancement of treatment processes and the evolution of POD. With the aging population increasing, the effectiveness of POD in treating older patients continues to be inadequate. Therefore, it is critically important to persistently and thoroughly investigate this area to enhance postoperative recovery and improve the quality of life for older patients.

5 Conclusion

Overall, our research focused on 10 crucial genes closely linked to POD, exploring their roles in key signaling pathways, types of cell death, and changes in the immune microenvironment, with the aim of deepening our understanding of POD development in older individuals. Our study confirmed that the pathogenic origins of POD are complex in the elderly population, showing significant variation among patients. Therefore, future research should carefully assess these factors, integrating current findings with the unique circumstances of patients to develop more effective treatment strategies. This clarifies future research trends for POD in elderly patients and highlights the factors that need to be considered in subsequent experiments, thereby improving the applicability of the research findings and advancing clinical treatments.

Data availability statement

Gene expression data in our study were sourced from the GSE163943 dataset in the Gene Expression Omnibus (GEO) database. The Ethics statement for GSE163943 dataset can be accessed via this link: https://pmc.ncbi.nlm.nih.gov/articles/PMC8171121/#S7. Our study only analyzes the GSE163943 dataset and does not include any new animal or human research data.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. 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

Z-hG: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. NS: Investigation, Methodology, Software, Visualization, Writing – original draft. X-cL: Data curation, Investigation, Software, Writing – review & editing. D-pR: Data curation, Formal analysis, Software, Writing – review & editing. S-sR: Data curation, Formal analysis, Methodology, Software, Writing – review & editing. LW: Data curation, Methodology, Software, Writing – review & editing. YW: Conceptualization, Project administration, Resources, Supervision, Validation, Writing – review & editing, Writing – original draft.

Funding

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

Conflict of interest

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

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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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.2025.1580355/full#supplementary-material

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frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 16 May 2025
DOI 10.3389/fmed.2025.1537697

OPEN ACCESS

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RECEIVED 01 December 2024
ACCEPTED 05 May 2025
PUBLISHED 16 May 2025

CITATION
Liu Y, Fan Y, Yang X, Gan H, Li X, Luo Y, Pang Q and Yang T (2025) Nomogram for predicting postoperative pulmonary infection in elderly patients undergoing major orthopedic surgery.
Front. Med. 12:1537697.
doi: 10.3389/fmed.2025.1537697

Nomogram for predicting postoperative pulmonary infection in elderly patients undergoing major orthopedic surgery

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Objective: The incidence of pulmonary infection following major orthopedic surgery in the elderly is high, significantly affecting prognosis. Identifying high-risk factors and stratifying patient risk more effectively is an urgent problem that needs to be addressed. This study aims to develop a nomogram for predicting postoperative pulmonary infection (PPI) in elderly patients undergoing major orthopedic surgery.

Methods: Data from preoperative variables, surgical procedures, and anesthesia factors of 814 elderly patients who underwent major orthopedic surgery between January 2020 and October 2023 were retrospectively collected to develop a nomogram. The primary outcome was PPI. Stata 16 and R 4.1.2 software were used for statistical analysis.

Results: Multivariate logistic regression revealed that gender (OR = 2.336, 95% CI1.135–4.807, p = 0.021), preoperative pulmonary disease (OR = 6.042, 95% CI 2.849–12.814, p = 0.000), preoperative sedation and analgesia (OR = 0.159, 95% CI 0.037–0.689, p = 0.014), intraoperative infusion volume ≥ 1,200 mL (OR = 2.530, 95% CI 1.166–5.489, p = 0.019) were identified as independent risk factors for PPI in elderly orthopedic patients. The risk factors in the nomogram included ASA, gender, preoperative pulmonary disease, cognitive impairment, and non-preoperative sedation and analgesia, and intraoperative infusion. Area under the curve (AUC) of the nomogram was 0.834, the slope was 1.000, and the net benefit of the decision curve analysis (DCA) curve was 0.01–0.60.

Conclusion: Researchers have developed and validated a predictive nomogram for PPI in elderly patients undergoing major orthopedic surgery, identifying 6 key variables, which can be used to predict PPI of aged patients undergoing major orthopedic surgery and identify high risk groups.

KEYWORDS

orthopedic surgery, postoperative infection, pulmonary, aged, nomogram

1 Introduction

Among countries, China has one of the fastest aging populations (1). The risks and challenges of surgical anesthesia for aged patients are substantial, especially for aged patients undergoing major orthopedic surgery. These patients are more susceptible to postoperative pulmonary infections (PPIs) because of preoperative frailty, numerous underlying systemic conditions, and restricted perioperative activity. The incidence of PPI in major orthopedic surgery in the elderly ranges from 3.5% to 14.4% (2, 3). Postoperative pulmonary complications have a significant impact on perioperative morbidity and mortality, prolong postoperative hospital stays, and greatly increase hospital costs (4).

Numerous studies have investigated the high-risk factors for PPI in aged patients, leading to the development of predictive models to identify susceptible individuals early. However, most studies to date have concentrated on hip replacement surgery (5, 6), leaving uncertainly regarding the applicability of these PPI prediction models to major orthopedic surgeries. Preoperative pain, stress and sleep disturbances can increase postoperative complications, which may affect PPI (7). And preoperative pain control can alleviate postoperative pain and improve sleep disorders (8). However, most studies only include patient factors and surgical-related factors, neglecting preoperative pain control and anesthesia-related perioperative factors. Numerous studies have shown that anesthesia and analgesia methods are associated with PPI (9, 10). Therefore, this study retrospectively analyzed the perioperative clinical data, including patient demographics, surgical procedures and anesthesia-related perioperative factors, and specifically preoperative sedative and analgesia practices, among aged patients undergoing major orthopedic surgery in our hospital. The aim was to develop a risk prediction model for PPI in aged patients undergoing major orthopedic surgery, to aid medical staff in early identification of high-risk patients and to offer theoretical support and a simple practical tool.

2 Materials and methods

2.1 Study design

This study was approved by the Institutional Ethics Committee of Shizhu Tujia Autonomous County People's Hospital, China (Scientific Ethics Review No. 18 in 2022). Due to the retrospective nature of the study and the anonymity of the data, informed consent was not necessary. To ensure anonymity, names and admission and surgical dates were removed during data extraction.

2.2 Patients and sample size

According to Harrell guidelines and reference study from Riley et al. (11), the number of outcome variables should be at least 10–20 times the number of variables. Based on prior studies, approximately 15% of elderly patients undergoing major orthopedic surgery developed PPI. In our study design, we aim to incorporate 12 predictive factors to enhance the accuracy of our prognosis models. To achieve this, we determine that a minimum of 800 patients was necessary to ensure the robustness and statistical significance of our findings. Accounting for a 20% dropout rate, we aimed to enroll at least 960 patients in the study.

Patients who underwent major orthopedic surgery at Shizhu Tujia Autonomous County People's Hospital spanning from January 2020 to October 2023 were enrolled. The inclusion criteria were as follows: (1) patients who underwent major orthopedic surgery (surgical time >60 min) in our hospital; and (2) age $\geq$ 65 years old. The exclusion criteria were as follows: (1) patients who underwent orthopedic surgery under local anesthesia; (2) superficial and minimally invasive surgeries such as mass excisions, tendon repairs, and arthroscopies; (3) severe trauma with brain trauma, unconsciousness, pulmonary contusion, hemothorax and pneumothorax, rib fractures, etc.; and (4) incomplete clinical medical records.

2.3 Data collection

In our hospital, the electronic medical record system and surgical anesthesia system were queried using special medical terms such as "fracture" or "arthroplasty" or "replacement" or "vertebra" or "spine" to identified relevant patient records and surgical-anesthesia procedure. Six researchers used a retrospective study method to extract data from patients' electronic medical records, test records, examination reports, and nursing records. All raw data were collected using self-designed case report form. Two investigators reviewed the data to ensure its accuracy and completeness. Any disagreement was settled by discussion among all researchers.

Observation indicators included (1) patient factors: age, sex, New York Heart Association (NYHA) classification, smoking history, combined pulmonary disease [chronic obstructive pulmonary disease (COPD), asthma, pulmonary infection, tuberculosis], cerebrovascular disease (history of stroke, brain atrophy), cognitive impairment (diagnosed dementia or Montreal Cognitive Assessment Scale < 26 points), diabetes, coronary heart disease, hypertension, preoperative arterial partial pressure of oxygen, pulmonary function, hemoglobin, leukocyte, neutrophil-to-lymphocyte ratio (NLR), albumin, and creatinine; and (2) surgery procedure and anesthesia-related perioperative factors: preoperative sedation and analgesia, anesthesia method, surgical duration, blood loss (ml), fluid volume (ml), blood transfusion, postoperative pain (defined as a VAS score > 3 points within 48 h after operation), postoperative analgesia method, and intensive care unit (ICU) stay.

2.4 Outcomes

The primary outcome was the incidence of pulmonary infection within 7 days of surgery, and the secondary outcomes were length of postoperative hospital stay (LOS) and in-hospital mortality. PPI refers to the diagnosis of postoperative pneumonia defined in the systematic review conducted by Abbott et al. (12): chest X-ray (without underlying cardiopulmonary disease) with at least 1 of the following imaging features: new or progressive persistent pulmonary infiltrates, consolidations, or cavities; at least 1 of the following symptoms: unexplained fever (>38°C), leukocyte ($<4 \times 10^9$/L) or leukocyte ($>12 \times 10^9$/L) and, for elderly individuals over 70 years old, disturbance of consciousness with no other explanation; at least 2 reasons: new onset cough, aggravated sputum, change in sputum

color, increased respiratory secretions, increased need for sputum suction; new onset or aggravated cough, dyspnoea, shortness of breath; pulmonary rales or bronchial breath sounds; and worsening of gas exchange (hypoxemia, increased oxygen demand, and increased need for mechanical ventilation).

2.5 Missing data

Data cleaning was performed before statistical analyses, and variables with more than 10% missing values were not included. For continuous variable values that were missing (within 10%), the mean or median was used instead according to whether the data follows a normal distribution or not.

2.6 Statistical analysis

Categorical variables are represented by the number of cases, and were analyzed using the chi-square test. Continuous variables are expressed as medians and interquartile ranges (IQRs), and were analyzed using the t test or rank-sum test. Univariate logistic regression analysis was performed to screen the risk factors, and the variables with $p < 0.1$ were included in the multivariate logistic analysis with forward-backward stepwise method based on the AIC criteria to screen the variables that were ultimately included in the nomogram model. Then, a nomogram was constructed based on the results of the multiple regression.

The area under the curve (AUC) and the calibration curve were used to evaluate the discrimination and accuracy of the nomogram model. Decision curve analysis (DCA) was used to assess the range of clinical validity of the model. All analyses were conducted using Stata 16 (Stata Corp) and R Software 4.1.2 (R Foundation for statistical computing) (Supplementary material 1). For all analyses, $p < 0.05$ was considered statistically significant.

3 Results

In this study, 10 patients were excluded due to severe trauma, and 4 patients were excluded due to incomplete data. Ultimately, 814 patients were enrolled in the analysis.

3.1 General characteristic of the included patients

The incidence of PPI in this study was 4.7% (38 cases), and 1 patient died due to a PPI. The median LOS in the PPI group was 14 days, and the median LOS in the non-PPI group was 10 days; the difference between the 2 groups was significant ($p = 0.003$). Preoperative arterial partial pressure of oxygen, pulmonary function and albumin were excluded from the analysis because the missing data exceeded 10%. Between the two groups of patients, there were significant differences in gender, ASA classification, combined pulmonary disease and cognitive impairment, preoperative sedation and analgesia, operation time, blood loss, intraoperative fluid infusion, blood transfusion, and postoperative ICU stay ($p < 0.05$, Table 1).

3.2 Univariate and multivariate logistic regression results

Univariate analysis showed that ASA classification, gender, combined pulmonary disease and cognitive impairment, preoperative sedation and analgesia, intraoperative fluid infusion, and blood transfusion were associated with PPI ($p < 0.05$). The multivariate analysis results showed that gender (OR = 2.336, 95% CI 1.135, 4.807, $p = 0.021$), preoperative pulmonary disease (OR = 6.042, 95% CI 2.849, 12.814, $p = 0.000$), intraoperative fluid infusion volume ≥1,200 mL (OR = 2.530, 95% CI 1.166, 5.489, $p = 0.019$) were independent risk factors and preoperative sedation and analgesia (OR = 0.159, and 95% CI 0.037, 0.689, $p = 0.014$) was independent protective factor for PPI in elderly patients undergoing major orthopedic surgery (Table 2).

3.3 Development of a nomogram for PPI

Eight variables, i.e., ASA, gender, pulmonary disease, cognitive impairment, preoperative sedation, intraoperative fluid infusion, surgical time, and blood transfusion were included in stepwise regression. Finally, a nomogram was constructed incorporating 6 risk factors: ASA, gender, pulmonary disease, cognitive impairment, absence of preoperative sedation and analgesia, and intraoperative fluid infusion (Figure 1). The scores for these indicators in the nomogram were 23.8, 45.5, 98, 56.1, 100, and 52.5, respectively.

3.4 Validation of the nomogram for PPI

The AUC was 0.834, indicating that the model exhibited strong discriminatory ability (Figure 2). A calibration curve was drawn, and the Hosmer–Lemeshow (HL) goodness-of-fit test was also conducted. The HL test result showed that $p = 0.696$, and the calibration curve was straight with a slope of 1.0, indicating good consistency between the predicted values and the observed results (Figure 3). The DCA indicated that, when the threshold probability was within a range of 0.01–0.60, the nomogram added more net benefit than the "treat all" or "treat none" strategies (Figure 4).

4 Discussion

Postoperative pulmonary infection (PPI) is a severe complication for elderly patients undergoing major orthopedic surgery, as evidenced by studies indicating that it not only prolongs the postoperative hospital stay but also increases the risk of readmission and death (13). One study revealed that nearly 25% of deaths in the first week after surgery were related to PPIs (14). In this study, the incidence of PPI was 4.7%, and only 1 patient died due to a PPI. Univariate and multivariate logistic regressions were used to analyze the effects of patient and surgical anesthesia factors on PPI in elderly orthopedic major surgery patients, and 6 variables were identified and incorporated into the nomogram for predicting PPI: ASA, gender, combined pulmonary disease, cognitive impairment, preoperative sedation and analgesia, and intraoperative fluid infusion. In addition, the AUC, calibration plot, and DCA showed satisfactory performance for the prediction model.

TABLE 1 Characteristics of the patients with or without PPI.

Variable	PPI (n = 38)	Non-PPI (n = 776)	Z value	p value
Age (year)	73.5 (69, 80)	71 (67, 78)	−1.429	0.153
Gender (male/female)	14/24	461/315		0.006
ASA (I/II/III/IV)	0/22/15/1	4/595/175/2		0.008
NYHA (I/II/III/IV)	7/29/2/0	227/512/37/0		0.354
Surgical site (Proximal/distal)	15/23	298/475		0.909
Emergency (yes/no)	1/37	21/755		0.978
Smoke (yes/no)	5/33	99/677		0.942
Comorbidity				
Pulmonary disease (yes/no)	23/19	133/836		0.000
Diabetes (yes/no)	3/35	74/702		0.736
Cardiac artery disease (yes/no)	3/39	76/893		0.869
Hypertension (yes/no)	15/23	314/462		0.903
Cerebrovascular disease (yes/no)	8/30	97/679		0.125
Cognitive impairment (yes/no)	4/34	11/765		0.000
Blood test				
Hemoglobin (g/L)	114 (102, 125)	117 (104,130)	1.282	0.200
Creatinine (umol/L)	63 (56, 72)	59 (51,70)	−1.208	0.227
Leukocyte (*10^9/L)	6.75 (4.67, 8.73)	6.66 (5.40,8.30)	0.388	0.698
NLR	3.85 (2.46, 8.39)	4.12 (2.78,6.66)	0.055	0.956
Preoperative sedation and analgesia (yes/no)	2/36	211/565		0.003
Anesthesia method (GA or GA + LA vs. SEA or LA)	16/22	300/476		0.670
Surgical time (min)	125 (95, 175)	115 (85, 149)	−2.194	0.028
Bleeding (ml)	150 (100, 300)	100 (50, 200)	−2.870	0.004
Intraoperative infusion (ml)	1,200 (1,000, 2,000)	1,000 (500, 1,300)	−3.708	0.000
Transfusion (yes/no)	15/23	173/603		0.014
Postoperative pain (yes/no)	11/27	254/522		0.627
Analgesia method (systematic/LA)	33/5	565/211		0.056
ICU stay (yes/no)	5/33	26/750		0.002
LOS (d)	14 (10, 15)	10 (7, 14)	−2.941	0.003

Data are median [lower quartile to upper quartile] and No. of cases. Z value for continuous variables. PPI, postoperative pulmonary infection; ASA, American society of Anesthesiologists; NYHA, New York Heart Association; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; GA, general anesthesia; SEA, spinal or epidural anesthesia; LA, local anesthesia; ICU, intensive care unit; LOS, postoperative length of hospital stay.

Many studies have shown that anemia, diabetes, number of comorbidities, ASA ≥ III and some specific laboratory biomarkers and significant clinical interventions are important risk factors for PPI (6, 15, 16). The risk factors incorporated into the prediction model of this study are largely consistent with those identified in prior research (17–19). Our results also found that preoperative sedation and analgesia was a protective factor for elderly orthopedic major surgery patients. Patients with orthopedic surgery often suffer from pain before operation, which affects exercise and sleep quality, and also increases preoperative stress and inflammation, which are closely related to the postoperative pain (7). Surgery also can initiate the pain process, evokes hyperalgesia, releases inflammatory factors, and leads to reduce immunity (20). Several clinical studies have shown that pre-emptive sedation and analgesia can decrease the level of postoperative pain, and allevate postoperative pain (6, 21, 22). The mechanism may involve preoperative pain control, which can help reduce perioperative IL-6 levels and hs-CRP levels, alleviate postoperative pain and improve sleep disorders (8, 21). Therefore, sedatives and analgesics should be used to improve the preoperative state of patients before orthopedic surgery.

ASA classification ≥ III means patients exhibit frailty and many comorbidities, resulting on a lower cardiopulmonary function compared to those classified as ASA I-II (22). Therefore, pulmonary complications are likely to occur after surgery. Male patients are mostly affected by long-term smoking and are often accompanied by COPD, asthma and pneumonia, which affect lung function (23). Anesthesia and surgery can reduce lung volumes, which is the primary physiologic mechanism that contributes to the development of atelectasis and other postoperative pulmonary complications (24). Compared with systemic opioids, epidural local anesthetics increased arterial partial pressure of oxygen and decreased the incidence of PPI

TABLE 2 Univariate and multivariate logistic analyses.

Variable	Univariate logistic analysis			Multivariate logistic analysis		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age (year) (≥75 vs. < 75)	1.541	0.732, 3.243	0.255			
Gender (male vs female)	2.509	1.278, 4.925	0.008	2.336	1.135, 4.807	0.021
ASA (III/IV vs. I/II)	2.461	1.265, 4.788	0.008	1.515	0.681, 3.369	0.308
NYHA (III/IV vs. I/II)	1.110	0.257, 4.786	0.889			
Smoke (yes vs. no)	1.036	0.395, 2.717	0.942			
Pulmonary disease (yes vs. no)	7.028	3.599, 13.724	0.000	6.042	2.849, 12.814	0.000
Diabetes (yes vs. no)	0.813	0.244, 2.708	0.736			
Cardiac artery disease (yes vs. no)	0.954	0.285, 3.187	0.938			
Hypertension (yes vs. no)	0.960	0.493, 1.868	0.903			
Cerebrovascular disease (yes vs. no)	1.867	0.832, 4.189	0.130			
Cognitive impairment (yes vs. no)	8.182	2.477, 27.024	0.001	2.814	0.645, 12.285	0.169
Surgical site (Proximal vs. distal)	1.040	0.534, 2.024	0.909			
Leukocyte (≥$10*10^9$ vs. < $10*10^9$)	1.141	0.434, 2.996	0.790			
NLR (≥7.0 vs. < 7.0)	1.157	0.552, 2.428	0.699			
Creatinine (≥96 umol/L vs. < 96 umol/L)	2.285	0.771, 6.769	0.136			
Preoperative sedation and analgesia (yes vs no)	0.149	0.036, 0.623	0.009	0.159	0.037, 0.689	0.014
Anesthesia method (GA or GA + LA vs. SEA or LA)	1.154	0.596, 2.233	0.671			
Surgical time (≥120 min vs. < 120 min)	1.735	0.903, 3.332	0.098	1.000	0.995, 1.005	0.954
Bleeding (≥200 mL vs. < 200 mL)	1.542	0.802, 2.963	0.194			
Fluid infusion (≥1,200 mL vs <1,200 mL)	2.874	1.475, 5.599	0.002	2.530	1.166, 5.489	0.019
Transfusion (yes vs. no)	2.273	1.161, 4.452	0.017	1.182	0.544, 2.570	0.673
Postoperative pain (yes vs. no)	0.837	0.409, 1.715	0.627			
Analgesia method (systematic vs. LA)	1.154	0.596, 2.233	0.671			
ICU stay (yes vs. no)	4.371	1.578, 12.104	0.005			
LOS (d)	2.803	1.309, 6.000	0.008			

OR, odds rate; CI, confidence interval; ASA, American society of Anesthesiologists; NYHA, New York Heart Association; NLR, neutrophil-to-lymphocyte ratio; GA, general anesthesia; SEA, spinal or epidural anesthesia; LA, local anesthesia; ICU, intensive care unit; LOS, postoperative length of hospital stays.

and pulmonary complications (4, 7). But the results of this study showed that the mode of anesthesia had no effect on PPI. The reason might be that most high-risk patients underwent epidural anesthesia or nerve block, or other local anesthesia technique. The commonly used sedatives and analgesics in wards in our hospital are mainly dezocine, tramadol, or NSAIDs, which have minimal impact on respiration. Aspiration is a factor that will be strongly linked to PPI. In our study, the incidence of postoperative vomiting was 11.3%, but no aspiration was recorded in any of the groups.

Studies reported that preoperative cognitive impairment associated with morbidity and mortality, including pulmonary complications after surgery (25, 26). The mechanism may involve cognitive impairment due to ineffective respiratory exercise, leading to higher rates of moderate-deep residual sedation during anesthesia recovery. This can result in prolonged postoperative ventilation, an increased incidence of delirium, and subsequently, ineffective coughing and atelectasis (27, 28).

We used data from elderly orthopedic surgery patients at our hospital to validate two other models from studies by Zhang et al. (5) and Tian et al. (29) The results showed that the accuracy of these models was relatively low, with AUC value of 0.674 and 0.758 (Supplementary Figures 1, 2). The HL calibration test results showed *p* values of 0.010 and 0.065, respectively. Variations in regional practices and the technical abilities of surgeons and anesthesiologists may contribute to differences in model outcomes derived from data collected across various hospitals. Furthermore, discrepancies in regional healthcare standards and hospital levels can lead to variation in the extension and comprehensiveness of patient examinations, which may result in certain indicators no being part of routine examinations, thus making it challenging to obtain relevant data. Studies have indicated that preoperative oxygen partial pressure below 72.5% in elderly patients undergoing hip fracture surgery is associated with PPI (30). Certain studies suggest that pulmonary function, as well as preoperative and early postoperative hypoalbuminemia, are linked to PPI in major orthopedic surgeries (31, 32). Elevated CRP levels can also serve as a predictor for PPI in some research (6). However, since many patients in this study did not routinely receive arterial blood gas analysis, pulmonary function tests, albumin or CRP level measurements prior to surgery, these factors were excluded from the

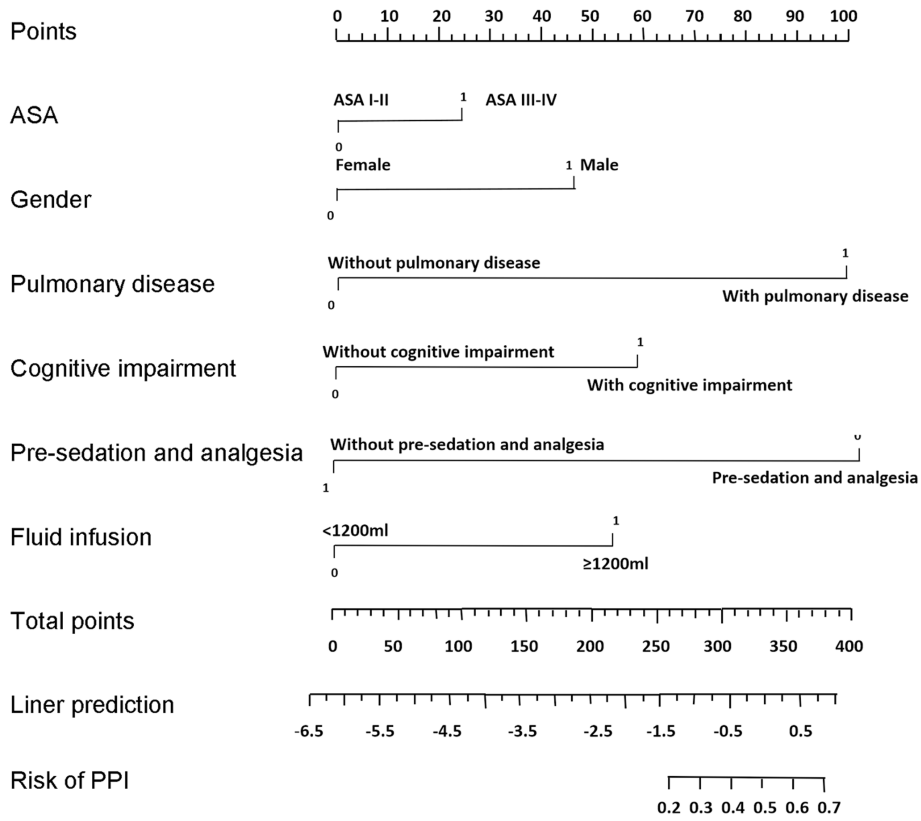

FIGURE 1
Nomogram for predicting the risk of PPI in elderly patients undergoing major orthopedic surgery. To use the nomogram, a vertical line is drawn up to the top point row to assign points for each variable. Then, the total number of points is calculated, and a vertical line is drawn downward from the total point row to obtain the probability of PPI.

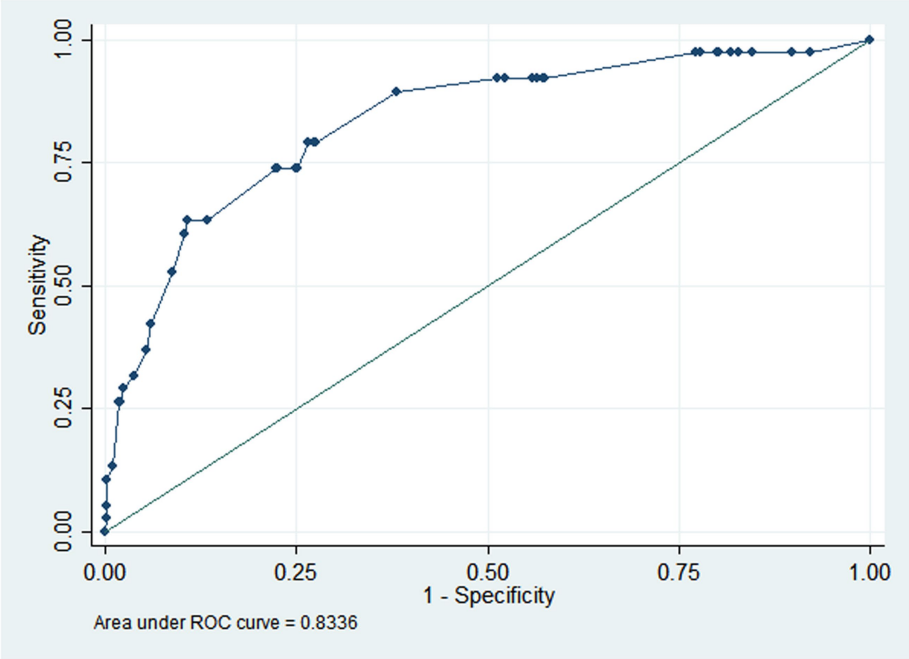

FIGURE 2
AUC of nomogram for predicting PPI in elderly patients undergoing major orthopedic surgery. The AUC was 0.834, indicating high discrimination. AUC, area under receiver-operating characteristic curve; PPI, postoperative pulmonary infection.

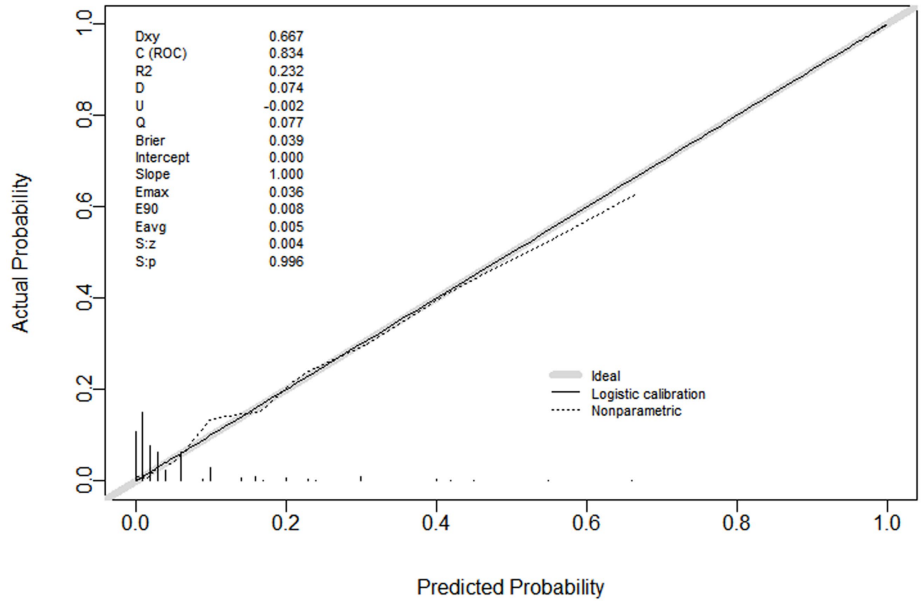

FIGURE 3
Calibration curve of nomogram for predicting PPI in elderly patients undergoing major orthopedic surgery. The slope was 1.0, the R^2 was 0.232. The calibration curve showed good concordance between predicted probability and actual probability. PPI, postoperative pulmonary infection.

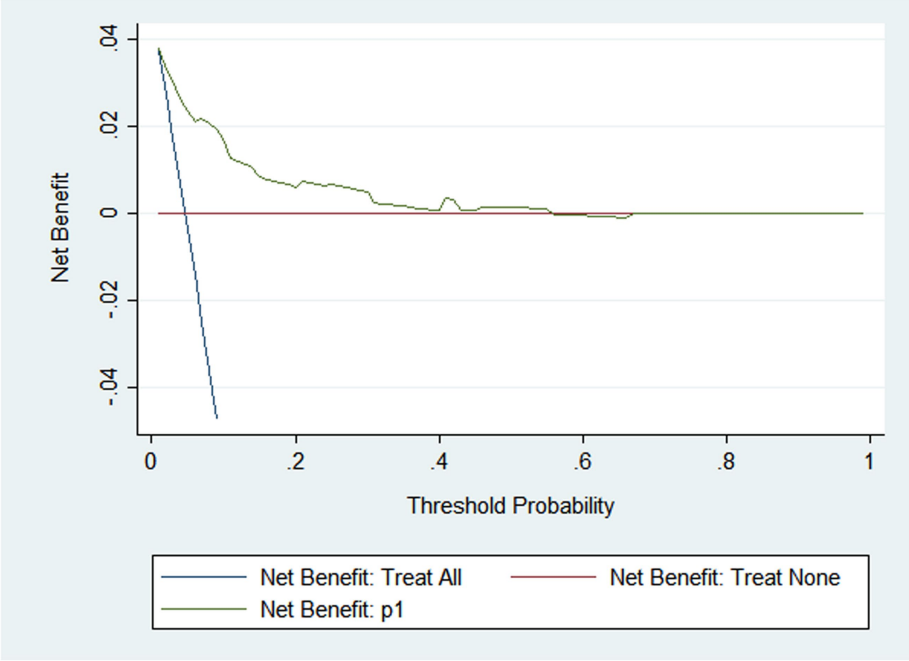

FIGURE 4
DCA of nomogram for predicting PPI in elderly patients undergoing major orthopedic surgery. DCA, decision curve analysis; PPI, postoperative pulmonary infection.

analysis. Nonetheless, their potential impact on PPI cannot be overlooked.

In our study, the nomogram's Area Under the Curve (AUC) was 0.834, and the calibration curve's slope was 1, *p* value was 0.696 from HL test, suggesting good consistency and calibration. The Decision Curve Analysis (DCA) demonstrated the clinical practicability of the prediction model, indicating that its discrimination ability for individual probabilities was satisfactory. Therefore, the prediction model with 6 simple clinical factors can assist clinicians in identifying high-risk patients with PPI before surgery.

However, this study has certain limitations. Firstly, the data were collected retrospectively, which may compromise the reliability of all

information, potentially introducing bias into the results and increasing the risk of misdiagnosis and missed diagnosis. Some cases of postoperative atelectasis may also fulfill the diagnostic criteria of PPI and thus confound the results. Secondly, being a single-center study, the sample size was inadequate, and some risk factors were not included due to incomplete data, potentially undermining the robustness of the results. Thirdly, prospective external verification was not performed, and the application value of the model needs to be confirmed by further research.

In conclusion, this study developed a 6-factor nomogram prediction model for predicting PPI in elderly patients undergoing major orthopedic surgery, considering patients, surgical and anesthesia related factors. The model can help in the identification of high-risk individuals early and in the formulation of optimal anesthesia and perioperative management strategies to reduce the occurrence of PPIs. However, a larger sample size and a multicenter study are needed to confirm these conclusions.

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 Ethical Committee of Clinical Research of the Shizhu Tujia Autonomous County People's Hospital. 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 study utilizes medical records/biological samples obtained from previous clinical treatments. 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 this study utilizes medical records/biological samples obtained from previous clinical treatments.

Author contributions

YLi: Conceptualization, Formal analysis, Writing – original draft. YF: Investigation, Methodology, Writing – original draft. XY: Investigation, Writing – original draft. HG: Investigation, Writing – original draft. XL: Investigation, Writing – original draft. YLu: Investigation, Writing – original draft. QP: Formal analysis, Software, Writing – review & editing. TY: Project administration, Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research 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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2025.1537697/full#supplementary-material

SUPPLEMENTARY MATERIAL 1
Codes used in Stata and R software.

SUPPLEMENTARY FIGURE 1
AUC of Zhang's research model for external validation with data from our hospital. The AUC was 0.674, indicating low accuracy.

SUPPLEMENTARY FIGURE 2
AUC of Tian's research model for external validation with data from our hospital. The AUC was 0.758, indicating medium accuracy.

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frontiers | Frontiers in Neurology

TYPE Systematic Review
PUBLISHED 13 June 2025
DOI 10.3389/fneur.2025.1580216

OPEN ACCESS

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RECEIVED 26 February 2025
ACCEPTED 27 May 2025
PUBLISHED 13 June 2025

CITATION
Yang C, Liu Y, Xiao B, Yang J, Zeng Q, Tan R and Ma H (2025) Evidence summary for the management of sleep disorders after malignant tumor surgery.
Front. Neurol. 16:1580216.
doi: 10.3389/fneur.2025.1580216

Evidence summary for the management of sleep disorders after malignant tumor surgery

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Introduction: This study aimed to extract, evaluate, and summarize the evidence related to the management of sleep disorders after malignant tumor surgery, providing a reference for evidence-based clinical practice.

Methods: A systematic and hierarchical search strategy was used to identify relevant evidence from authoritative databases and resources. Following the "6S" evidence pyramid model, we conducted a comprehensive review of the following databases: BMJ Best Practice, CINAHL, Cochrane Library, Clinical Trials, Embase, PubMed, UpToDate, Web of Science, Guidelines International Network, National Guideline Clearinghouse, and the National Guidelines Database. Additionally, key institutional websites and specialized databases were consulted, such as the' National Institute for Health and Care Excellence in the United Kingdom, 'the Joanna Briggs Institute Centre for Evidence-Based Health Care in Australia, 'the Registered Nurses' Association of Ontario in Canada, the Scottish Intercollegiate Guidelines Network, China National Knowledge Infrastructure, China Biomedical Literature Database, Wan Fang Data, VIP Database, and Medlive. The search included clinical decisions, evidence summaries, guidelines, recommended practices, expert consensuses, systematic reviews, and randomized controlled trials. The retrieval period spanned from the inception of each database to December 31, 2024. Two researchers trained in evidence-based nursing independently evaluated the quality of the literature, extracted and synthesized the evidence, and incorporated expert recommendations as appropriate. This rigorous approach ensured comprehensive coverage of international and regional evidence-based resources, providing a solid foundation for our research.

Results: Finally, we screened 12 articles with high-quality results (including 10 guidelines and 2 expert consensuses), providing 37 pieces of evidence covering four aspects: risk factors, evaluation methods, intervention measures, and effect evaluation after intervention.

Discussion: The summarized evidence offers a reference for clinicians in managing sleep disorders in patients after malignant tumor surgery. However, the selection and application of evidence should be combined with specific circumstances to improve the postoperative rehabilitation of patients with malignant tumors.

KEYWORDS

sleep disorders, malignant tumor, evidence summary, evidence-based nursing, postoperative management

1 Introduction

Sleep is a fundamental physiological requirement for human survival, essential for maintaining immune function, cognitive performance, emotional regulation, and physical recovery (1). Sustaining optimal sleep quality is particularly important during periods of physiological stress, such as surgery or illness.

Sleep disorders comprise a group of conditions characterized by disruptions in sleep quantity, quality, timing, or related behaviors that result in daytime impairment or distress (2). These conditions can be either acute or chronic and are typically categorized into insomnia, hypersomnia, circadian rhythm sleep–wake disorders, and sleep-related movement or respiratory disorders (2–4). According to the International Classification of Sleep Disorders, Third Edition (ICSD-3), acute sleep disturbances are often triggered by identifiable stressors and generally resolve within 3 months. In contrast, chronic disturbances persist beyond this period and are frequently associated with maladaptive cognitive and behavioral responses (5, 6).

Among patients with malignant tumors, sleep disturbances are highly prevalent and may be exacerbated by surgery, chemotherapy, radiotherapy, and the hospital environment (7). Insomnia is the most frequently reported subtype, particularly during the postoperative period. Contributing factors include pain, opioid use, environmental stimuli such as noise and light, and insufficient clinical attention to sleep-related issues (8–10). Studies have demonstrated that the prevalence of sleep disturbances varies depending on the type of surgery and the underlying malignancy (8, 9).

The pathophysiology of postoperative sleep disturbances is multifactorial. Biologically, surgical stress and sleep deprivation can trigger inflammatory responses, resulting in elevated levels of cytokines such as IL-1β, TNF-α, and IL-6, which negatively affect sleep quality (6, 11). Psychologically, factors such as anxiety, depression, and maladaptive coping mechanisms further contribute to the persistence of insomnia (5, 6). The "3-P" model—comprising predisposing, precipitating, and perpetuating factors—illustrates the complex interplay between biological vulnerability, perioperative stressors, and behavioral maladaptation in the development of chronic insomnia.

Both acute and chronic sleep disturbances after surgery have been associated with adverse clinical outcomes, including increased pain perception, delayed recovery, neurological complications, emotional distress, and reduced patient satisfaction (1, 12, 13). These consequences underscore the importance of early identification and targeted management of sleep disorders—particularly insomnia—in postoperative cancer care.

Nevertheless, the existing evidence on the management of postoperative sleep disturbances in cancer patients remains fragmented. Most available studies are observational in nature, involve small sample sizes, and exhibit considerable variability in assessment tools and intervention strategies. This inconsistency hinders the development of standardized clinical protocols and evidence-based recommendations.

Comprehensive and systematically developed evidence summaries are therefore urgently needed to support clinical decision-making and to establish a robust, unified foundation for practice. This study aimed to compile one of the most comprehensive available evidence on the management of sleep disorders following malignant tumor surgery. This study was registered through the Evidence-Based Nursing Center of Fudan University (registration number: ES20257203).

Abbreviations: CBT-I, Cognitive behavioral therapy for Insomnia; PSG, Polysomnography; GSDS, Lee's general sleep disturbance scale; PSQI, Pittsburgh sleep quality index; JBI, Joanna Briggs Institute.

2 Materials and methods

2.1 Problem establishment

We employed the PIPOST tool developed by the Evidence-Based Nursing Center of Fudan University to construct our evidence-based question. P (Population): Patients diagnosed with malignant tumors undergoing surgery; I (Intervention): Management strategies for postoperative sleep disorders, including assessment and intervention; P (Professional): Physicians and nurses who implement the evidence; O (Outcome): Improvement of sleep quality and related symptoms; S (Setting): Clinical inpatient settings; T (Type of evidence): Clinical guidelines, expert consensuses, and systematic reviews. This structured approach ensured that our evidence synthesis remained patient-centered and clinically applicable (42, 43).

2.2 Evidence retrieval strategy

Following the "6S" evidence resource pyramid model (14), a structured and systematic search was conducted across multiple authoritative databases and resources, adhering to a hierarchical approach. The search encompassed the BMJ Best Practice, CINAHL, Cochrane Library, ClinicalTrials.gov, Embase, PubMed, UpToDate, Web of Science, Guidelines International Network, National Guideline Clearinghouse, and National Guidelines Database. Additionally, institutional archives and specialized databases were reviewed, including materials from the National Institute for Health and Care Excellence in the United Kingdom, Joanna Briggs Institute (JBI) Centre for Evidence-Based Health Care in Australia, Registered Nurses' Association of Ontario in Canada, and the Scottish Intercollegiate Guidelines Network. For Chinese sources, we reviewed the China National Knowledge Infrastructure, China Biomedical Literature Database, Wanfang Data, VIP Database, and Medlive to ensure comprehensive coverage. The search period extended from the establishment of the database to December 31, 2024 (Table 1). When searching domestic and international websites or databases, the Chinese search terms included "Sleep disorders/insomnia, tumors/cancer, and postoperative," whereas the English search terms were "neoplasms/cancer/oncology/tumor, sleep initiation and maintenance disorders/insomnia," and "initiation and maintenance disorders/insomnia/sleep disorder/sleep disorders/sleep disturbance, postoperative." Taking PubMed as an example, combination of subject terms and free-text words, the search formula: ((neoplasms OR cancer OR oncology OR tumor) AND ((sleep initiation and maintenance disorders OR insomnia OR sleep disorder OR sleep disorders OR sleep disturbance) AND postoperative)). To ensure a comprehensive and inclusive retrieval of evidence, the term "sleep disorders" was defined broadly to encompass any condition or symptom involving disturbances in sleep initiation, maintenance, duration, quality, or circadian regulation that result in daytime dysfunction. This included, but was not limited to, insomnia, poor sleep quality, sleep fragmentation, excessive daytime sleepiness, and circadian rhythm

TABLE 1 Literature search strategies.

Database	Key words or related words	Boolean logic	Time range
BMJ/CINAHL/Cochrane Library/Clinical Trials/PubMed/UpToDate/Web of Science	Neoplasms/cancer/oncology/tumor sleep disorder/sleep initiation and maintenance disorders/sleep disorders/sleep disturbance/insomnia postoperative	((neoplasms OR cancer OR oncology OR tumor) AND ((sleep initiation and maintenance disorders OR insomnia OR sleep disorder OR sleep disorders OR sleep disturbance) AND postoperative))	Inception—Dec 2024
Embase	Neoplasms/cancer/oncology/tumor sleep disorder/sleep initiation and maintenance disorders/sleep disorders/sleep disturbance/insomnia postoperative	('neoplasms':ab,ti OR'cancer':ab,ti OR'oncology':ab,ti OR'tumor':ab,ti) AND ('sleep initiation and maintenance disorders':ab,ti OR'insomnia':ab,ti OR'sleep disorder':ab,ti OR'sleep disorders':ab,ti OR'sleep disturbance':ab,ti) AND ("postoperative":ab,ti)	
GIN/NGC/NICE/JBI/RNAO/SIGN	Sleep disorder/sleep initiation and maintenance disorders/sleep disorders/sleep disturbance/insomnia	sleep disorder/sleep initiation and maintenance disorders/sleep disorders/sleep disturbance/insomnia	
CNKI/CBM/VIP	Sleep disorders/Insomnia Tumors/Cancer Postoperative	(Sleep disorders OR Insomnia) AND (Tumors OR Cancer) AND Postoperative (In Chinese)	
WFD	Sleep disorders/Insomnia Tumors/Cancer Postoperative	((Sleep disorders | Insomnia) + (Tumors | Cancer)) + Postoperative (In Chinese)	
Medlive	Sleep disorders/Insomnia/Sleep quality	Sleep disorders/Insomnia/Sleep quality (In Chinese)	

10.3389/fneur.2025.1580216

disruption (2). We adopted this inclusive approach to capture diverse clinical terminologies used in practice and across different guidelines, rather than relying solely on one diagnostic classification system.

2.3 Inclusion and exclusion criteria

2.3.1 Inclusion criteria

1. Studies focusing on patients with malignant tumors who underwent surgical intervention.
2. Evidence pertaining to the recognition of risk factors, evaluation techniques, management strategies, and assessment of their impact on postoperative sleep disturbances in patients with malignant tumors.
3. Acceptable categories of evidence encompass clinical practice guidelines, expert consensus documents, evidence synopses, and systematic reviews.

2.3.2 Exclusion criteria

(1) Literature that has been repeatedly published or updated; (2) studies with incomplete or inaccessible data; (3) Publications of low quality based on established evaluation criteria; (4) Documents that are guideline interpretations or implementation plans.

2.4 Data extraction and synthesis strategy

Two researchers trained in evidence-based systems independently completed an assessment of the quality of the included literature based on predetermined inclusion and exclusion criteria. Their assessments were cross-verified, and discrepancies between the two evaluators were resolved through consultation with a third expert in evidence-based medicine. Two researchers who systematically studied the evidence-based nursing course evaluated the included literature and cross-checked it using appropriate evaluation tools. Any disagreements were resolved by a third expert in evidence-based medicine, who reached a consistent conclusion.

We used thematic analysis to identify and summarize recurring topics across the included guidelines and expert consensus documents. Four major themes were extracted: risk factors, assessment methods, intervention strategies, and evaluation.

The extracted content included: (1) evidence-based recommendations related to the management of sleep disorders following malignant tumor surgery; (2) classification of each recommendation into one of four domains—risk factors, assessment tools, intervention strategies, and outcome indicators; (3) the level and grading of evidence, if available; and (4) reported or expected outcomes such as improvements in sleep quality, reduction in insomnia symptoms, and enhancement of postoperative recovery (e.g., pain relief, psychological well-being, or fatigue reduction). In this review, "relevant evidence" is defined as any recommendation that addresses sleep-related disturbances—such as insomnia, fragmented sleep, reduced sleep quality, or circadian disruption—within the perioperative or cancer care setting. For synthesis, a thematic categorization approach was used. All extracted recommendations were grouped into the four main evidence domains. Within each domain, recommendations were further organized according to the type of intervention (e.g., cognitive, behavioral, pharmacological) or evaluation method. Overlapping evidence from multiple sources was consolidated, while unique recommendations were retained as supplementary guidance.

2.5 Evidence quality evaluation criteria

The quality of the guidelines was assessed using the AGREE II guideline Quality Assessment form (15). Agree II was revised in 2009 and updated in 2017 by the International Working Group for Research and Evaluation of Clinical Guidelines, comprised researchers from 13 countries, including Canada and the United Kingdom. This tool builds on the AGREE issued in 2003. The AGREE II comprises 23 items across six domains, with each item rated on a seven-point scale (1 = strong disagreement and 7 = strong agreement). The standardized score for each domain was calculated using the formula: [(actual score − minimum possible score) / (maximum possible score − minimum possible score)] × 100. All domain scores were evaluated collectively, and a unified threshold for the six domains was established through expert consensus. Guidelines received a quality rating of A if the standardized score in each domain was 70% or higher. If the standardized score ranged between 30 and 70%, the guideline quality was rated as B. To further enhance clarity and reduce redundancy, the quality rating criteria were reorganized as follows: guidelines earned an A rating when all six domains achieved a standardized score of at least 70%. Conversely, guidelines with a standardized score within the range of 30–70% in any domain were assigned a B rating. In this summary of evidence, the literature that failed to reach the level of grade B or above has been excluded.

The quality of the included guidelines was assessed using the JBI Center for Evidence-Based Health Care Expert Consensus Evaluation Criteria (2017 edition), which consists of six items and employs a grading system of "yes," "no," "unclear," and "not applicable" (16). For systematic evaluation, the 2014 edition of the JBI Evidence-Based Practice Center Standards was used. This tool includes 11 items, each evaluated based on the criteria of "yes," "no," "unclear," or "not applicable" (17). The evidence was synthesized by tracing back to the original source documents, and the appropriate JBI Center for Evidence-Based Health Care (2016 edition) tool was selected for quality assessment based on literature type.

Calculate the proportion of "Yes" responses and determine the overall rating based on the following criteria:

High quality (≥5 items rated "Yes"): The guideline meets quality standards in most key areas and is recommended for inclusion in the analysis.

Moderate quality (3–4 items rated "Yes"): The guideline meets quality standards in some areas but may have certain limitations, requiring cautious interpretation.

Low quality (≤2 items rated "Yes"): The guideline does not meet quality standards in most areas and is not recommended for inclusion in the analysis.

3 Results

3.1 Literature search and basic characteristics of the included literature

In total, 4,651 articles were initially identified through database searching. After removing duplicates, 3,363 articles remained.

Following a review of titles and abstracts, 570 articles were selected for further screening. After a full-text review based on the inclusion and exclusion criteria, 12 articles were finally included in this review, consisting of 10 clinical practice guidelines and 2 expert consensus statements. The literature screening process is illustrated in Figure 1, and the main characteristics of the included studies are summarized in Table 2.

The included publications were issued between 2019 and 2023, with the majority published in 2023 ($n = 5$), reflecting the timeliness and clinical relevance of the evidence. In terms of source distribution, nine articles were retrieved from PubMed, and three from CNKI, representing a blend of international and Chinese literature. These documents cover a wide range of themes related to postoperative sleep disturbances in patients with malignant tumors, including the diagnosis and treatment of insomnia, cancer-related fatigue, REM sleep behavior disorder, and comprehensive survivorship care. They were issued by authoritative institutions such as the American Academy of Sleep Medicine, the Brazilian Sleep Association, the National Comprehensive Cancer Network (NCCN), and national traditional Chinese medicine organizations, offering a diverse and multidisciplinary perspective on the subject.

3.2 Quality evaluation results of the included articles

3.2.1 Quality evaluation of clinical guidelines

Ten guidelines were included (3, 18–27). The evaluation results showed that the literature writing process was rigorous and the content was detailed, with a high overall quality, and all were eligible for inclusion (Table 3).

3.2.2 Quality evaluation of expert consensus

Two expert consensus documents were included (22, 27). Two expert consensus were evaluated using the JBI 2016 version of the expert consensus evaluation tool, and all six items were rated as "yes." These expert consensuses had a high quality and were eligible for inclusion.

3.3 Evidence summary

A total of 12 studies were included in the initial draft of the evidence summary (3, 18–27), from which 37 best-evidence statements were ultimately synthesized. The evidence spans four

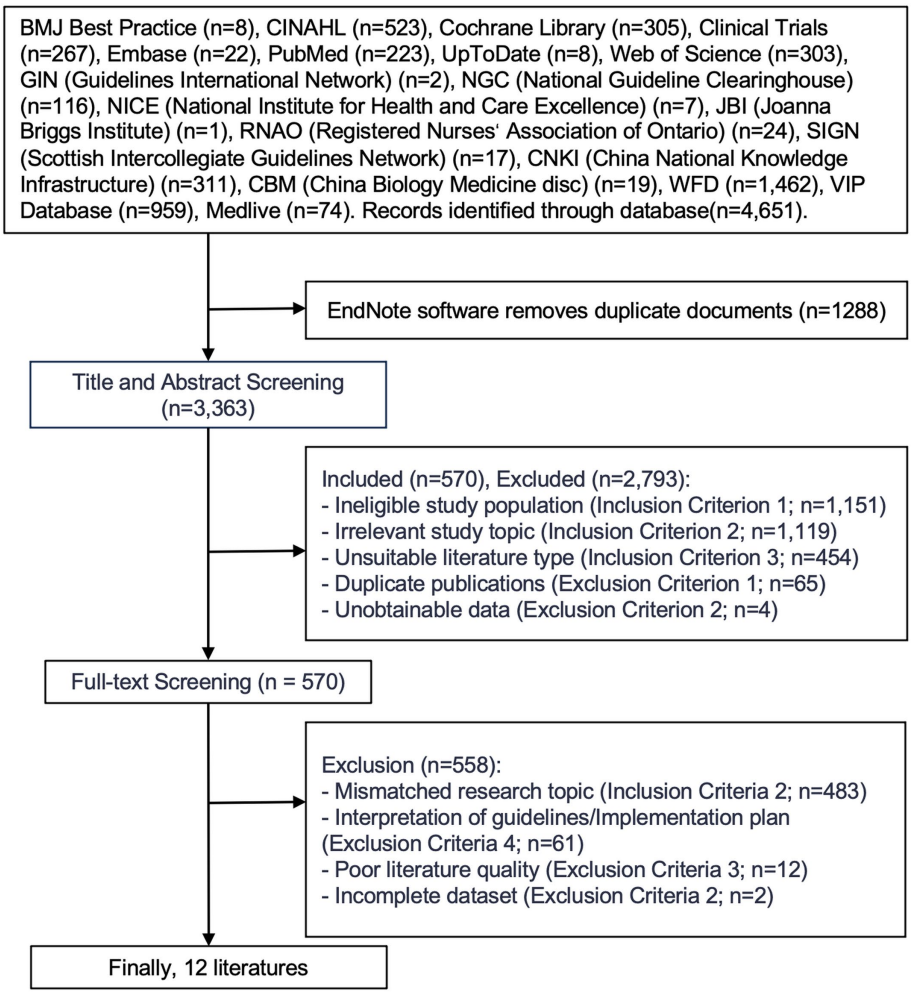

FIGURE 1
Flow chart of literature screening.

TABLE 2 Characteristics of included studies (n = 12).

Included literature	Literature sources	Literature types	Literature themes	Publication year
Luciano Ferreira Drager et al. (18)	PubMed	Guideline	2023 Guidelines on the Diagnosis and Treatment of Insomnia in Adults – Brazilian Sleep Association	2023
Wai Ching Lam et al. (19)	PubMed	Guideline	Hong Kong Chinese Medicine Clinical Practice Guideline for Cancer Palliative Care: Pain, Constipation, and Insomnia	2019
Jack D. Edinger et al. (20)	PubMed	Guideline	Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline	2020
Cristina Frange et al. (21)	PubMed	Guideline	Practice recommendations for the role of physiotherapy in the management of sleep disorders: the 2022 Brazilian Sleep Association Guidelines	2022
Dieter Riemann et al. (23)	PubMed	Guideline	The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023	2023
Hayun Choi et al. (24)	PubMed	Guideline	Korean Clinical Practice Guideline for the Diagnosis and Treatment of Insomnia in Adults	2020
Michael Howell et al. (25)	PubMed	Guideline	Management of rapid eye movement (REM) sleep behavior disorder: an American Academy of Sleep Medicine clinical practice guideline	2023
Tara Sanft et al. (3)	PubMed	Guideline	Survivorship, Version 1. 2023 Featured Updates to the NCCN Guidelines	2023
Zhang jian jun et al. (26)	CNKI	Guideline	Clinical practice guidelines for cancer-related fatigue in China (2021 edition)	2021
Wang yu ping, et al. (27)	CNKI	Guideline	Chinese guideline for diagnosis and treatment of insomnia (2023)	2023
TangLili et al. (30)	CNKI	Expert Consensus	Adult cancer patients insomnia diagnosis and treatment expert advice	2021
Kun-Ming Rau et al. (22)	PubMed	Expert Consensus	Management of cancer-related fatigue in Taiwan: an evidence-based consensus for screening, assessment, and treatment.	2023

major domains: risk factors, assessment methods, intervention strategies, and evaluation of intervention outcomes. Table 4 provides a detailed breakdown of the extracted evidence. The levels of evidence were classified as follows: 1a-meta-analysis of homogeneous randomized controlled trials (RCTs); 1b-a single, well-designed RCT; 2a-prospective cohort study; 2b-retrospective cohort study or low-quality prospective study; and 4b-single-center or small-sample cross-sectional study.

Within the domain of risk factors, the literature identified both biological and psychosocial contributors to postoperative sleep

TABLE 3 Results of clinical guideline quality evaluation (n = 10).

Inclusion guidelines	Percentage of standardization in each field of the guideline (%)						The number of fields with a proportion of ≥ 60% (unit)	The number of fields with a proportion of ≥30% (unit)	Level
	Scope and purpose	Participants	Rigorousness of formulation	Clarity of expression	Applicability of the guidelines	Independence of compilation			
Luciano Ferreira Drager et al. (22)	88.9	69.4	65.6	91.7	64.6	70.8	6	6	A
Wai Ching Lam et al. (18)	97.2	88.9	100	100	60.4	75.0	6	6	A
Jack D. Edinger et al. (19)	88.9	64.4	63.1	83.3	66.3	45.8	5	6	B
Cristina Frange et al. (20)	100	86.1	79.2	100	91.6	91.7	6	6	A
Dieter Riemann et al. (23)	100	72.2	80.2	100	77.1	70.8	6	6	A
Hayun Cho, et al. (24)	97.2	88.9	80.2	97.2	91.7	75.0	6	6	A
Michael Howell et al. (25)	100	77.8	86.5	100	91.7	83.3	6	6	A
Zhang jian jun et al. (26)	91.7	917	70.8	94.4	45.8	54.2	5	6	B
Wang yu ping et al. (27)	100	100	89.6	100	95.8	95.8	6	6	A
Tara Sanft et al. (3)	88.9	72.2	63.5	75	47.9	33.3	4	6	B

10.3389/fneur.2025.1580216

TABLE 4 Evidence summary for the management of sleep disorders after malignant tumor surgery.

Categories	Content of evidence	Level of evidence
Risk factors	The cancer itself and its treatment	
	Cancer factors: different types of cancer have an impact on the incidence of CRF. The incidence of CRF in patients with lung cancer is relatively high, up to 70–100%. Various cancers exhibit distinct biological characteristics, treatment approaches, and impacts on the body, potentially influencing sleep patterns indirectly (26).	1a
	Surgical trauma: Surgical trauma can cause an inflammatory response that can lead to changes in hormone levels, cause pain and discomfort, and interfere with sleep (18–23, 26, 27).	1a
	Type of anesthesia: General anesthesia may cause transient postoperative loss of consciousness and respiratory depression, affecting sleep coherence; Local anesthesia has minimal impact on overall sleep quality (19).	2a
	Pharmacological factors: Certain medications, such as selective serotonin reuptake inhibitors, have been shown to induce Rapid eye movement (REM) sleep behavior disorder (RBD). This finding indicates that the administration of drugs that can affect sleep patterns, including opioid analgesics and specific psychotropic agents, may contribute to post-surgical sleep disturbances in patients with malignant tumors (25).	2b
	Chemoradiotherapy side effects: nausea, vomiting, fatigue, and other discomfort affect sleep quality (19–23, 26).	2a
	Complications: Postoperative complications such as infection, bleeding, and atelectasis can affect sleep, increase psychological burden, and aggravate sleep disorders (20, 26, 27).	2b
	Psychological factors	
	Anxiety and depression: As a stressful event, surgery easily causes anxiety and depression in patients, which can affect the function of the nervous system. Patients' concerns about surgical outcome, such as tumor recurrence and metastasis, will increase psychological stress, interfere with sleep, and lead to sleep disorders (3, 18–24, 26, 27).	1a
	Nutritional status	
	Post-surgical patients with malignant tumors frequently experience a decline in nutritional status, and malnutrition can impair physical recovery, resulting in persistent fatigue, which subsequently affects sleep quality (26).	2b
	Environmental factors	
	Hospital-related factors such as noise and lighting can disrupt sleep patterns. Unfamiliar environment in hospital wards, changes in sleep habits, frequent medical operations, and noise of medical equipment may lead to sleep disorders (3, 18–24, 27).	2b
	Age factor	
	Age serves as a significant risk factor for RBD, with older adults being more prone to developing RBD. This finding implies that elderly patients undergoing malignant tumor surgery may have an increased susceptibility to post-surgical sleep disturbances (25).	1a
	Socio-demographic factors	
	Elderly patients and women with malignant tumors who undergo surgical procedures are more susceptible to sleep disturbances (25, 30).	1a
	Neurodegenerative diseases	
	REM sleep behavior disorder is commonly observed in conjunction with neurodegenerative conditions such as Parkinson's disease and dementia with Lewy bodies. Postoperative neurological complications or potential neuropathy in patients with malignant tumors may heighten the risk of developing sleep disorders (25).	1a
Methods of assessment	Clinical evaluation	
	Medical history collection and physical examination: A comprehensive evaluation of the patient's medical history, including detailed inquiries into sleep patterns, pain levels, and psychological state, in conjunction with a thorough physical examination, provides critical information on the patient's overall health condition and serves as a foundation for accurate diagnosis (18–27).	1a
	Subjective assessment	
	Sleep diary Maintaining a sleep diary that records key sleep-related data such as bedtime, wake-up time, and frequency of awakenings, offers valuable insights into the patient's sleep quality and is an essential tool for assessing sleep disorders (22).	1a

(Continued)

TABLE 4 (Continued)

Categories	Content of evidence	Level of evidence
	Subjective scale assessment Using standardized scales like the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Athens Insomnia Scale, Hamilton Anxiety Rating Scale (HAMA), and Hamilton Depression Rating Scale (HAMD) allows for a thorough evaluation of sleep quality, insomnia severity, and emotional status. These tools provide objective measures of the patient's sleep and psychological well-being (19–25).	1a
	Based on Traditional Chinese Medicine principles, patients are evaluated to determine their specific syndrome type, such as liver qi stagnation, spleen deficiency with liver qi stagnation, qi and blood deficiency, qi and yin deficiency, or heart and spleen deficiency. This differentiation guides the development of personalized treatment plans (18).	4b
	Objective assessment	
	Polysomnography (PSG), considered the gold standard for diagnosing sleep disorders, accurately assesses sleep architecture, respiratory function, and other relevant parameters, providing crucial data for diagnosis and efficacy evaluation (18–27).	1a
	Actigraphy: Actigraphy monitors sleep–wake cycles and activity levels, offering supplementary data that aids in assessing sleep patterns (27).	2b
Interventions	Non-pharmacological treatments	
	Sleep hygiene education: guiding patients in developing healthy sleep habits, such as maintaining a regular schedule for work and rest, creating a comfortable sleep environment, avoiding stimulating activities before bed, and minimizing medical interventions prior to sleep, is crucial for enhancing sleep quality (20, 21).	1a
	Cognitive behavioral therapy (CBT-I) This therapeutic approach encompasses techniques such as sleep restriction, stimulus control, cognitive restructuring, and relaxation training, all of which can effectively address patients' sleep-related cognitions and behaviors, thereby improving sleep disorders. Forms of treatment Face-to-face: Standard CBT-I model, personalized treatment, good efficacy, but higher cost. Digital network model: leveraging intelligent devices and specialized applications, this approach is not constrained by location and offers cost-effectiveness. However, it faces challenges with patient adherence and lacks personalized elements (19–25).	1a
	Relaxation training: methods like deep breathing exercises, progressive muscle relaxation, and mindfulness meditation are frequently utilized to alleviate patient tension and anxiety, thereby promoting better sleep (19).	2b
	Sound therapy Music therapy demonstrates efficacy in reducing sleep onset latency, enhancing sleep efficiency and quality. However, standardized protocol for music intervention regarding program selection, timing, frequency, or duration is lacking (24). Closed-loop pink noise stimulation during sleep, delivered via a pink noise simulator, can enhance slow wave activity and increase slow wave oscillations without inducing arousal, thereby improving sleep quality. However, its efficacy in treating insomnia requires further investigation (27).	1a 2b
	Light therapy: Light therapy as a natural and simple treatment, especially morning phototherapy, can improve sleep quality and increase sleep maintenance by adjusting the endogenous sleep–wake cycle, but the effect size is small to moderate, and additional research is needed to demonstrate clinical benefits in chronic insomnia.	2b
	Physical therapy	
	Transcranial magnetic stimulation (TMS): Repetitive TMS (rTMS) has the strongest evidence base. Low-frequency (≤1 Hz) TMS can reduce cortical excitability, serving as a safe and effective treatment for chronic insomnia. It can be used as a standalone therapy or in combination with other treatments. In China, applying low-frequency stimulation to the bilateral dorsolateral prefrontal cortex and parieto-occipital regions is recommended to enhance sleep quality (27).	1b
	Transcranial electrical stimulation: Transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) show promise in the treatment of insomnia. Small-sample studies on tDCS have demonstrated its safety, efficacy, and tolerability, with improvements in sleep quality. Moreover, tACS technology can enhance the amplitude of slow wave oscillations, thereby deepening sleep (27).	1b
	Medication	
	Dexmedetomidine: The administration of dexmedetomidine during the anesthesia period may help prevent the development of postoperative sleep disorders (27).	1a

(Continued)

TABLE 4 (Continued)

Categories	Content of evidence	Level of evidence
	Benzodiazepine (BZD) agonists: BZDs such as zolpidem and dexzopiclone can improve the symptoms of insomnia, but drug dependence and adverse reactions should be monitored. BZDs should be used in patients with liver and kidney dysfunction, myasthenia gravis, dementia with Lewy bodies, and moderate-to-severe obstructive sleep apnea (27).	1a
	Melatonin receptor agonists: For example, ramelamide and agomelatine can shorten sleep latency, improve sleep efficiency, and increase total sleep time. They are used for insomnia caused by circadian rhythm disorder with difficulty falling asleep as the main manifestation. They have no dependence and addiction, no withdrawal symptoms, no respiratory depression, and little residual effect on the next day (26, 27).	2a
	Dual orexin receptor antagonists: Suvaresan, lebolesen, and daliresan can be adjusted to significantly improve sleep efficiency, shorten sleep latency, and reduce wake time after sleep, with good safety and tolerance (27).	1a,b
	Antihistamine H1 receptor drugs: Doxylamine has sedative effect, can shorten sleep latency, and is used for treating acute insomnia (27).	1b
	Antidepressants: Antidepressants such as doxepin and trazodone have sedative effects and can improve insomnia symptoms, especially for patients with anxiety and depressive symptoms (22–24, 27).	2b
Effect evaluation	Evaluation of effectiveness	
	Sleep quality measures	
	Changes of PSG: Many studies have discovered that sleep latency was shortened, sleep efficiency was improved, and REM sleep and slow wave sleep returned to normal after the intervention of postoperative patients (20–27).	1a
	Subjective rating scale scores	
	For example, the patient's PSQI score was significantly reduced, indicating that sleep quality and insomnia severity were improved (19–25).	1a
	Daytime functional improvement	
	Reduced fatigue: As assessed using the FSS and other scales, patients' fatigue symptoms were reduced, their physical strength and energy were restored, and they were better able to perform daily activities (26).	1a
	Improved emotional state	
	Anxiety and depression were relieved The scores of HAMA and HAMD scales were decreased, the anxiety and depression of patients were alleviated, and the emotional stability was improved (27).	1a
	Safety evaluation	
	Adverse drug reactions: closely observe the adverse drug reactions, such as somnolence, dizziness, unsteady gait of sedative and hypnotic drugs, and the adverse drug reactions of antidepressant drugs. Studies have discovered that the rational use of drugs can reduce the occurrence of adverse reactions (27).	1a

1a, Meta-analysis of homogeneous randomized controlled trials; 1b, A single well-designed RCT study; 2a, Prospective cohort study; 2b, Retrospective cohort study or low-quality prospective study; 4b, Cross-sectional study conducted in a single center or with a small sample size.

disturbances in patients with malignant tumors (18–21). Key biological and treatment-related factors included cancer type, surgical trauma, anesthesia technique, pharmacological side effects (e.g., opioids, selective serotonin reuptake inhibitors), complications, and side effects of chemo-or radiotherapy. Psychosocial and environmental contributors such as anxiety, depression, nutritional status, hospital environment, and age-related vulnerability—particularly to REM sleep behavior disorder—were also frequently highlighted (18, 20, 22, 23). The level of supporting evidence for these factors ranged from 1a to 2b.

Assessment methods were divided into subjective and objective approaches. Subjective tools included sleep diaries and standardized instruments such as the Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Hamilton Anxiety Scale (HAMA), and Hamilton Depression Scale (HAMD) (18, 19, 23). Objective assessments primarily included polysomnography (PSG)—regarded as the gold standard—and actigraphy (21, 24). In Chinese clinical guidelines, Traditional Chinese Medicine (TCM) syndrome differentiation was also used to guide personalized assessment and treatment (26).

Intervention strategies involved a combination of non-pharmacological and pharmacological approaches. Non-pharmacological treatments included cognitive behavioral therapy for insomnia (CBT-I), relaxation training, music therapy, and light therapy (19, 21, 22, 25). Physical therapies such as transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (tDCS, tACS) were also reported (22, 25, 27). Pharmacological interventions included dexmedetomidine, benzodiazepine receptor agonists, melatonin receptor agonists, dual orexin receptor antagonists, antihistamines, and antidepressants (20, 21, 23).

The effectiveness of these interventions was evaluated based on improvements in PSG parameters, reductions in subjective sleep and emotional scores, relief of fatigue symptoms, and enhancement of daytime functioning (18, 22, 23, 25). Additionally, several studies emphasized the importance of monitoring adverse drug reactions to ensure treatment safety (20, 21).

In summary, the included studies provide comprehensive, high-quality, and multidisciplinary evidence for the assessment and management of sleep disturbances in postoperative cancer patients, thereby supporting evidence-based clinical decision-making (3, 18–27).

4 Discussion

4.1 Evidence synthesis process

This study adhered to stringent scientific standards, yielding high-quality evidence to guide clinical nursing practices. All research team members received comprehensive training in evidence-based nursing methodologies. Two researchers independently conducted evidence retrieval, quality assessment, data extraction, and evidence grading to ensure objectivity and reliability. Furthermore, sleep specialists oversaw quality control and reviewed the evidence to maintain scientific rigor of the synthesis process. Two expert consensuses were included, meeting all quality criteria. Ten guidelines were also included, and international peers rigorously reviewed and validated the evidence, ensuring their robustness and credibility (3, 18–27). These studies addressed risk factors, assessment methods, intervention strategies, and evaluation of sleep disorders following malignant tumor surgery. The research team critically evaluated the strengths and limitations of the evidence while considering the clinical context. Through a comprehensive analysis and synthesis, 37 optimal pieces of evidence were identified for managing postoperative sleep disorders. This evidence provides precise and scientifically sound guidance for enhancing the management of post-surgical sleep disorders, ultimately improving patient care and sleep quality. These four themes provide a structured and comprehensive overview of the current evidence and practical recommendations, contributing to a clearer understanding of postoperative sleep disorder management.

4.2 Early identification of risk factors for postoperative sleep disorders in patients with malignant tumors is essential

Postoperative sleep disturbance in patients with cancer arise from multiply risk factors. Surgical intervention, chemotherapy, radiotherapy, and multiple therapeutic modalities can contribute to the onset and worsening of sleep disorders over time (7). Certain adjuvant medications may also impact sleep patterns; however, their influence generally diminishes as treatment progresses (28). Psychological factors, such as pre-existing anxiety and depression, significantly impair sleep quality, particularly if these conditions are present before the initiation of cancer treatment. Implementing emotion regulation strategies can help mitigate sleep disturbances (29). Regarding sleep-related cognition and behavior, negative thought patterns, including excessive worry before bedtime and catastrophic thinking, can lead to chronic insomnia (30, 31). Demographic characteristics also exert a substantial influence; with women, younger individuals, unemployed populations, and those from lower-income households being more susceptible. The impact of educational attainment on sleep outcomes remains inconsistent, potentially owing to variations in study populations, sample sizes, and treatment methods. Disease-specific factors and pre-treatment health status are critical determinants of sleep quality. More advanced disease stages were correlated with more severe sleep disturbances. Additional contributing factors include regional lymph node metastasis, pretreatment use of analgesics, higher number of comorbidities, poorer functional status, elevated body mass index, and preexisting sleep issues (29). Given the complexity of these risk factors, healthcare providers should leverage the evidence presented here for early identification. Targeted preventive measures should be implemented to address modifiable risk factors and enhance patient wellbeing.

4.3 Comprehensive assessment through subjective and objective evaluations

Evaluating sleep disorders encompass subjective and objective evaluations. Currently, most studies use subjective scales for evaluation. Among the various assessment tools, the Pittsburgh sleep quality index (PSQI) developed by Buysse et al. (32) is the most widely utilized internationally and domestically. Additionally, Lee's general sleep disturbance scale (GSDS) is frequently employed and has demonstrated robust reliability and validity in cancer patient populations (33). Unlike the PSQI, the GSDS employs an 8-point scoring system that allows it to detect changes across different sleep factors more sensitively. Several studies have utilized the insomnia severity index and the Athens insomnia scale to assess insomnia. The insomnia severity index consists of seven items and focuses on assessing the severity of insomnia, emphasizing its adverse psychological impact. It has shown strong reliability and validity in patients with malignant tumors. The Athens insomnia scale, which includes eight items, primarily evaluates sleep quality, duration, and daytime dysfunction caused by insomnia (34). Its concise and practical nature enables accurate identification of insomnia cases. Polysomnography (PSG) provides comprehensive sleep measurements and is critical for diagnosing complex sleep disorders. However, PSG is generally unnecessary for evaluating insomnia symptoms and is unsuitable for the routine assessment of chronic insomnia. PSG should be considered in pathological sleepiness or report other sleep-related pathologies, such as sleep breathing disorders, periodic limb movements, or parasomnias (35). Some studies have combined objective measurement methods such as wrist actigraphy with subjective assessments using the PSQI to dynamically monitor patients' sleep conditions and gather more comprehensive and objective data. However, most studies rely solely on subjective scales because of time and financial constraints, often lacking integration with objective assessments such as measurement instruments and biochemical indicators. Future research should adopt a combined approach of subjective and objective assessments (36). Initially, subjective scales were used to evaluate patients. If multiple pieces of evidence suggest the presence of related sleep disorders, objective assessments such as PSG should be employed to reflect the dynamic changes in sleep disorders more accurately.

4.4 Key considerations for developing effective intervention measures

Intervention strategies for postoperative sleep disorders in patients with malignant tumors can be broadly categorized into non-pharmacological and pharmacological approaches. Additionally, global consensus on which pharmacological treatment provides optimal efficacy or the best risk–benefit ratio is lacking. Cognitive behavioral therapy for Insomnia (CBT-I) is widely recognized as the first-line treatment (37). CBT-I and pharmacological interventions may produce comparable short-term outcomes; however, only CBT-I has demonstrated sustained long-term benefits post-treatment. Combining CBT-I with medication can accelerate the initial treatment response but may compromise the long-lasting positive effects of CBT-I (38). In specific cases, alternative interventions such as the use of dexmedetomidine during surgery, music therapy, traditional Chinese medicine, and physical rehabilitation exercises have shown efficacy in managing sleep disorders (27, 39). Following clinical assessment, when patients are in the early stages of sleep disorders, priority should be given to implementing psychological care interventions. If symptoms remain unalleviated, pharmacological treatment may then be introduced as an adjunctive measure for symptom control. When resources allow, cranial nerve stimulation therapy or a comprehensive treatment approach can be considered. Anesthesiologists must systematically refine perioperative pain management strategies to mitigate the risk of postoperative sleep disturbances. Psychological counseling should be integrated into routine postoperative care protocols as a key component of psychological intervention. Moreover, a systematic and standardized framework for managing sleep disorders should be developed, leveraging multidisciplinary expertise from fields such as anesthesiology, psychiatry, and nursing to foster interdisciplinary collaboration. A comprehensive approach should consider the patient's medical condition, personal preferences, and available treatment resources to develop an intervention plan for postoperative sleep disorders in patients with malignant tumors.

4.5 Limitations

Despite considerable progress in the study of sleep disorders following malignant tumor surgery, several limitations remain. One of the primary challenges is the insufficient understanding of the complex interactions among various risk factors. In particular, the interplay between psychological and physiological elements—such as the inflammatory response induced by surgical trauma and psychological stress—has not been thoroughly elucidated (2, 28, 40). Further research is warranted to clarify these interrelationships, which may inform the development of more targeted and effective therapeutic strategies.

Cultural and regional differences in the management of sleep disorders also represent a critical area of concern. Variability in healthcare infrastructure, sociocultural attitudes, and accessibility of treatment may influence both the assessment and intervention approaches employed in different populations. Although the integration of multiple assessment modalities can enhance diagnostic accuracy, the validity and applicability of certain tools may vary across cultural and demographic contexts (19, 23, 25, 38, 39). Consequently, there is a pressing need to develop culturally sensitive, efficient, and clinically applicable assessment instruments that are adapted to specific populations, disease profiles, and healthcare workflows.

With regard to intervention strategies, novel therapies such as transcranial alternating current stimulation and pink noise stimulation have shown preliminary promise in enhancing sleep quality. However, existing studies are constrained by limited sample sizes and a lack of large-scale, high-quality clinical trials. The long-term efficacy and safety profiles of these interventions remain uncertain and must be substantiated through further rigorous investigation before their integration into routine clinical practice can be recommended (11, 18, 41).

This review provides a comprehensive synthesis of the current evidence concerning risk factors, diagnostic tools, therapeutic interventions, and treatment outcomes associated with postoperative sleep disorders in patients with malignant tumors. Nonetheless, future research is essential to establish more robust and cohesive links among these domains, thereby improving clinical relevance and informing optimized, patient-centered care strategies.

5 Conclusion

This evidence summary integrates 37 high-quality studies on the management of postoperative sleep disorders in patients with malignant tumors, emphasizing the multifactorial complexity of sleep disturbances in this population. The interplay of biological factors such as surgical trauma and anesthesia effects, along with socio-psychological factors like opioid use and emotional distress, significantly elevates the risk of sleep disorders. Accurate assessment necessitates a combination of subjective scales and objective monitoring tools. Additionally, traditional Chinese medicine syndrome differentiation can facilitate individualized diagnosis. Non-pharmacological interventions, including cognitive behavioral therapy, music therapy, and light therapy, have been demonstrated to be safe and effective primary options, while pharmacological and complementary therapies serve as supplementary approaches. Effectiveness evaluation should encompass multiple dimensions, such as sleep quality, emotional well-being, and functional recovery. Future clinical practice should consider patient preferences and resource availability, promote multidisciplinary collaboration, optimize treatment strategies, and ultimately enhance patient quality of life and prognosis.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: this article aims to systematically summarize and synthesize the evidence presented in systematic reviews, clinical practice guidelines, expert consensus statements, and related literature. The current query is not applicable to this context. Requests to access these datasets should be directed to YL,15923295225@163.com.

Author contributions

CY: Conceptualization, Investigation, Writing – original draft, Writing – review & editing. YL: Data curation, Methodology, Writing – original draft, Writing – review & editing. BX: Investigation, Writing – review & editing. JY: Methodology, Writing – review & editing. QZ: Data curation, Writing – review & editing. RT: Investigation, Writing – review & editing. HM: Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

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

Acknowledgments

We would like to thank Editage (www.editage.com) for English language editing.

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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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frontiers | Frontiers in Medicine

TYPE Clinical Trial
PUBLISHED 13 June 2025
DOI 10.3389/fmed.2025.1581503

OPEN ACCESS

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RECEIVED 22 February 2025
ACCEPTED 30 April 2025
PUBLISHED 13 June 2025

CITATION
Xiang M, Liu J, Wang J, Li F, Fan T and Tang J (2025) Association between educational level and postoperative delirium in older patients undergoing abdominal surgery: a two-sample cohort study.
Front. Med. 12:1581503.
doi: 10.3389/fmed.2025.1581503

Association between educational level and postoperative delirium in older patients undergoing abdominal surgery: a two-sample cohort study

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Background: Postoperative delirium (POD) is a critical complication in older patients following abdominal surgery, significantly contributing to delayed recovery and prolonged hospital stays. Understanding the risk factors associated with POD is essential for developing effective prevention and intervention strategies. This study investigates the potential impact of educational attainment on the incidence of delirium in this patient population.

Methods: This study utilized a two-sample cohort design to collect demographic and educational attainment, and clinical data, including, from older patients undergoing abdominal surgery. The assessment of delirium during the recovery phase was conducted using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the 3-Minute Diagnostic Interview for Confusion Assessment Method within the first three postoperative days. In the exploratory cohort, the relationship between education and postoperative delirium was determined by univariate analysis, followed by multivariate logistic regression to determine that education was an independent predictor. The identified risk factors were subsequently validated in an independent validation cohort to ensure robustness and generalizability.

Results: The exploratory cohort consisted of 342 cases, while the validation cohort included 150 cases. Exploratory cohort regression analysis identified lower educational attainment and procedures or anesthesia lasting longer than 4 h as independent risk factors for POD. Anesthesia time of more than 4 h was also an independent risk factor for delirium during resuscitation.

Conclusion: Lower educational attainment is significantly related to an increased chance of POD in older adults undergoing abdominal procedures. These findings suggest that preoperative assessments should incorporate educational level as a potential risk factor, providing a basis for targeted prevention and intervention strategies to mitigate POD.

KEYWORDS

older patients, postoperative delirium, abdominal surgery, risk factors, cognitive reserve

1 Introduction

Abdominal surgery, which includes procedures involving the hepatobiliary, pancreatic, gastrointestinal, urological, and gynecological systems (1), is a surgical intervention frequently executed in clinical practice, particularly among the older population. Postoperative delirium (POD) (2), an acute and transient neurological disorder characterized by impaired attention, altered cognition, and fluctuating consciousness, typically manifests within 24–72 h after surgery and may persist for several days to weeks (3). POD is a frequent and significant complication in older patients having abdominal surgery (4), with reported incidence rates as high as 50% (5). POD is associated with extended hospital stays, a rise in postoperative complication risks, and considerably higher healthcare costs. (6). Despite its clinical importance, the underlying pathophysiological mechanisms of POD remain poorly elucidated (7). Moreover, evidence supporting effective pharmacological prevention strategies is limited (8). Therefore, early identification, accurate prediction, and timely intervention are critical to improving clinical outcomes in these patients.

Cognitive reserve, which is closely associated with brain function, is increasingly recognized as a potential risk factor for POD. Cognitive reserve represents the brain's ability to cope with neuropathological damage, and higher educational achievement is believed to enhance this capacity, potentially reducing the risk of POD (9–11). However, the relationship between educational level and POD remains underexplored. Existing studies have primarily focused on clinical and demographic factors, such as age, preoperative cognitive impairment, and comorbidities (12, 13). Most POD prediction do not incorporate educational level as a key variable, which may limit their accuracy and generalizability (14, 15). In particular, there is insufficient evidence about how educational level affects POD in older patients having abdominal surgery.

In summary, this study aims to investigate the association between educational level and the risk of POD in older patients undergoing abdominal surgery by employing a two-sample cohort design, which includes an exploratory cohort and a validation cohort. The findings are expected to provide evidence for the early identification of patients who are at high risk for POD in the clinical older abdominal surgery population.

2 Materials and methods

2.1 Study design and participants

As shown in Figure 1, this study prospectively collected clinical data from 492 patients who had abdominal surgery at the Second Affiliated Hospital of Chongqing Medical University between August 2022 and July 2023. Eligibility criteria were: ① age range of 65–90 years; ② patients scheduled for elective surgery under general anesthesia; ③ patients scheduled for elective abdominal procedures; and ④ American Society of Anesthesiologists physical status classification of I to III. Exclusion criteria comprised the following: ① patients with known psychiatric disorders, communication difficulties, or cognitive impairments (preoperative Mini-Mental State Examination (MMSE) score < 24) prior to surgery; ② patients with severe hearing, visual, or speech impairments that hindered communication with the investigators; ③ patients on long-term sedatives, antidepressants, or with a history of alcohol abuse; and ④ patients who refused or were unable to complete cognitive assessments. The allocation principle was applied for analysis and validation. The inclusion and exclusion process for patients is demonstrated in Figure 1. The study was authorized by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (Approval No.: 2024-33).

2.2 Data collection

General information, including gender, age, educational level, American Society of Anesthesiologists classification, history of allergies, preoperative smoking status, preoperative alcohol consumption, and postoperative complications, were collected. Preoperative biochemical indicators such as hemoglobin concentration, serum protein concentration, absolute neutrophil count, and absolute white blood cell count were recorded. In addition, surgical type and major abdominal surgeries with a duration exceeding 2 h were analyzed.

2.3 Assessment methods

2.3.1 Preoperative emotional assessment

- The West China Mood Index was used to evaluate preoperative emotional status.

2.3.2 POD assessment (primary outcome measures)

- From postoperative days 1 to 3, trained investigators assessed the occurrence of POD using the 3D-CAM (3-Minute Diagnostic Interview for Confusion Assessment Method), with follow-ups conducted twice daily.
- Patients with at least one positive POD result within the first three postoperative days were considered to have developed POD and were assigned to the POD group.
- Patients without any positive POD results were included in the non-POD group.

2.3.3 Postoperative assessment in the PACU (post-anesthesia care unit) (secondary outcome measures)

- Sedation status was assessed using the Richmond Agitation-Sedation Scale.

Abbreviations: POD, postoperative delirium; PACU, Post-Anesthesia Care Unit; CAM-ICU, the Confusion Assessment Method for the Intensive Care Unit; 3D-CAM, 3-Minute Diagnostic Interview for Confusion Assessment Method; OR, odds ratio; CI, confidence interval; POD at 3 days, postoperative delirium occurring within 3 days after surgery; *P*-value, probability value, indicating statistical significance; IV, intravenous; PCIA, patient-controlled intravenous analgesia.

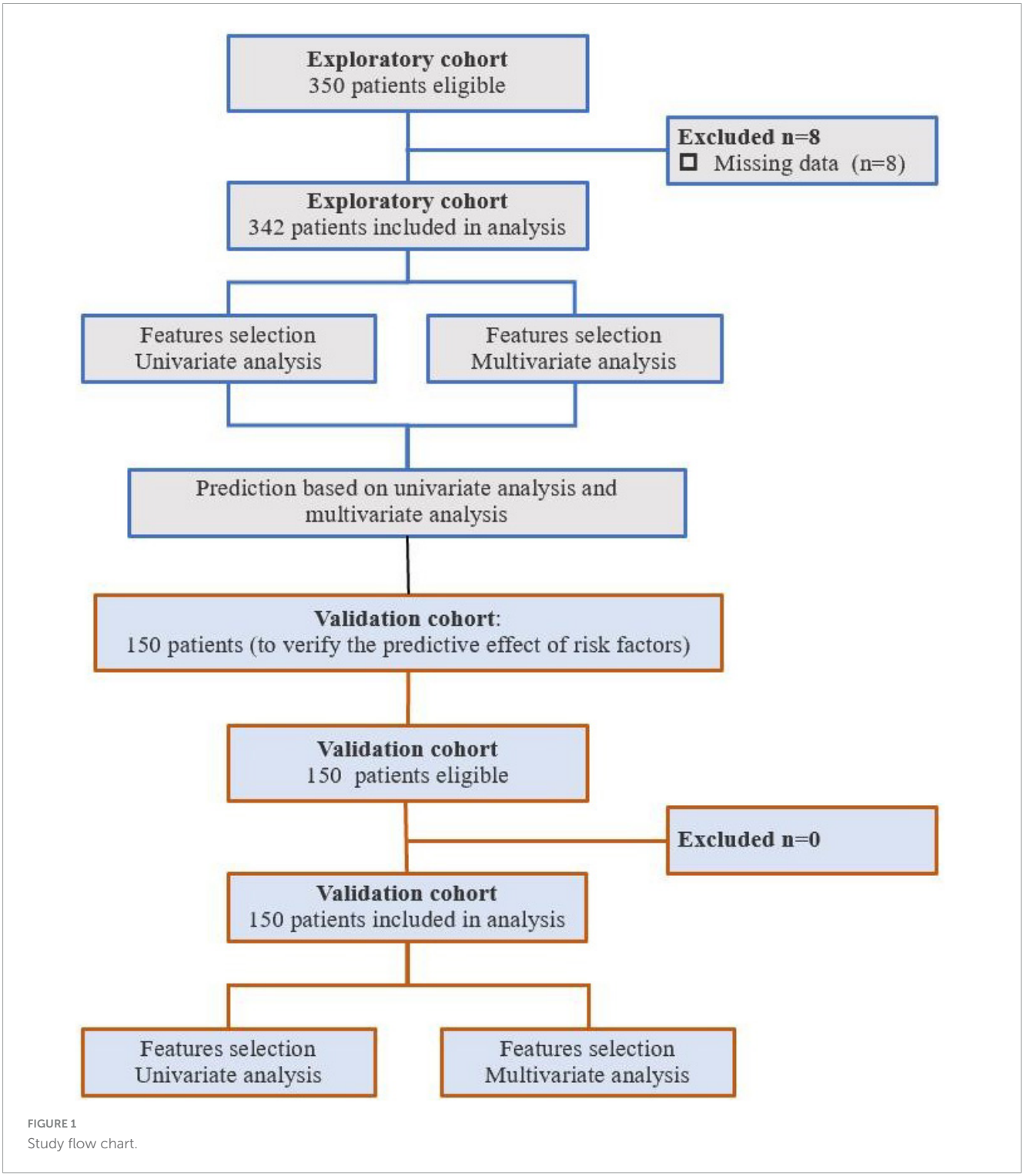

FIGURE 1
Study flow chart.

- Delirium during the recovery period was evaluated using the Confusion Assessment Method for the Intensive Care Unit.
- Patients with a positive Confusion Assessment Method for the Intensive Care Unit result during the recovery period were diagnosed with PACU POD and included in the PACU POD group.
- Patients without delirium were included in the non- PACU POD group.

2.4 Risk factor scoring and validation

A cohort study involving 342 patients was selected as the exploratory cohort, and an additional 150 patients meeting the same criteria were included as the validation cohort. Based on the information from the exploratory cohort and the presence or absence of delirium, relevant risk factors were identified. Logistic regression was used to determine the link between these variables and the risk of POD.

2.5 Sample size

According to the principle of 10 events per variable (EVP), eight factors including age, BMI, education level, ASA, surgery time, anesthesia time, surgical type and hemoglobin were included, and considering a 5% loss to follow-up rate, 25% (16) the incidence of postoperative delirium in elderly patients undergoing gastric and colorectal surgery under general anesthesia, the exploratory cohort plans to include 337 patients. The validation cohort mainly considers the factor of educational level and a sample size of 150 cases in the validation cohort is sufficient.

2.6 Statistical analysis

Statistical Methods: Continuous variables were summarized according to their distributional properties. Variables following normal distribution were expressed as mean ± standard deviation, whereas those deviating from normality were reported as median (interquartile range, IQR). For intergroup comparisons, independent samples *t*-tests were used for normally distributed continuous variables, while the Mann–Whitney U test was applied for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages, and group comparisons were performed using the chi-square test or Fisher's exact test, as appropriate. To confirm the inclusion of potential predictors connected to the outcome, variables showing a *P*-value of less than 0.1 in the univariate logistic regression analysis were added as covariates in the multivariate logistic regression to pinpoint independent risk factors. Using SPSS 26 (IBM Corp, USA) and R 4.4.0 (R Foundation for Statistical Computing, Austria), all statistical analyses were carried out, considering a two-tailed *P*-value below 0.05 as statistically significant.

3 Results

3.1 Basic characteristics

This study included two cohorts comprising 350 and 150 patients, respectively. Based on predefined exclusion criteria, 8 (missing data) and 0 patients were excluded from each group, resulting in 342 patients in the exploratory set and 150 patients in the validation set. Table 1 provides a detailed comparison of demographic and clinical variables among the exploratory set and validation set. There is no statistical difference in the main characteristics between the two cohorts.

The median age of patients in both the exploratory and validation sets was 71 years (exploratory cohort: IQR 68–75 years; validation cohort: IQR 67–75 years). The proportions of females were 38.0 and 39.3% in the exploratory and validation cohort, respectively. The median body mass index was 22.86 kg/m^2 (IQR 20.43–25.09) and 23.02 kg/m^2 (IQR 20.86–25.14) in the exploratory and validation cohort, respectively. Analysis of educational levels revealed similar proportions of patients with middle school and college education in both cohorts (exploratory cohort: 48.2 and 35.4%; validation cohort: 50.0 and 37.3%).

The exploratory cohort had 73.7% of patients with a history of comorbidities, compared to 73.3% in the validation cohort. In the exploratory cohort, 36.3% of patients experienced postoperative delirium (POD) in the post-anesthesia care unit (PACU), compared to 33.3% in the validation cohort. The overall incidence of POD within the first 3 days after surgery was 19.0 and 33%, respectively. Additional detailed characteristics of the cohorts are summarized in Table 1.

3.2 Univariate logistic regression analysis for POD at 3 days and PACU POD

In the exploratory cohort, univariate logistic regression analysis (Table 2) revealed several variables significantly associated with postoperative delirium (POD) at 3 days. An increase in age was linked to a higher risk of POD (OR = 1.06, 95% CI: 1.01–1.11, $P = 0.028$). Conversely, elevated hemoglobin levels were associated with a reduced risk of POD (OR = 0.94, 95% CI: 0.89–0.99, $P = 0.028$). Compared to participants with primary education or less, those with a college education demonstrated a lower risk of POD (OR = 0.99, 95% CI: 0.97–1.00, $P = 0.019$). Prolonged surgical duration exceeding 4 h was significantly associated with an elevated risk of POD (OR = 2.90, 95% CI: 1.67–5.04, $P < 0.001$), as was anesthesia duration longer than 4 h (OR = 2.28, 95% CI: 1.31–3.95, $P = 0.003$).

In the validation cohort, univariate logistic regression analysis (Table 2) demonstrated significant associations with postoperative delirium (POD) at 3 days. Participants with a college education exhibited a reduced risk of POD compared to those with primary education or less (OR = 0.45, 95% CI: 0.21–0.96, $P = 0.0389$). Prolonged surgical duration exceeding 4 h was associated with an elevated risk of POD (OR = 3.55, 95% CI: 1.74–7.23, $P < 0.001$), as was anesthesia duration longer than 4 h (OR = 2.28, 95% CI: 1.13–4.61, $P = 0.022$). These findings corroborate the significant relationships between education level, surgical duration, anesthesia duration, and the risk of POD at 3 days, as previously observed in the exploratory cohort.

In addition to POD at 3 days, this study also explored risk factors for POD in the PACU (Table 3). In the univariate logistic regression analysis of the exploratory cohort data, the following results were observed: compared to individuals with primary school or lower education level, those with a college education had a lower risk of PACU POD (OR = 0.49, 95% CI: 0.25–0.96, $P = 0.038$); surgical time greater than 4 h was significantly associated with an increased risk of PACU POD (OR = 2.03, 95% CI: 1.28–3.21, $P = 0.003$); anesthesia time greater than 4 h was also associated with an increased risk of PACU POD (OR = 1.85, 95% CI: 1.18–2.89, $P = 0.007$).

In the validation cohort, univariate logistic regression analysis (Table 3) identified significant associations between prolonged surgical and anesthesia durations and an increased risk of PACU POD. Surgical time exceeding 4 h showed a trend toward higher risk (OR = 1.87, 95% CI: 0.94–3.75, $P = 0.076$), while anesthesia time greater than 4 h was significantly associated with elevated risk (OR = 2.97, 95% CI: 1.44–6.12, $P = 0.003$). Although higher education levels did not achieve statistical significance, a trend toward reduced PACU POD risk was observed (middle school:

TABLE 1 Basic characteristics of all patients.

Variables	Exploratory cohort (n = 342)	Validation cohort (n = 150)	P-value
Age, median (IQR)	71 (68, 75)	71 (67, 75)	0.91
Female	130 (38)	59 (39.3)	0.781
BMI, median (IQR)	22.86 (20.43, 25.09)	23.02 (20.86, 25.14)	0.608
Education level			0.572
Primary school or below	165 (48.2)	75 (50)	
Middle school	121 (35.4)	56 (37.3)	
College	56 (16.4)	19 (12.7)	
ASA, n (%)			<0.001
ASA I	20 (5.8)	21 (14)	
ASA II	172 (50.3)	89 (59.3)	
ASA ≥ III	150 (43.9)	40 (26.7)	
Disease history	252 (73.7)	110 (73.3)	0.935
HEI, median (IQR)	0 (0, 2)	0.5 (0, 2)	0.67
Hemoglobin, median (IQR)	122 (108, 134)	118 (108, 131)	0.147
WBC (×10^9/L), median (IQR)	5.73 (4.5, 7.32)	5.7 (4.57, 7.42)	0.895
NC (×10^9/L), median (IQR)	3.8 (2.8, 5.05)	3.92 (2.8, 5.12)	0.854
LC (×10^9/L), median (IQR)	1.25 (0.87, 1.55)	1.25 (0.84, 1.53)	0.936
MC (×10^9/L), median (IQR)	0.39 (0.29, 0.52)	0.39 (0.29, 0.51)	0.711
PLT (×10^9/L), median (IQR)	211 (165, 266)	203.5 (155.75, 264)	0.592
NLR, median (IQR)	3.16 (2.16, 4.52)	3 (2.3, 4.79)	0.764
dNLR, median (IQR)	0.87 (0.83, 0.9)	0.87 (0.83, 0.9)	0.984
MLR, median (IQR)	0.32 (0.23, 0.47)	0.32 (0.24, 0.48)	0.948
nMLR, median (IQR)	3.48 (2.47, 4.92)	3.34 (2.51, 5.2)	0.851
SIRI, median (IQR)	1.19 (0.71, 2)	1.16 (0.72, 2.28)	0.828
Surgery time > 4 h	119 (34.8)	57 (38)	0.495
Anesthesia time > 4 h	149 (43.6)	79 (52.7)	0.062
PCIA	312 (91.2)	134 (89.3)	0.506
PACU POD	124 (36.3)	50 (33.3)	0.532
Postoperative POD at 3 days	65 (19)	50 (33.3)	0.001

Data are presented as n (%) and median (IQR). IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; HEI, Huaxi emotional-distress index; WBC, white blood cell count; NC, neutrophil count; LC, lymphocyte count; MC, monocyte count; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; nMLR, neutrophil-to-monocyte ratio; SIRI, systemic inflammation response index; PCIA, patient-controlled intravenous analgesia; PACU, post-anesthesia care unit; POD, postoperative delirium.

OR = 0.47, 95% CI: 0.22–1.01, P = 0.053; college: OR = 0.51, 95% CI: 0.17–1.55, P = 0.234).

3.3 Multivariate logistic regression analysis for POD at 3 days and PACU POD

In this study, variables exhibiting a P-value below 0.1 in the univariate logistic regression analysis were incorporated into the multivariate logistic regression. Forest plots were subsequently generated to visualize the outcomes for both cohorts. In addition, collinearity analysis was performed before multivariate logistic regression analysis, and the variance inflation factor between all variables was less than 2. The analysis results showed that in the exploratory cohort, age, college education level, hemoglobin level, and surgical duration were independently associated with POD at 3 days (Figure 2A). Specifically, age was positively correlated with POD at 3 days (OR = 1.06, 95% CI: 1.01–1.12, P = 0.024); although middle school education did not reach statistical significance, a trend toward a reduced risk of POD at 3 days was observed (OR = 0.64, 95% CI: 0.35–1.17, P = 0.144). College education was negatively correlated with POD at 3 days (OR = 0.35, 95% CI: 0.13–0.91, P = 0.031); higher hemoglobin levels were negatively correlated with POD at 3 days (OR = 0.99, 95% CI: 0.97–1.00, P = 0.033); and a surgical time greater than 4 h significantly increased the

TABLE 2 Univariable logistic regression analysis of risk factors for POD at 3 days.

Characteristics	Exploratory cohort		Validation cohort	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.06 (1.01–1.11)	0.028	1.03 (0.97–1.1)	0.342
Female	1.2 (0.69–2.08)	0.515	0.81 (0.4–1.63)	0.555
BMI	0.94 (0.87–1.02)	0.16	0.95 (0.86–1.06)	0.376
Education level				
Primary school or below	Reference		Reference	
Middle school	0.64 (0.35–1.17)	0.144	0.45 (0.21–0.96)	0.038
College	0.39 (0.15–0.97)	0.043	0.36 (0.11–1.18)	0.092
ASA				
ASA I			Reference	
ASA II	0.51 (0.18–1.44)	0.205	0.83 (0.3–2.28)	0.711
ASA ≥ III	0.54 (0.19–1.52)	0.24	1.48 (0.49–4.46)	0.487
Disease history	1.12 (0.6–2.08)	0.729	1.45 (0.65–3.21)	0.362
HEI	0.96 (0.82–1.13)	0.633	1.05 (0.92–1.19)	0.474
Hemoglobin	0.99 (0.97–1)	0.019	1 (0.98–1.01)	0.737
WBC	1.04 (0.93–1.15)	0.524	1.09 (0.96–1.25)	0.182
NC	1 (0.95–1.06)	0.923	1 (0.94–1.06)	0.921
LC	0.83 (0.51–1.37)	0.467	0.87 (0.46–1.62)	0.655
MC	0.89 (0.29–2.75)	0.843	1.33 (0.44–3.98)	0.615
PLT	1 (1–1)	0.318	1 (1–1.01)	0.255
NLR	1 (0.95–1.05)	0.958	1.02 (0.95–1.1)	0.547
dNLR	1.02 (0.85–1.24)	0.797	0.68 (0.13–3.45)	0.639
MLR	1.08 (0.48–2.43)	0.847	1.57 (0.57–4.34)	0.382
nMLR	1 (0.96–1.05)	0.95	1.02 (0.95–1.1)	0.516
SIRI	0.99 (0.92–1.08)	0.883	1.01 (0.93–1.11)	0.79
Surgery time > 4h	2.9 (1.67–5.04)	<0.001	3.55 (1.74–7.23)	<0.001
Anesthesia time > 4h	2.28 (1.31–3.95)	0.003	2.28 (1.13–4.61)	0.022
PCIA	2.23 (0.66–7.6)	0.199	3.907 (0.85–17.91)	0.079

POD, postoperative delirium; BMI, body mass index; ASA, American Society of Anesthesiologists; HEI, Huaxi emotional-distress index; WBC, white blood cell count; NC, neutrophil count; LC, lymphocyte count; MC, monocyte count; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; nMLR, neutrophil-to-monocyte ratio; SIRI, systemic inflammation response index; PCIA, patient-controlled intravenous analgesia.

risk of POD at 3 days (OR = 4.32, 95% CI: 1.18–15.82, $P = 0.027$).

In the validation cohort, education level remained independently associated with POD at 3 days (Figure 2B). Specifically, secondary education showed a significant relationship with POD at 3 days (OR = 0.44, 95% CI: 0.2–0.97, $P = 0.042$). Although college education did not achieve statistical significance, a trend toward a reduced risk of POD at 3 days was observed (OR = 0.36, 95% CI: 0.1–1.29, $P = 0.118$). Surgical durations exceeding 4 h remained significantly associated with an elevated risk of POD at 3 days (OR = 4.22, 95% CI: 1.18–15.82, $P = 0.013$). Furthermore, the use of patient-controlled intravenous analgesia was also linked to an increased risk of POD at 3 days, although this association did not reach statistical significance (OR = 2.27, 95% CI: 0.46–11.29, $P = 0.316$).

This study further analyzed the independent risk factors for PACU POD. In the exploratory cohort, multivariate logistic regression analysis showed that education level was independently associated with PACU POD (Figure 3A). The relationship between secondary education and PACU POD was not statistically significant (OR = 0.86, 95% CI: 0.52–1.40, $P = 0.539$), while college education was significantly associated with PACU POD (OR = 0.46, 95% CI: 0.23–0.92, $P = 0.029$).

In the validation cohort, compared to those with primary school or lower education levels, those with middle school and college education levels showed a trend toward reducing the risk of PACU POD. However, the result did not reach statistical significance. For secondary education, a trend toward a reduced risk of PACU POD was observed, though it did not reach statistical significance (OR = 0.47, 95% CI: 0.21–1.02, $P = 0.057$). Similarly, college education showed a non-significant trend toward risk reduction (OR = 0.53, 95% CI: 0.17–1.69, $P = 0.283$). In contrast, anesthesia durations exceeding 4 h were significantly associated with an elevated risk of PACU POD (OR = 3.47,

TABLE 3 Univariable logistic regression analysis of risk factors for PACU POD.

	Exploratory cohort		Validation cohort	
Characteristics	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.03 (0.98–1.07)	0.249	1 (0.93–1.07)	0.982
Female	1.17 (0.74–1.83)	0.507	0.62 (0.31–1.27)	0.195
BMI	1 (0.99–1.01)	0.933	0.98 (0.88–1.09)	0.727
Education Level				
Primary school or below	Reference		Reference	
Middle school	0.81 (0.5–1.31)	0.384	0.47 (0.22–1.01)	0.053
College	0.49 (0.25–0.96)	0.038	0.51 (0.17–1.55)	0.234
ASA				
ASA I	Reference		Reference	
ASA II	1.73 (0.6–5)	0.308	1.55 (0.52–4.64)	0.436
ASA ≥ III	1.79 (0.62–5.18)	0.285	2.13 (0.65–7)	0.211
Disease history	1.11 (0.67–1.84)	0.677	1.23 (0.56–2.69)	0.602
HEI	0.92 (0.8–1.05)	0.221	0.85 (0.68–1.07)	0.178
Hemoglobin	1 (0.99–1.01)	0.704	1.01 (1–1.03)	0.103
WBC	0.95 (0.86–1.04)	0.272	0.97 (0.84–1.11)	0.654
NC	0.95 (0.87–1.04)	0.305	0.94 (0.81–1.09)	0.407
LC	0.9 (0.61–1.34)	0.607	1.05 (0.57–1.94)	0.873
MC	1.34 (0.56–3.2)	0.507	1.78 (0.56–5.64)	0.325
PLT	1 (1–1)	0.289	1 (1–1)	0.751
NLR	0.97 (0.92–1.02)	0.294	0.92 (0.82–1.04)	0.192
dNLR	0.76 (0.48–1.21)	0.251	0.01 (0–2.9)	0.114
MLR	1.32 (0.68–2.56)	0.409	1.39 (0.51–3.77)	0.519
nMLR	0.98 (0.93–1.02)	0.33	0.94 (0.84–1.04)	0.222
SIRI	0.99 (0.93–1.06)	0.822	1 (0.91–1.1)	0.983
Surgery time > 4h	2.03 (1.28–3.21)	0.003	1.87 (0.94–3.75)	0.076
Anesthesia time > 4h	1.85 (1.18–2.89)	0.007	2.97 (1.44–6.12)	0.003
PCIA	1.36 (0.6–3.07)	0.457	2.341 (0.64–8.63)	0.201

POD, postoperative delirium; BMI, body mass index; ASA, American Society of Anesthesiologists; HEI, Huaxi emotional-distress index; WBC, white blood cell count; NC, neutrophil count; LC, lymphocyte count; MC, monocyte count; PLT, platelet count; NLR, neutrophil-to-lymphocyte ratio; dNLR, derived neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; nMLR, neutrophil-to-monocyte ratio; SIRI, systemic inflammation response index; PCIA, patient-controlled intravenous analgesia.

95% CI: 1.29–9.35, $P = 0.014$). These results are presented in Figure 3B.

4 Discussion

This study, through two cohort studies, identified and validated that university education level, surgical duration, and anesthesia time are independently associated with POD within 3 days after surgery. Although there were differences in the incidence of postoperative delirium between the exploration cohort and the validation cohort, education level was confirmed to be an independent risk factor in both cohorts, and its influence degree was higher than other related factors. This finding suggests that education level as a risk factor for postoperative delirium has universal applicability across populations and should be paid special attention in clinical practice. Lower educational attainment was associated with a significantly increased risk of POD within 3 days postoperatively, while surgical or anesthesia durations exceeding 4 h also significantly increased the risk of POD. Additionally, extended anesthesia time (>4 h) was independently correlated with the development of PACU POD. The findings emphasize the significance of accounting for educational attainment and surgical or anesthesia duration when assessing and managing the risk of POD.

Previous studies have predominantly investigated contributors to POD risk in older abdominal surgery patients using single-center retrospective or prospective cohort designs (17–22). In contrast to previous research, this study innovatively employed a dual independent cohort design, comprising an exploratory cohort and a validation cohort, to systematically analyze and validate risk factors for POD. Furthermore, the study categorized POD into two critical phases—PACU POD and POD within 3 days and independently validated risk factors for each

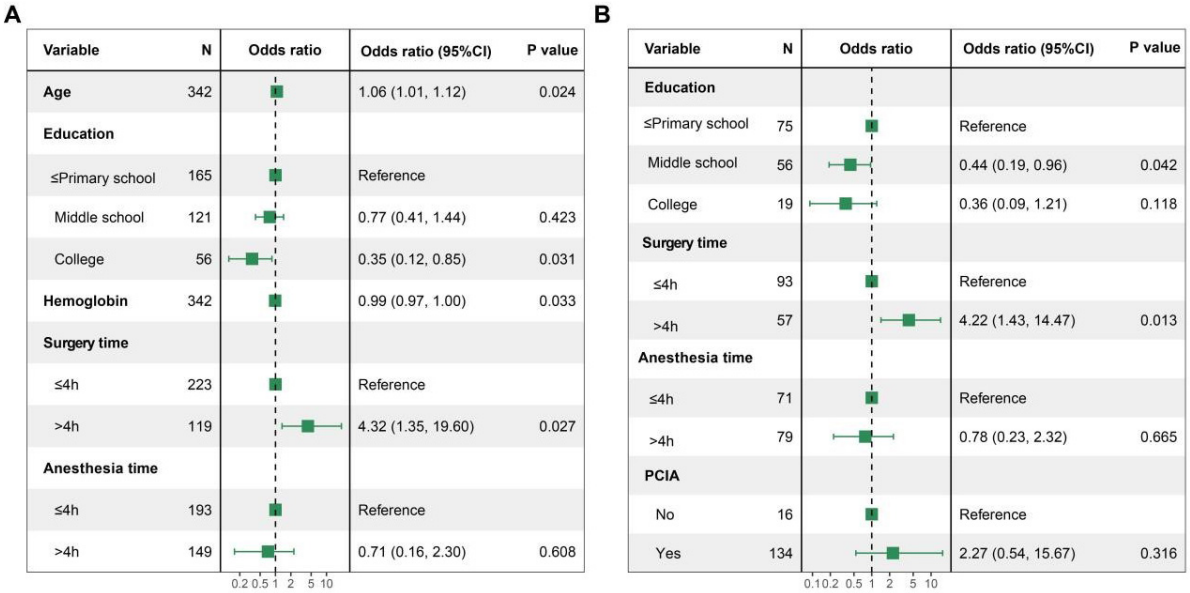

FIGURE 2
Forest plots for POD at 3 days in two cohorts. **(A)** Multivariate logistic regression analysis for POD at 3 days in the exploratory cohort; **(B)** multivariate logistic regression analysis for POD at 3 days in the validation cohort. POD, postoperative delirium.

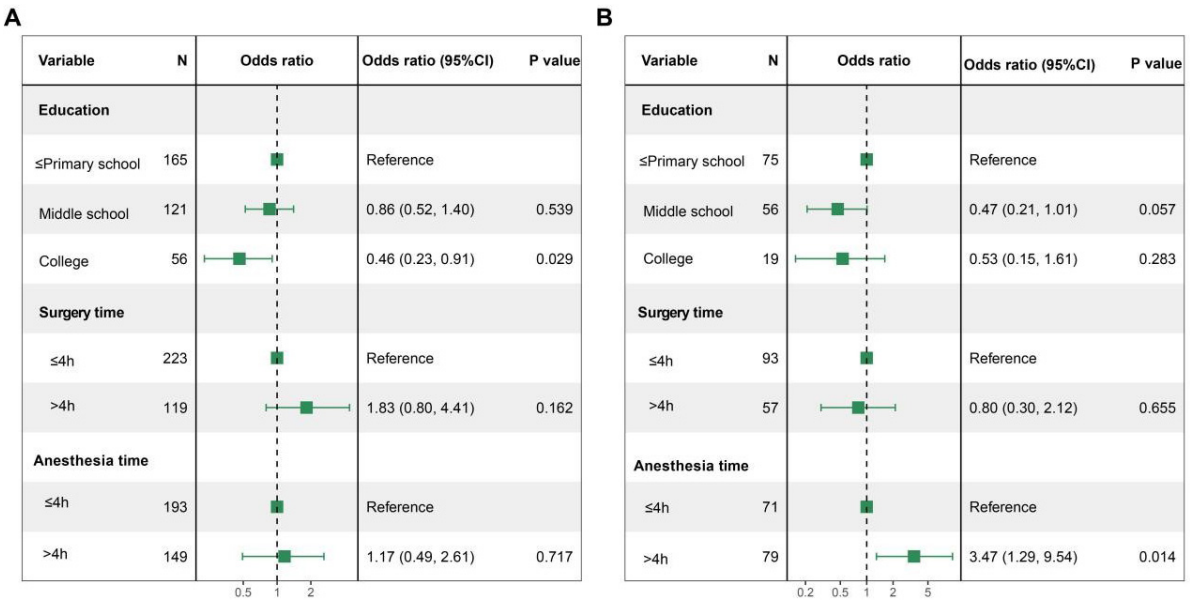

FIGURE 3
Forest plots for PACU POD in two cohorts. **(A)** Multivariate logistic regression analysis for PACU POD in the exploratory cohort; **(B)** multivariate logistic regression analysis for PACU POD in the validation cohort. PACU, post-anesthesia care unit; POD, postoperative delirium.

phase. This study employed a dual-assessment strategy for postoperative delirium detection, utilizing the non-verbal-adapted CAM-ICU (23) for immediate post-anesthesia evaluation in sedated or mechanically ventilated patients, followed by the verbal-based 3D-CAM (24) for subsequent assessments as cognitive function recovered, ensuring comprehensive delirium subtype identification throughout the perioperative recovery continuum. This phased research design not only enhances the reliability of the findings but also comprehensively covers the entire course of POD occurrence, providing more robust evidence for clinical prevention and management.

Lower educational attainment was found to be a significant predictor of POD in this study, likely attributable to the protective role of cognitive reserve, which tends to be more robust in those with advanced educational attainment. These individuals are likely better equipped to comprehend and adhere to preoperative and postoperative medical instructions, thereby potentially mitigating the risk of POD. This finding emphasizes

the need to integrate educational background into delirium risk assessment and management, enabling tailored patient education and support strategies to optimize outcomes (25). In addition, patients with higher education usually have a broader social support network and can obtain more emotional and practical support after surgery (26–28) so as to reduce the risk of postoperative delirium. Some previous studies on the risk factors of POD may have ignored the influence of education level. This omission may be due to the limitations of the study design, or the association between education level and POD has not been fully revealed. However, as a potential socio-economic factor, education level may play an important role in the mechanism of POD (10).

This study identified lower educational attainment as a significant risk factor for POD during the resuscitation phase in the exploratory cohort. Also, it showed a trend of increasing the risk of delirium during resuscitation in the confirmatory cohort. This phenomenon may be related to the cumulative damage of neurons, dendrites, receptors, and microglia in older patients, making them more prone to delirium under biological stress (29). The compensatory ability for neuroinflammation and blood-brain barrier dysfunction induced by surgery and anesthesia is weak. The release of proinflammatory cytokines and markers of nerve injury can damage large-scale neuronal networks, leading to acute cognitive dysfunction (30–32), eventually triggering the destruction of large-scale neuronal networks in the brain, which leads to acute cognitive dysfunction (33). Individuals with high cognitive reserve usually have more abundant neural pathways to cope with various cognitive challenges. According to the neural network theory, the neural network formed by synaptic connections between neurons is not static but has high plasticity, which can continuously develop and reorganize with the accumulation of individual learning and experience (11, 34). This neural plasticity is considered to be one of the important mechanisms for individuals with high cognitive reserve to show stronger adaptability in the face of neurodegenerative diseases or brain injury (35). However, the exact association between education level and POD risk and its potential mechanism still needs to be further verified and clarified through large-scale, multicenter, prospective studies in order to provide a more reliable evidence-based basis for clinical intervention.

This study also found that with the increase in age, the risk of POD increased significantly 3 days after the operation, a finding consistent with previous research (33). Previous studies have repeatedly established age as a significant independent predictor of adverse outcomes following various types of surgeries (1). This may be caused by brain tissue degeneration and changes in central neurotransmitters in older patients (36, 37). In addition, this study also found that the operation time and anesthesia time were related to POD. Prolonging anesthesia time meant that more fluid input, more complex surgery, more challenging intraoperative conditions, and the use of a variety of drugs were needed, which were related to the occurrence of POD (38).

This study still has some limitations. First, the sample sizes of the two independent cohorts in this study are relatively small, which may restrict the generalizability of the research findings. In the future, larger scale multi-center studies should be carried out to construct and verify POD models using the risk factors identified in this study, and to improve the external validity of the results. Furthermore, the single-center design of the current study may introduce potential selection bias. To address this limitation, future research should adopt a multicenter approach, which would significantly improve the external validity and broader applicability of the findings. Second, potential confounding factors, such as type of surgery; depth of anesthesia; socio-economic status and pre-existing cognitive impairment, are not fully adjusted, which may affect the observed association. Third, the level of education is widely classified, and more detailed stratification can provide a better understanding of the relationship between education and POD. Finally, the follow-up period was 3 days after surgery, and the post operative cognitive decline dysfunction for a longer time after surgery was not evaluated. Cases of delayed or persistent delirium may be ignored. Future studies should address these limitations to further clarify the risk factors of postoperative delirium.

In brief, a lower education level is a risk factor for POD 3 days after the operation, and operation or anesthesia time of more than 4 h also significantly increases the risk of POD. These findings emphasize the importance of education level in reducing the incidence of POD in preoperative assessment and postoperative care. It is necessary to conduct further research to explore the potential mechanism and formulate targeted intervention measures for high-risk cohorts. It is recommended to further investigate the role of education level as a significant risk factor for postoperative delirium (POD). Multicenter studies with larger sample sizes should be conducted to validate and expand upon these findings.

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 study was authorized by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (Approval No.: 2024-33). 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

MX: Writing – review and editing, Writing – original draft, Conceptualization. JL: Formal Analysis, Writing – original draft. JW: Data curation, Writing – original draft. FL: Data curation, Writing – original draft. TF: Data curation, Writing – original draft. JT: Project administration, Writing – review and editing.

Funding

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

Acknowledgments

We extend their gratitude to all participants and collaborators who contributed to this study. Special thanks are due to the research team for their dedication and efforts in data collection and 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.

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frontiers | Frontiers in Neurology

TYPE Review
PUBLISHED 26 August 2025
DOI 10.3389/fneur.2025.1526021

OPEN ACCESS

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RECEIVED 12 November 2024
ACCEPTED 21 April 2025
PUBLISHED 26 August 2025

CITATION
Ren X, Huiqiao L, Wu Y, Zhang T, Chen P, Li L, Zhao G and Wang F (2025) Perioperative neurocognitive disorders: a comprehensive review of terminology, clinical implications, and future research directions.
Front. Neurol. 16:1526021.
doi: 10.3389/fneur.2025.1526021

Perioperative neurocognitive disorders: a comprehensive review of terminology, clinical implications, and future research directions

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Perioperative neurocognitive disorders (PNDs) encompass a spectrum of cognitive impairments that may affect patients before, during, or after surgical procedures, with significant implications for patient outcomes, and healthcare expenditures. This comprehensive review examines the evolution of PND terminology, clinical manifestations, diagnostic criteria, incidence rates, risk factors, underlying mechanisms, preventive measures, management strategies, and future research directions. The authors emphasize the importance of early diagnosis and intervention to enhance postoperative recovery and underscore the necessity of a multidisciplinary approach to patient care.

KEYWORDS

perioperative neurocognitive disorders, postoperative cognitive dysfunction, neurocognitive recovery, perioperative risk factors, delirium diagnosis, surgical outcomes, cognitive rehabilitation

1 Introduction

Perioperative neurocognitive disorders (PNDs) encompass a spectrum of cognitive impairments that may affect patients before, during, or after the surgical procedure. The conceptualization and nomenclature of PNDs have undergone significant evolution, with an increasing emphasis on early diagnosis, prevention, and intervention, to improve patient outcomes. PNDs comprise a range of Cognitive impairment can manifest at various stages of the surgical process (1). These include pre-existing cognitive impairment, delirium occurring up to seven days post-surgery, delayed neurocognitive recovery (diagnosed up to 30 days post-surgery), and postoperative neurocognitive disorder diagnosed thereafter, until 12 months. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) provides the criteria for diagnosing these disorders (2).

PNDs can significantly impair the quality of life of patients and their ability to perform daily activities. Moreover, they may increase morbidity, mortality, and health care expenditures. Early identification of PNDs facilitates timely intervention, potentially mitigating cognitive decline and improved postoperative recovery (3). Strategies for prevention and treatment encompass avoiding potential contributors, implementing non-pharmacological and pharmacological interventions, and utilizing anesthetics with a reduced cognitive impact. The evolution of PNDs terminology and understanding has

resulted in a more comprehensive approach to diagnosing and managing these disorders, ultimately enhancing patient care quality.

2 Historical evolution of the PNDs terminology

Various factors have influenced the development of PNDs, including advancements in medical studies, enhanced understanding of cerebral anatomy and physiology, and the establishment of diagnostic criteria, and assessment tools.

We conducted a comprehensive literature review to identify studies on PNDs. The search methodology was meticulously crafted to reflect the historical progression, underlying mechanisms, and clinical ramifications described in this manuscript. The primary databases used were PubMed, Web of Science, and Google Scholar. The search terminology encompassed PND-related phrases such as "perioperative neurocognitive disorders," "postoperative cognitive dysfunction," "postoperative delirium," "delayed neurocognitive recovery," "anesthetic neurotoxicity," "cognitive impairment," "postoperative cognitive," as well as "POCD" and "POD." Only articles published in English were considered. Table 1 highlights the key studies on PNDs. Figure 1 shows the changes in the terminology of PNDs.

Early medical literature documented cognitive and mental disorders associated with surgical procedures, or anesthesia. In 1887, Dr. Savage, a British physician, recorded cases of severe psychosis following operations and hypothesized that anesthetic substances, particularly chloroform, and can potentially induce insanity (4).

Before the 1980s, cognitive changes following surgery were often attributed to normal aging processes or considered a side effect of anesthesia, without specific terminology. Confusion or delirium after surgery is prevalent; however, these conditions lack precise definitions (5). Systematic documentation of these conditions emerged in the late 19th and early 20th centuries, respectively. Researchers have identified a subset of patients, predominantly Older adults exhibit cognitive decline postoperatively. This observation has prompted increased attention and research on the enduring cognitive effects of surgical intervention. Terminology such as "anesthesia-induced delirium" or "postoperative confusion" was adopted to characterize the mental alterations associated with surgical procedures and anesthesia administration (6).

As cognitive impairments beyond those immediately following anesthesia have been recognized, and the terminology has evolved to encompass this broader spectrum. The mid-20th century saw the introduction of modern anesthesia, enabling surgeons to conduct more intricate operations, such as heart bypass surgeries. This advancement subsequently heightened recognition of Cognitive issues after surgery (7). The terms "postoperative cognitive dysfunction" (POCD) and "postoperative delirium" (POD) were coined to describe the decline in cognitive abilities of surgical patients. POCD was initially used to describe cognitive deterioration following surgery, particularly in elderly patients. Acute changes in attention and cognitive function characterize the development of postoperative delirium. These two terms are commonly employed in the scientific literature to refer to cognitive impairments that manifest after surgery and persist for different durations.

As the 20th century progressed, the field of postoperative cognitive change expanded in terms of its terminology. A new classification system, "postoperative neurocognitive disorders", was established, encompassing both delirium and cognitive dysfunction. This development introduced a more refined nomenclature to accurately describe the cognitive alterations observed in patients following surgical procedures (8). During this period, research has focused on identifying the risk factors, elucidating the underlying mechanisms, and developing preventive strategies.

In recent years, the definition of PNDs has been expanded to include a broader spectrum of cognitive deficits that may occur not only after surgery but also before or during the procedure (9). The evolution of terminology reflects an enhanced understanding of how cognitive alterations can manifest throughout the perioperative process. This updated nomenclature more accurately portrays the range of cognitive disorders and acknowledges that these changes may occur throughout the surgical trajectory, from preoperative evaluation to postoperative recuperation. The scope of this term has been expanded to include PNDs, encompassing cognitive changes that can manifest before, during, and after surgery, including delirium. PNDs now recognize delirium as a crucial element with potentially enduring implications.

Significant publications and classification systems, particularly the Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organization's International Classification of Diseases (ICD), have played crucial roles in shaping the terminology and comprehension of PNDs throughout history. These key resources have markedly influenced the development of these concepts over time (2).

The DSM has defined diagnostic criteria for neurocognitive disorders since 1952, with editions refining these classifications. Notably, the DSM-III introduced a standardized framework, and the DSM-5, released in 2013, has significantly influenced the understanding of PNDs. The DSM-5 categorizes these disorders into major and mild neurocognitive disorders and delirium, with specific criteria for each category. The DSM-5 classifies delirium according to its causes, aiding the identification of PNDs for targeted prevention and treatment (9).

In addition, the International Classification of Diseases (ICD) plays a crucial role in shaping the terminology and understanding of PNDs. For instance, ICD-10 contains categories for cognitive disorders relevant to PNDs, including dementia and memory disorders. The most recent version, the ICD-11, incorporates codes for cognitive disorders associated with surgical procedures, thereby improving the global classification and acknowledgment of these conditions (10). The ongoing development of ICD has influenced the international classification and acknowledgment of cognitive disorders related to surgical procedures.

The nomenclature for PNDs has progressed from early descriptive terms to a more comprehensive label, reflecting an expanded and sophisticated understanding of the various cognitive impairments linked to surgical procedures. This evolution in terminology has been influenced by advancements in medicine, modifications in diagnostic standards, and the growing recognition

TABLE 1 Summary of key studies related to PNDs.

References	Study	Methodology	Key findings	Contributions to the field
Savage (4)	Insanity Following the Use of Anæsthetics in Operations	Case reports documenting psychiatric symptoms following anesthesia.	Chloroform and other anesthetics may induce psychiatric complications post-surgery.	Early recognition of anesthesia-related cognitive and psychiatric disturbances
Turville and Dripps (71)	The anesthetic management of the aged	Observational study on anesthesia management in elderly patients.	Elderly patients are more susceptible to adverse effects of anesthesia, including cognitive decline.	Highlighted the need for tailored anesthesia management in older adults.
Bedford (5)	Adverse cerebral effects of anesthesia on old people	An observational study documenting cognitive and psychiatric complications in elderly patients after anesthesia.	Anesthesia, particularly in older adults, can lead to cognitive decline and psychiatric symptoms.	Highlight the potential cognitive risks of anesthesia in elderly patients, laying the groundwork for future research on POCD.
Papper (72)	Anesthesia in the aged	Review of anesthesia effects in elderly patients.	Elderly patients are more vulnerable to cognitive decline post-anesthesia due to reduced physiological reserve.	Emphasized the importance of considering age-related physiological changes in anesthesia management.
Simpson et al. (73)	The effects of anesthesia and elective surgery on old people	Observational study on cognitive outcomes in elderly patients after surgery.	Elderly patients experience significant cognitive decline after surgery, particularly with longer procedures.	Highlighted the long-term cognitive risks associated with surgery in older adults.
Kornfeld et al. (74)	Psychiatric complications of open-heart surgery	Observational study on psychiatric outcomes after cardiac surgery.	Open-heart surgery is associated with a high incidence of psychiatric complications, including delirium and cognitive decline.	First to link cardiac surgery with psychiatric and cognitive complications, influencing future research on POCD.
Shaw et al. (75)	Neurologic and neuropsychological morbidity following major surgery	Comparative study of cognitive outcomes after coronary artery bypass (CABG) and peripheral vascular surgery.	CABG is associated with higher rates of neurologic and neuropsychological morbidity compared to peripheral vascular surgery.	Highlighted the differential cognitive impact of surgical procedures, particularly cardiac surgery.
Murkin et al. (76)	Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery	Consensus statement on neurobehavioral outcomes after cardiac surgery.	Standardized assessment tools are needed to evaluate cognitive outcomes after cardiac surgery.	Provided a framework for standardized cognitive assessment in PND research.
Moller et al. (77)	Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study	Longitudinal study on long-term cognitive outcomes in elderly patients after surgery.	25.8% of elderly patients experienced long-term cognitive dysfunction after non-cardiac surgery.	Established the concept of long-term POCD and identified age as a significant risk factor.
Van Dijk et al. (78)	Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery	Randomized trial comparing cognitive outcomes after off-pump vs. on-pump CABG.	Off-pump CABG was associated with better short-term cognitive outcomes compared to on-pump CABG.	Highlighted the role of surgical technique in cognitive outcomes, influencing the adoption of off-pump techniques.
Selnes et al. (79)	Cognitive outcomes 3 years after coronary artery bypass surgery	Longitudinal study comparing cognitive outcomes after CABG vs. non-surgical controls.	CABG patients showed no significant difference in cognitive outcomes compared to non-surgical controls at 3 years.	Challenged the notion that CABG causes long-term cognitive decline, emphasizing the need for further research.
Monk et al. (80)	No improvement in neurocognitive outcomes after off-pump vs. on-pump coronary revascularisation	Meta-analysis comparing neurocognitive outcomes after off-pump vs. on-pump CABG.	No significant difference in neurocognitive outcomes between off-pump and on-pump CABG.	Suggested that surgical technique alone may not be the primary determinant of cognitive outcomes.
Monk et al. (81)	Predictors of cognitive dysfunction after major noncardiac surgery	A prospective study identifying predictors of cognitive dysfunction after non-cardiac surgery.	Age, education level, and pre-existing cognitive impairment are significant predictors of postoperative cognitive dysfunction.	Identified key risk factors for PNDs, informing preoperative risk assessment and intervention strategies.
Evered et al. (9)	Recommendations for the Nomenclature of Cognitive Change Associated with Anesthesia and Surgery	Review and consensus-based recommendations for standardizing PND terminology.	The proposed updated nomenclature includes preoperative NCD, postoperative delirium (POD), delayed neurocognitive recovery (DNR), and postoperative NCD.	Provided a standardized framework for diagnosing and classifying PNDs, facilitating better communication and research consistency.

(Continued)

TABLE 1 (Continued)

References	Study	Methodology	Key findings	Contributions to the field
Ren et al. (22)	Dysfunction of the Glymphatic System as a Potential Mechanism of Perioperative Neurocognitive Disorders	Review of the role of the glymphatic system in PNDs, focusing on waste clearance, neuroinflammation, and anesthesia effects.	Glymphatic dysfunction, caused by anesthesia, surgery, and sleep disturbances, contributes to PNDs by impairing waste clearance and promoting neuroinflammation.	Introduced the glymphatic system as a key mechanism in PNDs, emphasizing its role in waste clearance and neuroinflammation and suggesting potential therapeutic targets.
Feng et al. (28)	Association between cerebrovascular disease and perioperative neurocognitive disorders	A retrospective cohort study investigated the relationship between pre-existing cerebrovascular disease (CVD) and PNDs.	CVD was an independent risk factor for PNDs, with an odds ratio of 10.193.	Demonstrated a strong association between cerebrovascular disease and PNDs, emphasizing the importance of preoperative vascular health assessment.

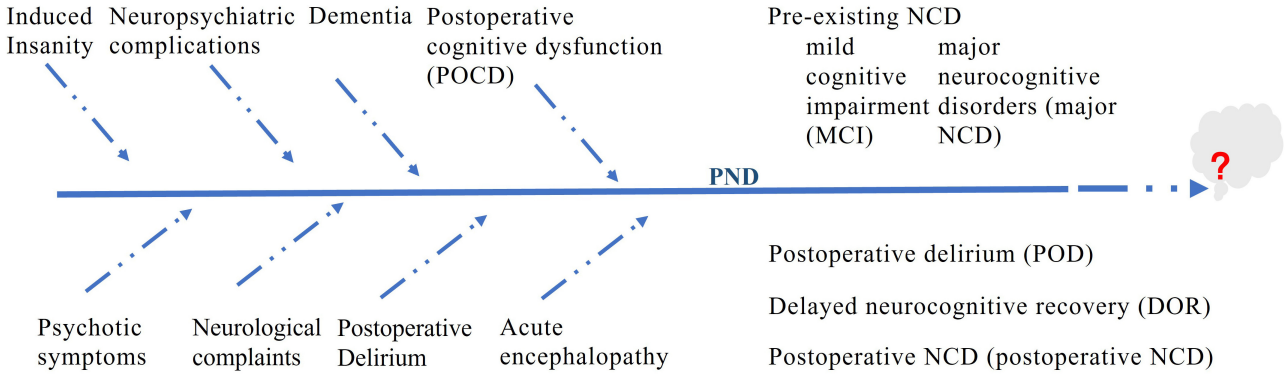

FIGURE 1
Evolution of terminology for perioperative neurocognitive disorders.

of the significance of cognitive functions in patient care. As research progresses, we anticipate that our understanding and terminology will continue to develop and capture the intricacies of these disorders more accurately in the future. Terminology will evolve as our knowledge deepens and new diagnostic tools and criteria emerge.

3 Clinical manifestations and diagnosis

PNDs exhibit diverse clinical features involving a wide array of cognitive, behavioral, and emotional alterations that can substantially affect a patient's recovery after surgery. The cognitive aspects of PNDs include impaired memory, confusion, reduced mental processing speed, and challenges in focusing and maintaining attentiveness. Behavioral symptoms may include restlessness, increased irritability, lack of interest, and hostility. Emotional manifestations can range from feelings of anxiety and depression to unpredictable mood changes and emotional instability. These symptoms can manifest immediately after surgery to several months post-surgery and may persist with varying intensity (11).

The detection of PNDs is complex and requires clinical evaluation, patient history, and cognitive assessments without a definitive standard. The DSM-5 defines PNDs as cognitive decline with significant functional impairments that cannot be explained by other disorders and occur post-surgery (9, 12). The following four categories of PNDs are defined according to the DSM-5 (Table 2):

TABLE 2 Key terminology and definitions related to PNDs.

Term	Definition
Perioperative neurocognitive disorders (PNDs)	Cognitive deficits occurring before, during, and after surgery, encompassing delirium and cognitive dysfunction.
Preoperative NCD	Cognitive impairment before surgery is classified as mild or major based on severity and affects daily activities.
Postoperative delirium (POD)	Acute, fluctuating attention, awareness, and cognition disturbances typically occur within 1 week post-surgery.
Delayed neurocognitive recovery (DNR)	This term denotes cognitive decline diagnosed within 30 days of surgery.
Postoperative NCD	Cognitive decline was identified between 30 days and 12 months post-surgery.

Preoperative NCD: Cognitive impairment before surgery. Based on their severity, these impairments can be further classified as mild or major, affecting the patient's capacity to perform activities of daily living.

Postoperative delirium (POD) is characterized by acute and fluctuating disturbances in attention, awareness, and cognition that manifest rapidly. It is typically identified within the first

week post-surgery and necessitates thorough evaluation to differentiate it from other cognitive alterations.

Delayed neurocognitive recovery (DNR): This term denotes cognitive decline diagnosed within 30 days of surgery. It supersedes the previous term, "early POCD", and acknowledges the potential for cognitive function recovery.

Postoperative NCD: Cognitive decline identified between 30 days and 12 months after surgery.

The "postoperative" qualifier is no longer applied beyond the 12-month unless the diagnosis is established within this timeframe.

The transition from POCD to PNDs aims to align perioperative cognitive impairment research with the clinical diagnostic criteria utilized in other medical fields, facilitating improved recognition and communication among experts across various disciplines. This updated nomenclature underscores the significance of a comprehensive assessment, including objective cognitive testing, evaluation of activities of daily living, and cognitive concerns reported by patients or informants.

In addition to the DSM-5 criteria, other neurocognitive assessment tools are used to evaluate the cognitive function of patients with PNDs. The Mini-Mental State Examination (MMSE) is a brief screening tool that assesses cognitive domains, such as memory, attention, language, and visuospatial skills. It is commonly used to detect cognitive impairment but may lack sensitivity for mild cognitive changes (13). The Montreal Cognitive Assessment (MoCA) is a more sensitive tool for detecting mild cognitive impairment. It assesses domains such as executive function, memory, and attention. It is particularly useful for identifying early cognitive decline in the surgical population (14). Trail Making Test (TMT) is a test that evaluates executive function, including cognitive flexibility and processing speed. It is often used to assess frontal lobe function (15). The Digit Span Test, part of the Wechsler Adult Intelligence Scale, assesses short-term memory and attention and can be used to diagnose PNDs (16). Furthermore, informant reports and functional assessments are crucial for diagnosing PNDs (17). Informant reports, such as those from family members or caregivers, provide valuable insights into patients' cognitive and behavioral changes. Functional assessments, such as the Activities of Daily Living (ADL) scale, evaluate a patient's ability to perform daily tasks and measure the impact of cognitive impairment on daily functioning (18).

The integration of these diagnostic tools and criteria allows for a more comprehensive evaluation of PNDs, facilitating early identification and intervention. Early diagnosis is critical for implementing targeted prevention and treatment strategies, improving postoperative outcomes, and enhancing patients' quality of life.

4 Risk factors and mechanisms

The reported frequency and occurrence of PNDs exhibit considerable variation, which is attributed to differences in the studied populations, surgical procedures, and diagnostic criteria used. Nevertheless, it is posited that a substantial proportion of patients, particularly older individuals, may experience some degree of cognitive deterioration following surgical interventions (19). A specific study found that cognitive impairment was observed in 53% of patients who underwent coronary artery bypass graft surgery, measured 5 years post-procedure. The study also noted that 36% of patients exhibited cognitive dysfunction at 6 weeks postoperatively, while 24% demonstrated impairment at 6-month mark (20).

TABLE 3 Key Risk Factor Related to PNDs.

Risk factor types	Risk factors	Description
Non-modifiable	Age	Older adults are at higher risk for cognitive decline post-surgery.
	Genetic factors	Specific gene variations may increase susceptibility to PNDs.
	Preexisting medical conditions	Conditions like cardiovascular disease, respiratory disease, and diabetes raise the risk.
	Existing cognitive deficits	Pre-existing conditions like dementia or mild cognitive impairment make PND outcomes worse.
Modifiable	Surgical procedure complexity	More complex surgeries lead to higher risks of PNDs.
	Anesthetic techniques	The type and method of anesthesia may influence cognitive outcomes.
	Perioperative care practices	Maintenance of normal body temperature, blood pressure, and pain control can affect PND risk.
	Sleep management	Addressing sleep disturbances post-surgery is crucial to reduce the risk of PNDs.
	Others	Anti-inflammatory and aerobic exercise help improve PNDs.

Several factors influence the development and prevalence of PNDs. These contributing elements can be categorized into modifiable and non-modifiable factors, with both types playing a role in the onset of these disorders (Table 3). Understanding these factors is crucial for developing preventive strategies and personalized treatment approaches for patients undergoing surgery.

4.1 Non-modifiable risk factors

Age is a crucial non-alterable risk factor for PNDs, with elderly individuals demonstrating heightened vulnerability to cognitive deterioration following surgical interventions (21). Aging can lead to a fragile brain, which can develop cerebrovascular lesions, altered cerebrospinal fluid flow, and waste accumulation (22), inducing neuroinflammation and causing altered cognitive function postoperatively (23).

Genetic predisposition may also affect the likelihood of experiencing PNDs. Studies have indicated that certain gene variants linked to inflammasome pathways are correlated with an elevated risk of developing inflammatory and neurodegenerative

disorders, potentially facilitating the emergence of PNDs (24). In addition to these biological mechanisms, other genetic predispositions, specifically the presence of the apolipoprotein (APOE) ε4 allele, can further modulate an individual's susceptibility to PNDs (25). Advances in genomic research may uncover distinct genetic markers or variations that increase the risk of PNDs, paving the way for customized preventive strategies and therapeutic interventions (24, 25).

Preexisting medical conditions, such as cardiovascular disease, respiratory disease, and diabetes, can increase the risk of PNDs due to physiological stress during the perioperative period (26). Magnetic resonance imaging (MRI) studies have linked decreased hippocampal volume to PNDs, indicating that cerebrovascular factors may play a role in their development (27). Cerebrovascular changes significantly affect the pathophysiology of PNDs and contribute to cognitive impairment. A large-scale retrospective cohort study of 13,899 surgical patients investigated the relationship between pre-existing cerebrovascular disease (CVD) and PNDs. The findings revealed that CVD is an independent risk factor for PNDs, suggesting a strong association (28).

Furthermore, existing preoperative cognitive deficits, such as dementia or mild or major cognitive impairment, can increase the likelihood of PNDs and adversely affect their outcomes. Research indicates that cognitive exercises performed before surgery may enhance cognitive function post-procedure, potentially reducing the incidence of PNDs (9).

4.2 Modifiable risk factors

PNDs are significantly influenced by the complexity and invasiveness of surgical interventions, with more intricate procedures generally associated with a higher likelihood of occurrence. Surgical operations can induce fluctuations in blood pressure and cerebral blood flow (CBF), potentially leading to ischemia-reperfusion injury and compromising the integrity of the blood-brain barrier (BBB) (29). Such physiological changes can result in neuronal damage, particularly in vulnerable regions, such as the hippocampus, which is crucial for memory function. The nature of the surgical procedure is also critical, as more invasive operations, especially those involving the heart or major abdominal areas, are often correlated with an increased risk of PNDs (30). Evidence suggests that surgical trauma in peripheral tissues can trigger an inflammatory response, releasing damage-associated molecular patterns (31) and inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These cytokines may compromise the BBB, allowing inflammatory mediators to infiltrate the central nervous system (CNS). This infiltration can initiate neuroinflammation, leading to neuronal dysfunction and subsequent cognitive decline (11). Most experts consider neuroinflammation to be a key factor in the pathomechanism of PND (32).

Perioperative care practices during surgical interventions, including anesthetic agent selection, anesthetic depth, normothermia maintenance, and blood pressure monitoring, can significantly impact the incidence of PNDs (33). The choice of anesthetic agent influences postoperative cognitive outcomes. Inhaled anesthetics, such as isoflurane and sevoflurane, have been linked to an increased risk of postoperative cognitive dysfunction (POCD) in elderly populations (34). These agents may induce neuroinflammation and compromise BBB integrity, leading to cognitive decline in older adults. Conversely, intravenous anesthetics such as propofol and dexmedetomidine have potential neuroprotective effects. Propofol can reduce neuroinflammation and oxidative stress, potentially mitigating cognitive deterioration (35). Dexmedetomidine, an α2-adrenergic agonist, has been found to enhance glymphatic function and decrease the incidence of delirium and cognitive impairment in older patients (22, 36). While anesthetic neurotoxicity remains debated, some studies suggest that these substances may directly affect neuronal function and survival (37). Additionally, anesthetics can interact with neurotransmitter systems, particularly the cholinergic system, which is crucial for cognitive functions such as memory and attention (38). Anesthesia-induced disruptions in neurotransmitter systems may contribute to post-surgery cognitive deficits (39).

Depth of anesthesia is another critical factor influencing cognitive outcomes. Studies have demonstrated that excessively deep anesthesia, as measured by the Bispectral Index (BIS), is associated with an increased risk of PNDs. Maintaining an appropriate depth of anesthesia, guided by BIS monitoring, can help reduce the risk of cognitive decline during surgery. Additionally, multimodal anesthesia, which combines different anesthetic agents and techniques, has improved cognitive outcomes by minimizing the dose of individual agents and reducing their adverse effects (33).

Perioperative hemodynamic management is crucial for reducing the risk of PNDs. Hypotension and blood pressure fluctuations during surgery can lead to cerebral hypoperfusion, increasing the risk of cognitive decline. Maintaining stable hemodynamics through careful monitoring and the use of vasoactive agents, such as norepinephrine and phenylephrine, can help preserve CBF and reduce the risk of PNDs (29).

Postoperative pain management is a modifiable risk factor. Poor pain control can cause sleep disturbances, stress, and neuroinflammation, all of which contribute to the cognitive decline. Effective pain management using opioids and non-opioid analgesics can reduce the risk of PND (40). Post-surgery sleep disruptions increase neuronal activity and produce waste products, such as lactate, which are cleared through glymphatic fluid transport (41, 42). These disturbances can impair the waste-clearing efficiency of the glymphatic system, leading to amyloid-beta (Aβ) accumulation in critical brain regions, including the thalamus and medial temporal areas (22, 42). Sleep meliorating through pharmacological and non-pharmacological interventions, such as melatonin or cognitive-behavioral therapy, can improve sleep quality and lower the risk of cognitive decline (40).

PNDs arise from multiple factors, including neuroinflammation, cerebrovascular changes, and anesthetic effects, which are not yet fully understood. Ongoing research is vital for developing strategies to reduce the occurrence and severity of PND in surgical patients, as it is influenced by patient and surgical factors. Understanding these interactions is key to improving patient care and outcomes in the perioperative phase.

5 Prevention and management strategies

Preventing and managing PNDs is essential for minimizing surgical risks, especially in older patients. Both drug- and non-drug-based approaches have been investigated to address postsurgical cognitive decline. Non-pharmacological methods have gained attention because of their potential to enhance cognitive function and overall wellbeing without the side effects associated with medication.

Physical activity has emerged as a key non-drug strategy for reducing the occurrence and intensity of PNDs (43). A recent literature review emphasized that exercise may improve cognitive dysfunction-related conditions, including PNDs, through various mechanisms, such as reducing neuroinflammation, influencing gut bacteria, preserving muscle mass, improving mitochondrial function, and affecting synaptic plasticity (44, 45). Animal studies on swimming and running have demonstrated a reduction in inflammatory proteins and changes in the gut microbiota, leading to improved cognitive function after surgery (44).

Preventive strategies include cognitive training, optimized anesthesia, and cognitive rehabilitation. Effectiveness is evaluated through RCTs, longitudinal studies, and meta-analyses, showing that cognitive training improves postoperative function in elderly patients (20, 46, 47). However, variability in study designs and outcomes presents challenges, underscoring the need for standardized protocols to facilitate comparisons.

Pharmacological approaches aim to target the specific biological mechanisms involved in PNDs. However, it is worth noting that drug-based management of PNDs is complex because of the diverse nature of these disorders. The medications studied include those targeting inflammation (36–38), dexmedetomidine (36), neurotransmitter activity (48), and neuroprotection (49). For instance, drugs that inhibit acetylcholinesterase and block NMDA receptors have been explored for PNDs, although evidence remains limited, and treatment efficacy has not been consistently demonstrated (50).

Owing to the diverse nature of PNDs, personalized treatment strategies are essential. These strategies should consider the patient's pre-surgery cognitive condition, health issues, surgical procedure, anesthesia management, and individual preferences (51). Ongoing cognitive evaluations can assist in tracking improvements and modifying the treatment approach as required. A comprehensive rehabilitation plan incorporating physical, occupational, and cognitive-behavioral therapies may be advantageous in addressing PNDs (52). This holistic approach can target various aspects of recovery, ranging from physical capabilities and movement to mental and emotional health. Addressing PNDs effectively requires a multi-pronged strategy encompassing non-drug interventions, such as physical activity, medications targeting the underlying mechanisms, and tailored care plans that adapt to the patient's evolving needs and progress. Additional studies are required to determine the most successful approach to enhance patient outcomes.

6 Future research directions

PNDs present a complex challenge with notable knowledge gaps in neurology, anesthesiology, geriatrics, and psychiatry. Although researchers have explored aspects such as neuroinflammation and the effects of anesthetics, the underlying processes remain poorly understood. Interdisciplinary collaboration has the potential to advance diagnostic and preventive treatment strategies.

Advanced noninvasive brain imaging techniques have emerged as powerful tools for understanding the structural and functional changes associated with PNDs. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) provide insights into brain alterations linked to PNDs (53, 54). fMRI evaluates cerebral activity by monitoring blood oxygenation and the perivascular space, highlighting the surgical and anesthetic effects on neural circuits (55). It reveals functional brain changes, especially in hippocampal and prefrontal cortex connectivity. Fislage et al. also showed disrupted connectivity in patients with postoperative delirium (56). Diffusion tensor imaging (DTI) assesses white matter integrity, aiding in the detection of connectivity disruptions that lead to cognitive decline (57). PET reveals metabolic changes in regions associated with memory and cognition, such as the hippocampus and prefrontal cortex, while amyloid accumulation detected by PET is linked to the intensity of perioperative delirium (58). Other noninvasive brain stimulation methods, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), show promise for PNDs treatment. TMS uses magnetic fields to activate brain regions, potentially enhancing cognition (59), while tDCS applies a low electrical current to stimulate areas, possibly improving cognitive performance and alleviating PND symptoms (60). These approaches offer potential diagnostic and preventive treatment strategies.

The integration of machine learning and artificial intelligence (AI) in neuroimaging data analysis is an exciting area of research. Machine learning algorithms analyze complex fMRI, PET, and DTI datasets to identify patterns and biomarkers associated with PNDs (61). Predicting postoperative delirium by analyzing preoperative risk factors and intraoperative information highlights the potential of machine learning for tailored risk evaluations and targeted interventions. AI-driven models can predict cognitive outcomes based on preoperative and postoperative imaging data, enabling the early identification of at-risk patients and personalized interventions (62). The application of machine learning and AI to complex datasets from neuroimaging, genetic research, and electronic health records may uncover new patterns and predictors of PNDs and personalized treatment responses. These technologies could revolutionize PND diagnosis and management by providing more accurate and timely assessments of cognitive function.

Future studies should explore the intricate molecular and cellular mechanisms underlying PNDs.

The discovery of biological indicators in the blood or cerebrospinal fluid that indicate the presence or likelihood of PNDs could facilitate early detection and treatment monitoring.

These indicators may include proteins and other biochemical markers associated with neuroinflammation and neuronal injury (63). Advanced techniques may facilitate the identification of biological markers for the early detection and monitoring of cognitive decline, particularly in patients with MCI who are often overlooked.

The development of advanced cognitive assessment tools, including virtual reality and mobile applications, may provide more sensitive measures of cognitive function, allowing for better monitoring of PNDs and intervention effects (64). Investigating the impact of lifestyle elements, such as nutrition, rest, and physical activity, on PNDs risk could provide recommendations for preoperative preparation to reduce cognitive decline (65). As our knowledge deepens, innovative technologies and methodologies are expected to emerge, fostering optimism about improved patient outcomes.

7 Clinical implications

PNDs pose significant challenges in clinical practice, impacting patient recovery with extended hospital stays, increased health care costs, and reduced quality of life. Clinical manifestations include cognitive, behavioral, and emotional changes, such as memory impairment, disorientation, slowed thinking, attention deficits, agitation, irritability, and mood swings.

Diagnosing PNDs requires a multifaceted approach involving clinical assessment, cognitive testing, and exclusion of other potential causes of cognitive impairment. The DSM-5 provides a framework for diagnosing neurocognitive disorders; however, its criteria may not fully capture perioperative cognitive changes.

Enhanced perioperative and postoperative care is crucial for mitigating the incidence of PNDs. Preoperatively, cognitive assessment tools such as the MMSE and MoCA should be used to identify at-risk patients. Optimizing comorbid conditions, such as hypertension and diabetes, is vital for reducing cognitive risks.

In the postoperative phase, care should prioritize early identification and intervention. Regular cognitive assessments are recommended using tools such as the Confusion Assessment Method for delirium and MoCA for cognitive dysfunction. The implementation of cognitive rehabilitation programs, including memory training and attention exercises, can enhance cognitive function (66). In selected cases, pharmacological interventions such as cholinesterase inhibitors, NMDA receptor antagonists, and dexmedetomidine may be considered, although evidence supporting these treatments is limited. The integration of these approaches can improve patient outcomes and reduce the incidence of PND (50).

A multidisciplinary strategy is crucial for managing PNDs and requires expert collaboration to develop personalized care plans. Educating patients about PND risks and cognitive health strategies is essential for proactive care and improving patient outcomes. A lower socioeconomic status limits healthcare access, worsens comorbidities, and deteriorates postoperative cognitive outcomes (67). Cultural factors influence care-seeking behaviors, treatment adherence, and symptom reporting (68). Understanding perioperative cognitive changes while committing to education, collaboration, and research, improves patient care.

8 Controversy over the term of PNDs

The concept of "PNDs" encompasses various cognitive issues and has sparked significant debate and disagreement within the medical field, largely due to the intricacies involved in characterizing, identifying, and comprehending the underlying processes of these cognitive alterations experienced by surgical patients (69). Skeptics contend that this broad classification may result in ambiguity and potentially obscure the fundamental mechanisms and distinct clinical manifestations of these conditions. A unified diagnostic approach is essential for enhancing the credibility of research outcomes and clinical methodologies (1). There is a demand for more precise differentiation between various cognitive impairments and their specific attributes. Some individuals may not display indications of cognitive dysfunction until after their surgical procedure, making it challenging to detect and address these issues. The diversity of research methodologies, subject demographics, and outcome assessments complicates the integration of findings and restricts the ability to draw robust conclusions that could influence medical practice. Although factors such as inflammation, anesthetic-induced neurotoxicity, and vascular changes have been suggested, the exact mechanisms remain unknown.

Assigning PNDs diagnoses to patients can result in stigma toward both patients and their families. The fear of being categorized as having cognitive impairment post-surgery may prevent individuals from seeking the necessary assistance or support, potentially impacting their recovery and overall wellbeing (70). The term "PNDs" might confuse patients and the public, potentially causing anxiety about surgery-related cognitive decline. To address fears and misunderstandings, improving communication and education about PNDs, their associated risks, and the nature of post-surgical cognitive changes is essential. The debates surrounding "PNDs" underscore the need for continued research, better communication, and cooperation among medical professionals to address the intricacies of postsurgical cognitive alterations. As this field progresses, more precise terminology and diagnostic standards may be developed, which will help inform medical practice and patient care.

9 Conclusion

This review describes the changing nomenclature and multiple risk factors for PNDs and considers variables such as patient age, type of surgery, pre-existing medical conditions, and perioperative nursing practices. This emphasizes the need for comprehensive strategies to manage PNDs, including enhanced perioperative protocols, patient awareness initiatives, and shared decision-making, to reduce the risk and promote recovery. Effectively addressing PNDs in clinical settings requires

a preemptive stance on prevention and treatment by medical professionals who implement research-supported strategies. This encompasses thorough preoperative evaluations, appropriate anesthetic technique selection, and the adoption of postoperative care guidelines prioritizing cognitive wellbeing. Furthermore, this study advocates for ongoing scientific exploration and advancement to uncover efficacious interventions and enhance our understanding of PNDs. By broadening our knowledge base and refining clinical practices, the healthcare community can effectively tackle the challenges associated with PNDs and enhance perioperative outcomes. Collaborative efforts among healthcare providers, researchers, and patients are crucial for fostering a clinical environment that reduces the occurrence and impact of PNDs.

Author contributions

XR: Conceptualization, Writing – original draft, Writing – review & editing. LH: Writing – original draft, Conceptualization, Investigation. YW: Writing – review & editing, Conceptualization, Resources. TZ: Conceptualization, Writing – original draft, Writing – review & editing. PC: Conceptualization, Writing – review & editing. LL: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. GZ: Investigation, Writing – review & editing. FW: Supervision, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research 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.

Generative AI statement

The author(s) declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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frontiers | Frontiers in Neurology

TYPE Clinical Trial
PUBLISHED 20 November 2025
DOI 10.3389/fneur.2025.1580759

OPEN ACCESS

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RECEIVED 21 February 2025
ACCEPTED 11 July 2025
PUBLISHED 20 November 2025

CITATION
Liu J, Ding L, Ma W, Wang J, Song X, Cao Y and Wu C (2025) Effects of electroacupuncture on the incidence of postoperative supraventricular arrhythmia and sleep quality in patients undergoing thoracoscopic surgery: a randomized controlled trial.
Front. Neurol. 16:1580759.
doi: 10.3389/fneur.2025.1580759

Effects of electroacupuncture on the incidence of postoperative supraventricular arrhythmia and sleep quality in patients undergoing thoracoscopic surgery: a randomized controlled trial

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Background: Supraventricular arrhythmia and sleep disturbance frequently occur after thoracoscopic surgery for lung cancer. The present study is designed to evaluate the hypothesis that electroacupuncture is an effective treatment of supraventricular arrhythmia and sleep disorders following thoracoscopic lung cancer surgery.

Methods: Adult patients scheduled for single-port thoracoscopic lung cancer surgery were randomly assigned to the Electroacupuncture (EA) and control groups. The primary outcome of this trial was the incidence of new-onset supraventricular tachycardia (SVT) including atrial flutter, atrial fibrillation, atrial tachycardia and atrioventricular junctional tachycardia during the first 24 h after surgery.

Results: The authors analyzed 77 patients (EA, 38; control, 39). The incidence of new-onset SVT was significantly lower in the EA group compared with the control group during the first 24 postoperative hours; 4 (10.5%) vs. 13 (33.3%), respectively, $p = 0.02$. Patients in the EA group had longer total sleep time (119.0 vs. 209.5, $p = 0.02$), longer duration of nonrapid eye movement sleep on the first postoperative night ($p < 0.05$). The awake time was significantly shorter compared with the control group (134.5.0 vs. 225.0, $p = 0.01$). Dosage of remifentanil and incidence of intraoperative hypotension were significantly reduced in the EA group (911.1 vs. 1095.9, $p = 0.01$). However, VAS scores after surgery did not differ between groups. In all the patients recruited, adverse effects such as redness, swelling and inflammatory reactions were not observed at the acupuncture site.

Conclusion: The results of this study suggest that perioperative electroacupuncture treatment could be a promising strategy to reduce the incidence of new-onset SVT and improve sleep disturbance in patients undergoing thoracoscopic surgery for lung cancer. This potential impact on future treatments should inspire hope and optimism in the medical community.

Clinical trial registration: https://www.chictr.org.cn/indexEN.html, identifier ChiCTR2300077984.

KEYWORDS

electroacupuncture, thoracoscopic surgery, supraventricular tachycardia, sleep disturbance, lung cancer

1 Introduction

As a malignant tumor, lung cancer has a high incidence and fast growth rate not only in China but also all over the world. Thoracoscopic surgery has been widely adopted for lung cancer. Despite its small incision and minimal tissue trauma, the incidence of postoperative arrhythmias and sleep disturbances remains high (1, 2). Our previous study showed that new-onset arrhythmia was observed in about 40% of the patients undergoing thoracoscopic surgery, the most common of which was postoperative supraventricular tachycardia (POSVT) (31.8%) (3). This may increase the risk of hemodynamic instability and endanger the postoperative safety of lung cancer patients (4). Sleep disturbance is also a common symptom in patients with lung cancer, which may contribute to a decelerated postoperative recovery (5).

Electroacupuncture (EA), a nonpharmacological adjunctive intervention, has been employed in clinical practice and has proved to be an effective treatment for patients with atrial fibrillation (6–8). Moreover, although some studies have reported that the application of EA is effective in improving sleep quality and regulating circadian sleep rhythms (9), whether the use of EA is associated with a lower incidence of postoperative arrhythmias and better sleep quality in patients after thoracic surgery has not yet been confirmed. To verify, we performed this randomized clinical trial to explore the efficacy of EA in preventing supraventricular arrhythmia and sleep disorders undergoing thoracic surgery.

2 Methods

2.1 Ethics approval and informed consent

The present study was approved by the Ethics Committee of First Affiliated Hospital of Guangzhou University of Chinese Medicine (Approval No. K-2023-128) in November 2023. It was registered at the Chinese Clinical Trial Registry (Registration No. ChiCTR2300077984). Written informed consent was obtained from each patient enrolled. The work has been reported per the CONSORT criteria.

2.2 Participants

Inclusion criteria were: ASA (American Society of Anesthesiologists) physical status 1 to 3, single-port thoracoscopic lung cancer surgery; age between 20 and 80 years old; volunteered to participate in this trial. Exclusion criteria included any cardiac, pulmonary, hepatic or renal dysfunction; pre-existed cardiac arrhythmia; history of thoracic surgery or sleep disturbances (subjective sleep quality in the participant's daily life was assessed according to the preoperative Sleep Quality Numerical Rating Scale, which is a numerical scale from 0 to 10, with 0 indicating excellent sleep quality and 10 indicating complete sleep deprivation throughout the night. A score of 6 or higher on the Sleep Quality Numerical Rating Scale indicates a sleep disorder, while a score of less than 6 indicates a non-sleep disorder. Sleep disorder was excluded based on this criterion) (10), perioperative electrolyte disturbances; abnormal thyroid function or mental impairment; usage of antiarrhythmic drugs in 3 days before the surgery; skin infection or nerve damage at the selected acupuncture points; patients already enrolled in other clinical trials.

2.3 Randomization and blinding

A statistical researcher generated Randomization sequences using SPSS in a 1:1 ratio. According to the randomization sequence, eligible patients were randomly divided into one of the two groups (the EA or the control group). Group allocation was concealed in serially numbered, sealed opaque envelopes by a researcher blind to the groups. On the operation day, the EA provider opened the envelope and documented the predetermined group allocation of each patient in a secluded place and a consistent tone. The surgeons, anesthesiologists, patients, data collectors and statisticians were unaware of the groups throughout the study.

2.4 Interventions

The selection of EA acupoints is determined in consultation with an acupuncturist expert. The location of Neiguan (PC6) and Gongsun (SP4) are described in The National Standards for Acupoint Location (11). In the EA group, patients initially received EA treatment 30 min before anesthetic induction at Neiguan (PC6) and Gongsun (SP4) acupoints on the surgical side of the patient. This treatment lasted until the end of the surgery and was repeated for 30 min at the 24th hour after the surgery. Sterilized and disposable needles (size 0.25 × 25 mm, Suzhou Medical Supplies Factory Co., Ltd., China) were inserted to a depth of 3–5 mm at Neiguan (PC6) and Gongsun (SP4) acupoints on the surgical side of the patient. The needles were carefully manipulated until a de qi sensation (most commonly fullness, numbness, and soreness) was experienced by the patient. Then, the needles were connected to an EA stimulator (SDZ-II, Suzhou Medical Supplies Factory Co., Ltd., China). The stimulation was performed with a frequency of 2/100 Hz and at the maximum current the patient can tolerate, usually between 8 and 12 mA. In the control group, needles were inserted to the same depth at non-specific acupoints near PC6 and SP4. The acupuncturist then used the same operation as PC6 and SP4 in the EA group.

After sterilizing the skin in the surgical area, the areas were covered with sterile sheets to ensure blinding of the study. All the EA

Abbreviations: SVT, Supraventricular tachycardia; EA, Electroacupuncture; ASA, American Society of Anesthesiologists; REM, Rapid eye movement; NREM, Non-REM sleep; TST, Total sleep time; VAS, Visual analog scores; OLV, One lung ventilation.

treatment and anesthesia induction in both groups were performed by the same qualified anesthesiologist with the patients placed in a supine position. The anesthesiologist was specially trained in acupuncture and had more than 5 years of experience in acupuncture. Another anesthesiologist blind to the grouping was responsible for the subsequent anesthesia management. All the surgeries were performed by the same surgical team. The surgeons, anesthesiologist, patients, data collectors, ECG physicians, sleep physicians and statisticians were unaware of the groups throughout the study. Group assignments were not revealed to outcome assessors, and they did not participate in the EA treatment.

2.5 Anesthetic technique

On the day of the surgery, noninvasive blood pressure, electrocardiography and pulse oximetry were routinely monitored after patient admission to the operating room. After preoxygenation for 5 min, intravenous induction was started with 0.3 μg kg^{-1} sufentanil, 1 to 2.5 mg kg^{-1} propofol and 0.1 mg kg^{-1} vecuronium bromide. Patients were then intubated with a double-lumen tube of appropriate size for one-lung ventilation. Auscultation and fiberoptic bronchoscopy were performed to confirm the correct placement of the tube. The ventilator parameters were: oxygen flow rate 2 L min^{-1}, FiO2 60%, VT 6 to 8 mL kg^{-1}, RR 12 times min^{-1}, to maintain a normal end-tidal carbon dioxide pressure. Remifentanil 0.1–0.2 μg kg^{-1} $min^{-1}$and sevoflurane 1–3% were used in combination for anesthesia maintenance. The infusion rate of remifentanil and sevoflurane was adjusted to keep bispectral index values between 40 and 60. The neuromuscular blockade was maintained by the addition of vecuronium intermittently. Before surgical skin incision, parecoxib sodium 50 mg was injected intravenously. At 5 min before the end of the surgery, 0.1 μg kg^{-1} sufentanil was administered for analgesia transition and 0.5% (0.2 mL kg^{-1}) ropivacaine was infiltrated into the surgical wound. A patient-controlled intravenous analgesia (PCIA) pump was connected for postoperative analgesia (sufentanil 1.5 μg/mL, PCIA dose: 3 mL, background dose: 2 mL/h, interval: 20 min, and duration: 2 days).

Intraoperative hypotension, defined as more than 20% reduction in systolic blood pressure from the baseline (measured before anesthesia induction) was treated by adequate infusion and intravenous ephedrine or noradrenaline. Bradycardia (heart rate less than 45 bpm), was treated with 0.5 mg atropine intravenously during the procedure. In addition, hypertension or tachycardia (more than 20% increase from baseline) was managed by increasing the concentration of sevoflurane or the rate of remifentanil infusion and intravenous injection of urapidil.

2.6 Postoperative period

Patients were closely monitored in the thoracic surgery ward after surgery. The ECG with a multichannel 24-h Holter ECG was continuously monitored during the first 24 h postoperatively. An experienced physician, who was unaware of the group allocation, was responsible for analyzing the 24-h Holter results with a DMS ECG Holter System (DM Systems Co, Ltd., Beijing, China). SVT including atrial flutter, atrial fibrillation and other SVT was documented. β-receptor blockers were used to terminate serious SVT by a thoracic physician blind to the grouping.

During the first postoperative night, sleep status was monitored using Lifelines Trakit TM Sleep (an ambulatory sleep recorder, 7 Clarendon Court, Over Wallop, Nr. Stockbridge, Hants, UK). An experienced physician who was unaware of the grouping analyzed the sleep condition. Sleep pattern was divided into rapid eye movement (REM) sleep and non-REM sleep (NREM). NREM sleep was further divided into stage N1, stage N2 and stage N3 sleep.

2.7 Study outcomes

The primary outcome of this trial was the incidence of SVT including atrial flutter, atrial fibrillation, atrial tachycardia and atrioventricular junctional tachycardia during the first 24 h after surgery. Supraventricular ectopic beat and ventricular premature beat were also documented. Total sleep time (TST), defined as the sum of time spent in sleep during the first postoperative night (from 18:00 to 08:00), time of REM sleep and time of non-REM sleep were recorded as the secondary outcomes. Awake time was the total time spent awake between the initial sleep onset and the last sleep end during the first postoperative night. By dividing TST by the sum of TST and awake time sleep efficiency was calculated. Meanwhile, usage of β-receptor blockers and postoperative pain score were recorded. Postoperative pain scores were expressed by visual analog scores (VAS).

2.8 Sample size

The primary outcome of this study was the incidence of POSVT during the first 24 h after thoracoscopic surgery. Our previous study had shown that the incidence of POSVT was 40% in patients undergoing non-cardiac thoracic surgery (1). Due to scarce similar studies, we carried out a pilot study before the start of this trial. We found that the incidence of POSVT after thoracoscopic surgery was reduced to about 11% with EA treatment. Therefore, it was supposed that POSVT would occur in 40% of the control group and 11% of the EA group. With a two-sided significance level of 5%, power of 80% and drop-out rate of 10%, the minimum number of patients required to detect a significant difference between the two groups was set at 80 (40 patients in each group).

2.9 Statistical methods

Continuous variables were presented as mean (SD) for normal distribution or median (IQR (interquartile range) [range]) for skewed distributions. The normality of data was previously tested with Shapiro–Wilk test. Categorical variables were reported as counts (percentage). Continuously normally distributed data were compared using independent samples *t*-test and continuously nonnormally distributed data using Mann–Whitney *U*-test. Categorical variables were analyzed using χ^2 test or Fisher's exact test. Analyses were performed using SPSS (IBM SPSS Statistics Version 22; SPSS Inc., Chicago, IL, United States). Results were considered statistically significant with p values less than 0.05.

3 Results

Between December 2023 and July 2024, 132 patients were screened for eligibility. 52 (39%) were excluded according to the exclusion criteria, and 80 patients were enrolled in this study. In the EA group, one patient had an additional incision during thoracoscopic procedure, and another patient had the ECG leads detached during ECG monitoring. Therefore, these two patients were withdrawn from the study. In the control group, there was also a patient who dropped out of the study due to massive intraoperative bleeding and the requirement for ICU delivery postoperatively (Figure 1). Finally, 77 patients finished the study and were included in the analysis. In all the patients recruited, adverse effects such as redness, swelling and inflammatory reactions were not observed at the acupuncture site.

There were no significant differences between groups in baseline demographics and patient characteristics (Table 1). The dose of remifentanil was significantly reduced in the EA group; 1095.9 (362.2) vs. 911.1 (233.8) μg, $p = 0.01$. The incidence of intraoperative hypotension in the EA group was significantly lower than in the control group; 15 (38.5%) vs. 6 (15.8%), $p = 0.05$. No other significant differences were observed between the groups during anesthesia (Table 2).

Postoperative arrhythmia was commonly observed in patients after thoracoscopic surgery for lung cancer. Compared with the EA group, the incidence of new-onset SVT was significantly higher in the control group during the first 24 h; 13 (33.3%) vs. 4 (10.5%), $p = 0.02$ (Table 3). There were no significant differences in the incidence of supraventricular ectopic beat and ventricular premature beat between groups (Table 3). A significantly more frequent use of β-blockers during the first 24 postoperative hours was observed in the control group; 11 (28.2%) vs. 3 (7.9%), $p = 0.04$ (Table 3).

There were significant differences in the TST and sleep efficiency during the first postoperative night between the two groups; 119

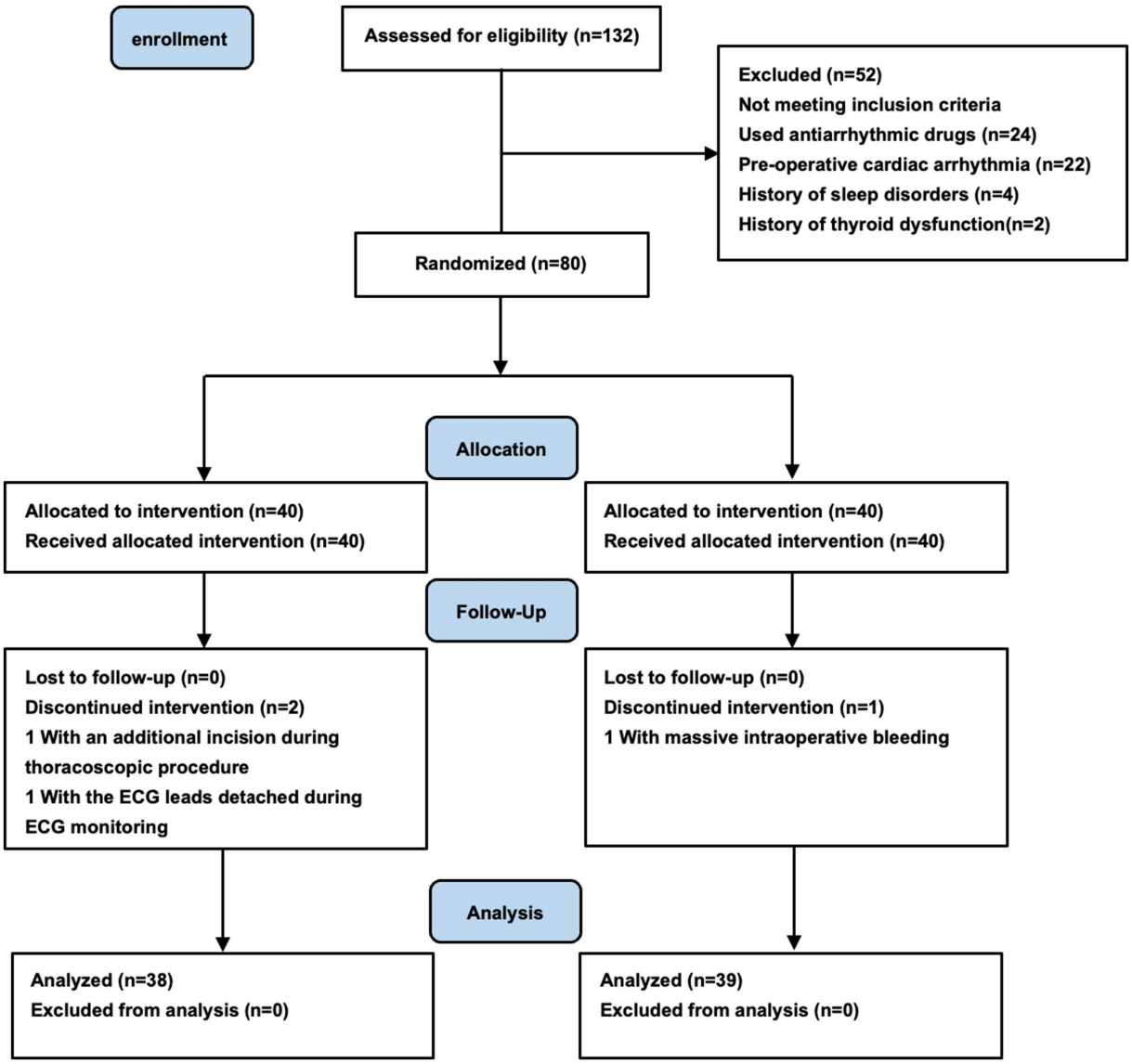

FIGURE 1
Study flow diagram.

TABLE 1 Baseline demographics and characteristics.

Characteristic	Control group, *n* = 39	EA group, *n* = 38	Difference in mean, medians or proportions (95%CI)	*P* value
Age (year)	61.3 ± 10.5	60.3 ± 11.9	1.02 (−4.06 to 6.01)	0.69
Sex (M/F)	20/19	15/23	0.12 (−0.10 to 0.34)	0.41
Weight (kg)	60.2 ± 10.0	60.4 ± 6.0	−0.16 (−3.91 to 3.58)	0.93
Height(cm)	161.4 ± 7.3	161.7 ± 7.7	−0.22(−3.64 to 3.19)	0.90
ASA, *n*				
I	13 (33.3%)	8 (21.1%)	0.12 (−0.07 to 0.32)	0.23
II	22 (56.4%)	29 (76.3%)	−0.20 (−0.41 to 0.01)	0.07
III	4 (10.3%)	1 (2.6)	0.08 (−0.03 to 0.18)	0.18
History of smoking, *n*	14 (35.9%)	11 (28.9%)	0.07 (−0.14 to 0.28)	0.52
Type of surgery, *n*				
Segmentectomy	25 (64.1%)	22 (57.9%)	0.06 (−0.16 to 0.28)	0.58
Lobectomy	14 (35.9%)	16 (42.1%)	−0.06 (−0.28 to 0.16)	0.58
SQ-NRS	2 [1 to 3]	2 [1 to 3]	0 (0 to 0)	0.74

Values are mean ± SD or number (proportion) or median [IQR]. EA, electroacupuncture; M/F, Male/Female; SQ-NRS, Sleep Quality Numerical Rating Scale; ASA, American Society of Anaesthesiologists; IQR, interquartile range; CI, Confidence Interval.

TABLE 2 Intraoperative data.

Intraoperative data	Control group (*n* = 39)	EA group (*n* = 38)	Difference in mean, medians or proportions (95%CI)	*p* value
Duration of surgery (min)	153 ± 53	146 ± 46	6.87 (−15.54 to 29.28)	0.54
Duration of OLV (min)	137 ± 53	130 ± 45	6.27 (−16.13 to 28.67)	0.58
Dose of propofol (mg)	116 ± 24	119 ± 14	−2.54 (−11.32 to 6.25)	0.57
Dose of vecuronium (mg)	8 [7 to 8]	8 [8 to 9]	0.00 (−1.00 to 0.00)	0.07
Dose of sufentanil (μg)	24.1 ± 4.0	24.0 ± 2.8	0.02 (−1.56 to 1.61)	0.98
Dose of remifentanil (μg)	1095.9 ± 362.2	911.1 ± 233.8	184.82 (46.02 to 323.62)	0.01
Blood loss (ml)	25 [20 to 30]	28 [20 to 36]	−2.50 (−5.00 to 0.00)	0.33
Intraoperative infusion volume (ml)	1,450 [1,200 to 1,600]	1,350 [1,062 to 1,500]	100 (−50 to 250)	0.14
Intraoperative hypertension	2 (5.1%)	0 (0%)	0.05 (−0.02 to 0.12)	0.25
Intraoperative hypotension	15 (38.5%)	6 (15.8%)	0.23 (0.04 to 0.42)	0.05
Intraoperative tachycardia	2 (5.1%)	0 (0%)	0.05 (−0.02 to 0.12)	0.25
Intraoperative bradycardia	4 (10.3%)	1 (2.6%)	0.08 (−0.03 to 0.18)	0.37

Values are mean ± SD, number (proportion) or median [IQR]. EA, electroacupuncture; OLV, one lung ventilation; IQR, interquartile range.

(48–193 [10–294]) vs. 209.5 (73.8–261.5 [16–349]), $p = 0.02$ and 0.34 (0.14–0.57 [0.03–0.95]) vs. 0.60 (0.23–0.79 [0.03–0.95]), $p = 0.02$, respectively. Compared with the EA group, patients in the control group experienced significantly longer awake time; 225.0 (153.0–316.0 [17–372]) vs. 134.5 (72.8–248.3 [16–349], $p = 0.01$). The sleep duration of stage N1 and stage N2 was significantly longer in the EA group; 95.0 (38.0–123.0 [10–208]) vs. 135 (56.2–177.3 [9–242]), $p = 0.05$ and 28 (12–58 [0–125]) vs. 68.5 (21.0–94.3 [0–139]), $p = 0.02$, respectively (Table 4).

From 1 h to 48 h after surgery, the VAS scores were all comparable between the two groups and postoperative pain was well controlled (Figure 2). Comparisons at different time points showed that in the control group, the VAS scores at 1 h postoperatively differed significantly from those at 6 h, 12 h, and 48 h postoperatively, with mean differences and 95% CI of −1.38 (−1.79 to −0.98), $p < 0.001$; −0.64 (−1.05 to −0.23), $p < 0.001$; 0.41 (0.00–0.82), $p = 0.05$. In the EA group, significant differences of VAS scores were found only at 6 h and 48 h postoperatively, with results of −0.87 (−1.40 to −0.34), $p < 0.001$; 0.71 (0.28–1.14), $p < 0.001$.

Univariate and multivariate logistic regression analyses examined the relationship between EA and POSVT (Table 5). In univariate analysis, EA was a protective factor for POSVT (OR 0.24, 95% CI 0.07–0.81, $p = 0.02$). Other important variables in the univariate analysis included age, duration of surgery, duration of OLV (one lung ventilation), dose of propofol, dose of sufentanil, dose of remifentanil, blood loss, ASA classification, types of surgery. After adjusting for age, duration of surgery, duration of OLV, doses of propofol, dose of sufentanil, dose of remifentanil, blood loss, ASA classification, and types of surgery, EA remained protective against POSVT (OR 0.18, 95% CI 0.04–0.77, $p = 0.02$). In contrast, in both univariate and

TABLE 3 Incidence of postoperative arrhythmia.

	Control group, (n = 39)	EA group, (n = 38)	Difference proportions (95%CI)	P value
POSVT	13 (33.3%)	4 (10.5%)	0.18 (0.01 to 0.35)	0.02
Segmentectomy	8 (32.0%)	2 (9.1%)	0.23 (0.01 to 0.45)	0.12
Lobectomy	5 (35.7%)	2 (12.5%)	0.23 (−0.07 to 0.53)	0.29
SVEBs	23 (59.0%)	18 (47.4%)	0.12 (−0.11 to 0.34)	0.31
VPBs	26 (66.7%)	17 (44.7%)	0.22 (0.00 to 0.44)	0.05
Use of β-blockers	11 (28.2%)	3 (7.9%)	0.20 (0.04 to 0.37)	0.04

Values are number (proportion). EA, electroacupuncture; POSVT, postoperative supraventricular tachycardia; SVEB, supraventricular ectopic beat; VPB, ventricular premature beat; CI, Confidence Interval.

TABLE 4 Sleep stages.

	Control group, (n = 39)	EA group, (n = 38)	Difference in medians (95%CI)	P value
TST (min)	119 [48 to 193]	209.5 [73.8 to 261.5]	−90.5 (−109 to −10)	0.02
Sleep efficiency	0.34 [0.14 to 0.57]	0.60 [0.23 to 0.79]	−0.26 (−0.32 to −0.02)	0.02
Awake time (min)	225.0 [153.0 to 316.0]	134.5 [72.8 to 248.3]	90.5 (14 to 112)	0.01
Stage N1 (min)	95.0 [38.0 to 123.0]	135 [56.2 to 177.3]	−40 (−59 to −1)	0.05
Stage N2 (min)	28 [12 to 58]	68.5 [21.0 to 94.3]	−40.5 (−50 to −5)	0.02
Stage N3 (min)	0 [0 to 0]	0 [0 to 2]	0 (0 to 0)	0.08
REM (min)	0 [0 to 0]	0 [0 to 0]	0 (0 to 0)	>0.99

Values are median IQR [range].
Values are median [IQR]. EA, electroacupuncture; TST, total sleep time; REM, rapid eye movement sleep; CI, Confidence Interval.

multivariate logistic analyses, variables other than EA did not seem to significantly affect on POSVT.

We performed subgroup analyses to explore the relationship between EA and POSVT in different subgroups (Figure 3). These subgroups were analyzed based on factors such as age, gender, ASA classification, smoking history, duration of surgery, and types of surgery to reveal significant associations between several factors and POSVT. However, these factors did not show significant associations with outcomes. No interactions were observed between subgroups. For detailed results of the subgroup analysis, please refer to Figure 3.

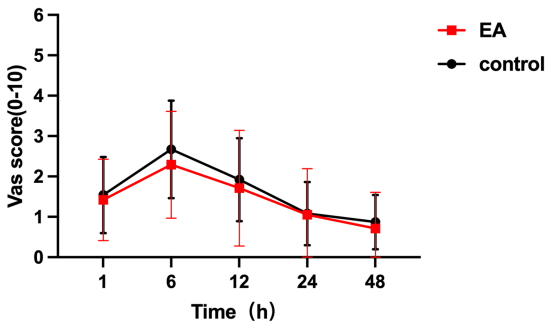

FIGURE 2
VAS scores from 1 to 48 h postoperatively in the EA group and the control group. No significant difference between groups.

4 Discussion

In this study, we investigated the effect of EA treatment on the incidence of supraventricular arrhythmia and sleep disorders in patients undergoing thoracoscopic surgery for lung cancer. The main results indicated that peri-operative EA treatment was effectively reduced the incidence of POSVT and improved the sleep quality. It was also beneficial for maintaining intraoperative hemodynamic stability. Last not the least, the minimally invasive EA treatment appears to be safe and well tolerated in all the patients recruited. To the best of our knowledge, this is the first study to explore the effect of EA treatment on the prevention of SVT and sleep disorders in patients undergoing thoracoscopic surgery.

SVT has been recognized as a common complication after thoracoscopic surgery. It is associated with hemodynamic instability, prolonged hospital stay and increased risk of perioperative mortality (12, 13). Potential factors associated with POSVT included cardiac autonomic nervous system imbalance, oxidative activation, inadequate pain control and postoperative inflammatory response (14–17). Autonomic imbalance has been shown as the most frequent trigger of POSVT (18, 19). Our two previous studies showed that reducing in the tone of cardiac autonomic sympathetic nerves may help decrease the occurrence of POSVT (3, 20).

In 1958, traditional acupuncture was first used to complement the anesthetic. Acupuncture has been shown to enhance the rehabilitation of patients perioperatively, and it has also developed rapidly (21, 22).

In the present study, we found the beneficial effect of EA treatment in reducing SVT in patients after thoracoscopic surgery for lung cancer. The results were consistent with the study by Lomuscio et al. (23) Lomuscio et al. have proved that acupuncture helps decrease the

TABLE 5 Univariate and multivariate analysis of factors associated with POSVT.

Variable	Univariate			Multivariate		
	OR	95% CI	*P*	OR	95% CI	*P*
Intervention						
Simulated EA		Reference			Reference	
EA	0.24	0.07 to 0.81	0.02	0.18	0.04 to 0.77	0.02
Age	1.05	0.99 to 1.11	0.10	1.03	0.96 to 1.11	0.44
Duration of surgery	1.00	1.00 to 1.02	0.23	1.02	0.90 to 1.15	0.80
Duration of OLV	1.00	1.00 to 1.02	0.22	1.02	0.90 to 1.15	0.79
Dose of propofol	1.00	0.97 to 1.02	0.77	1.00	0.95 to 1.06	0.84
Dose of sufentanil	1.02	0.88 to 1.19	0.79	0.99	0.72 to 1.35	0.93
Dose of remifentanil	1.00	0.99 to 1.00	0.37	1.00	0.99 to 1.00	0.28
Blood loss	0.99	0.95 to 1.03	0.64	0.94	0.87 to 1.01	0.91
ASA						
I		Reference			Reference	
II	1.85	0.46 to 7.36	0.39	4.44	0.64 to 30.62	0.13
III	4	0.46 to 34.92	0.21	7.61	0.40 to 145.30	0.18
Types of surgery						
Segmentectomy		Reference			Reference	
Lobectomy	1.54	0.52 to 4.56	0.44	1.17	0.30 to 4.68	0.82

SVT, supraventricular tachycardia; CI, confidence interval; EA, electroacupuncture; ASA, American Society of Anaesthesiologists; OLV, One Lung Ventilation.

recurrences of atrial fibrillation after electrical cardioversion and the antiarrhythmic efficacy of acupuncture was similar to that of amiodarone. In another study, the findings indicated that acupuncture may exert an antiarrhythmic effect in patients with both persistent and paroxysmal atrial fibrillation (24). The antiarrhythmic effect of acupuncture may be exerted by modulating the cardiac autonomic nervous system (25). Acupuncture has been widely proven effective in reducing the incidence of atrial fibrillation, both in basic research and clinical trials (25, 26). An experiment in a canine model suggested that acupuncture decreased cardiac sympathetic activity and suppressed atrial electrical remodeling by decreasing the levels of inflammatory cytokines in the atrium (27). In the present study, we chose Neiguan (PC6) and Gongsun (SP4) acupoints because they are related to the regulation of the cardiac autonomic nervous system in the theory of Traditional Chinese Medicine. While non-specific acupoints are not thought to have similar specific effects. Studies have noted that EA treatment may attenuate sympathoexcitatory cardiovascular responses by promoting the secretion of brain inhibitory neurotransmitters, including opioids and gamma-aminobutyric acid (28). Moreover, it has also been reported that EA treatment might affect the firing rate of the amygdala nucleus which exerts a modulatory function on the cardiac autonomic nervous system (29). Autonomic imbalance has been shown as the most common cause of POSVT (19). This may explain the mechanism by which EA treatment reduces the incidence of POSVT.

In addition, our results indicated that most patients experienced severe insomnia characterized by decreased TST and NREM sleep during the first postoperative night after thoracoscopic surgery for lung cancer. Postoperative sleep disorders are frequently observed in patients undergoing major surgery (30). Despite the high prevalence, insomnia was often not given enough attention and was not adequately treated due to the side effects of current medication treatment (31). Our present study demonstrated the significant therapeutic effects of EA on patients with postoperative insomnia. This is consistent with the results of another study on the effect of acupuncture on insomnia in breast cancer patients (32). The study showed that acupuncture could be considered as an effective management of chemotherapy-associated insomnia in breast cancer patients. Another study by Zhang *et al.* also investigated the clinical efficacy of acupuncture and found that acupuncture can significantly improve insomnia (33). The mechanisms of EA in treating insomnia are still under investigation. Clinical studies indicated that acupuncture may improve sleep quality through multiple pathways. Among them, autonomic nervous system plays a pivotal role in sleep physiology. Insomnia is usually accompanied by autonomic nervous dysfunction. Acupuncture may improve sleep quality by regulating the autonomic nervous system (34). Acupuncture can also regulate neurotransmitters. It may promote sleep quality by lowering cortisol levels in the stress response and increasing the level of 5-HT, a key inhibitory neurotransmitter involved in the regulation of the sleep cycle (35). Another mechanism of acupuncture in treating sleep disturbances is its anti-inflammatory effect. Studies have reported that EA treatment might alleviate the production of inflammatory cytokines, including IL-4 and IL-10 (36, 37). Inflammation is supposed to be associated with various sleep disorders (38). Therefore, EA treatment may promote sleep quality by reducing inflammatory cytokines.

Intraoperative hypotension is prevalent among patients undergoing thoracic surgery. We observed that the incidence of hypotension was as high as 38% during surgery, which may be due to the relatively advanced age of patients (more than 60 years old). We found that EA treatment can reduce the incidence of intraoperative hypotension. The hemodynamics of patients in the EA

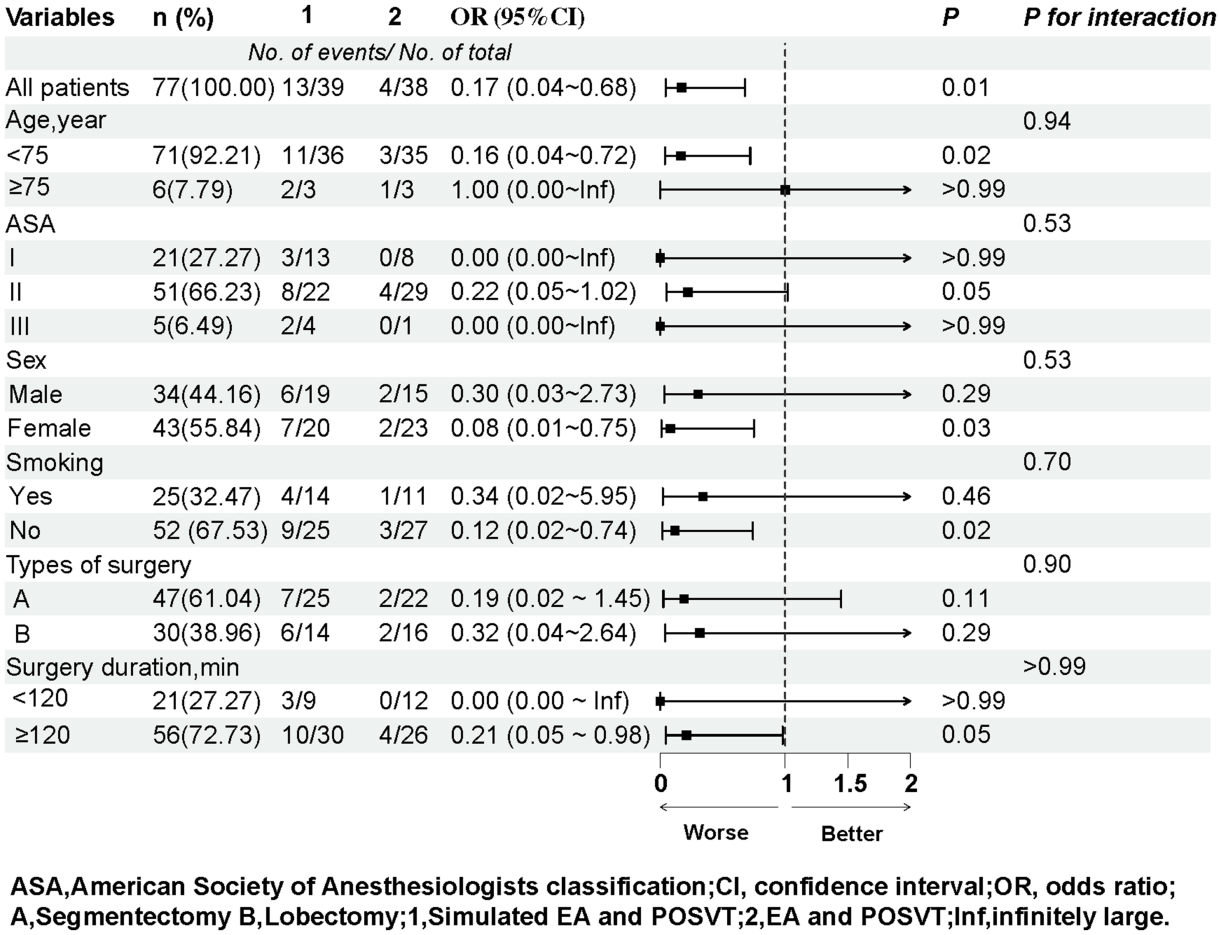

FIGURE 3
Subgroup analyses of the association between the EA and control group.

group seems to be more stable. This effect of EA treatment in patients undergoing thoracic surgery is rarely investigated and reported. The cardiac autonomic nervous system is suppressed during general anesthesia, and patients are predispositional to hypotension. EA may reduce the incidence of hypotension by regulation of an imbalanced autonomic nervous system (39). At present, the most common treatments for SVT after thoracoscopic surgery mainly include β-blockers, calcium channel blockers, and amiodarone. However, all of these medications are associated with hypotension and bradycardia, with occurrences as high as 49 and 25%, respectively (40, 41). They are usually contraindicated in patients with hemodynamic instability. Due to the hemodynamic advantages, EA may be a promising and feasible method to prevent POSVT during thoracic surgery.

Our data showed that EA treatment reduced intraoperative remifentanil consumption by almost 17%, indicating an analgesic effect of EA. Nevertheless, postoperative pain scores were similar in both groups. Although there is a study with similar results to ours exits (42), we cannot rule out the cause of heterogeneity. Several literatures have reported the analgesic effect of EA treatment and the mechanism may be related to endogenous opioid system activation (43–46).

In our study, the control group received EA treatment at non-acupoints as a reasonable placebo. Non-acupoints stimulation minimizes the differences in patient management between groups. It was reported that stimulation of acupoints could evoke antiarrhythmic and anti-inflammatory effect, while non-acupoint stimulation failed to exert the same effect (47).

4.1 Study limitations

Our study also has a few limitations. Firstly, this present study investigated the effect of EA treatment on the incidence of postoperative supraventricular arrhythmia and sleep quality in patients after thoracic surgery. However, the relationship between postoperative new-onset arrhythmias and sleep disturbances cannot be determined. Secondly, the sample size of this study is relatively small, and is a single-center clinical study. Our center is a tertiary hospital. The patients who come for surgery are relatively older and have more complex conditions and more comorbidities compared with the patients in lower-level hospitals. This may limit the generalizability of the results to other populations or settings and thus affect the study's external validity. A larger multicenter clinical trial with a longer follow-up period to investigate the sustained effects of EA treatment on postoperative arrhythmias and sleep disturbances would be a valuable extension of this study.

5 Conclusion

In conclusion, POSVT and sleep disturbances are commonly observed in patients undergoing thoracoscopic surgery for lung cancer. EA treatment as a minimally invasive procedure appears to be effective in reducing the incidence of POSVT and improving postoperative sleep quality.

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 Ethics Committee of First Affiliated Hospital of Guangzhou University of Chinese Medicine. 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

JL: Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. LD: Data curation, Investigation, Project administration, Writing – original draft, Writing – review & editing. WM: Data curation, Investigation, Writing – original draft. JW: Data curation, Investigation, Writing – original draft. XS: Conceptualization, Formal analysis, Writing – review & editing. YC: Conceptualization, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. CW: Conceptualization, Funding acquisition, Resources, Supervision, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This work was funded by National Natural Science Foundation of China (82374451).

Acknowledgments

We gratefully thank the financial support from National Natural Science Foundation of China (82374451) and all the patients in 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.

Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

Publisher's note

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