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ORIGINAL RESEARCH

The Effect of Opioid-Free Anesthesia with Esketamine on Postoperative Cognitive Dysfunction in Elderly Patients Undergoing Thoracoscopic Surgery: A Prospective, Randomized, Controlled Trial

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Background: Postoperative cognitive dysfunction (POCD) occurs at a higher rate in elderly patients undergoing thoracoscopic surgery, significantly affecting postoperative recovery and quality of life. However, effective interventions and anesthesia-related risk factors remain poorly understood.

Purpose: This study aimed to evaluate the impact of esketamine-based opioid-free anesthesia (OFA) on POCD in elderly patients undergoing thoracoscopic lung cancer surgery.

Patients and Methods: In this study, 80 elderly patients undergoing thoracoscopic lung cancer surgery were randomly allocated to receive either opioid-free anesthesia with esketamine (OFA group) or opioid-based anesthesia (Control group). The primary outcome was the incidence of POCD within 3 days. Logistic regression was used to identify risk factors for POCD.

Results: The incidence of POCD was 20% and 42.5%, respectively, in the OFA group and the Control group (risk ratio [RR], 0.47; 95% confidence interval [CI], 0.24 to 0.92; risk difference [RD], −22.5%; 95% CI, −44.8% to −0.2%; $p = 0.054$). Compared to the Control group, patients in the OFA group had lower simple reaction time at 1 and 3 days post-surgery (1-day: $p = 0.031$; 3-day: $p = 0.020$). In addition, patients in the OFA group demonstrated higher mean values for mean arterial pressure (MAP), heart rate (HR), cardiac output (CO), cardiac index (CI), stroke volume (SV), and systemic vascular resistance index (SVRI), as well as smaller variation ranges for these parameters, compared to the Control group (all $p < 0.05$), Furthermore, age (OR, 2.738; 95% CI, 1.37 to 6.30; $p = 0.008$), CO range (OR, 4.673; 95% CI, 2.25 to 11.82; $p < 0.001$), and time to first analgesic request (OR, 0.399; 95% CI, 0.18 to 0.76; $p = 0.01$) were validated to correlate with POCD.

Conclusion: Esketamine-based OFA did not significantly reduce POCD incidence, and it was associated with improved postoperative reaction time and reduced intraoperative hemodynamic fluctuations.

Keywords: opioid-free anesthesia, esketamine, postoperative cognitive dysfunction, thoracoscopic surgery, hemodynamics

Introduction

Postoperative cognitive dysfunction (POCD) is a common central nervous system complication characterized by impairments in attention, memory, and executive function, which not only affect patients' short-term recovery but may also have profound implications for their long-term quality of life.[1] The incidence of POCD reaches 25% in patients aged 65 years and older within one week after surgery, and this rate escalates to 53% in elderly patients undergoing high-risk

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procedures.[2] The development of POCD is multifactorial, involving patient age, intraoperative opioid administration, hemodynamic fluctuations, and surgical complexity.[3–5]

Thoracic surgery, particularly thoracoscopic procedures, presents unique challenges due to anatomical manipulation of major vessels, surgical complexity, and the frequent requirement for one-lung ventilation. One-lung ventilation is commonly associated with decreased oxygen saturation and pronounced hemodynamic instability, ultimately resulting in reduced cerebral blood flow and positioning thoracic surgery as a high-risk category for POCD development.[6] Furthermore, the intense pain associated with thoracic procedures necessitates substantial opioid administration for effective analgesia.[7] However, emerging evidence suggests that excessive opioid use may adversely affect cognitive function by disrupting glutamatergic and GABAergic neurotransmitter systems, thereby impairing neuronal signal transmission and synaptic plasticity.[8] Animal studies have demonstrated that prolonged or high-dose opioid exposure can induce neuronal apoptosis and glial cell activation, mechanisms potentially linked to POCD pathogenesis.[9] Additionally, opioid-induced respiratory depression leads to carbon dioxide retention and hypoxemia, subsequently compromising cerebral blood flow and oxygen delivery, thereby increasing POCD risk.[10]

In response to these concerns, anesthesiologists have increasingly questioned the necessity of perioperative opioid use, leading to the emergence of "opioid-free anesthesia" (OFA) and "opioid-sparing anesthesia" concepts. OFA represents a multimodal approach that achieves analgesia, sedation, and muscle relaxation through various non-opioid agents and techniques, thereby avoiding opioid-related adverse effects.[11,12] Contemporary OFA strategies have evolved beyond simple reliance on nonsteroidal anti-inflammatory drugs (NSAIDs) and local anesthetics to incorporate ultrasound-guided regional blocks, α2-adrenergic agonists (dexmedetomidine), and N-methyl-D-aspartate (NMDA) receptor antagonists.[13,14]

Esketamine, a potent NMDA receptor antagonist, provides surgical analgesia while conferring neuroprotective properties.[15] Research indicates that esketamine modulates brain neurotransmitters by enhancing glutamate release and serotonin levels, promoting neuronal activity and repair, thereby offering protection against surgery-induced neuronal damage and potentially reducing POCD incidence while facilitating postoperative cognitive recovery.[15] Moreover, esketamine demonstrates efficacy in ameliorating depressive symptoms, and given the established association between postoperative depression and POCD, esketamine may indirectly benefit cognitive function and reduce POCD occurrence.[16] There have been several clinical studies on the effect of esketamine on POCD, but significant gaps still exist in the research. For example, Lee et al[17] investigated the effect of administering esketamine solely during the induction phase on postoperative cognitive function in elderly orthopedic patients. The study found that, although ketamine reduced postoperative analgesic requirements, its impact on improving POCD was not significant. A key limitation of this study is that its assessment of POCD primarily focused on intellectual function, whereas research indicates that early changes in POCD typically manifest as a decline in reaction time, rather than in intellectual abilities. Furthermore, the study did not utilize an OFA approach based on esketamine, despite OFA being proposed as a multimodal anesthesia strategy that may reduce opioid use and improve postoperative cognitive function. Another study[18] indicated that the anesthesia protocol using esketamine improved the recovery time of anesthesia awareness and stabilized blood pressure and heart rate during the recovery phase compared to conventional anesthesia. However, with regard to postoperative cognitive function, the study only assessed the Montreal Cognitive Assessment (MOCA) score, which does not provide conclusive evidence regarding whether esketamine reduces the risk of POCD in elderly patients. Furthermore, a systematic review by Viderman et al[19] found that ketamine's effects on postoperative cognitive function vary depending on surgical type and dosage. The review also emphasized the need for further clinical studies to validate these effects, particularly in non-cardiac surgeries and specific patient populations.

Based on the limitations of the aforementioned studies, this research seeks to address these gaps. We focus on elderly patients undergoing thoracoscopic lung cancer surgery and utilize esketamine-based OFA in a randomized, controlled, double-blind clinical trial to explore the potential of esketamine in reducing POCD incidence.

Materials and Methods

Study Design and Ethics

This prospective, randomized, double-blind trial was conducted at Liaoning Cancer Hospital & Institute, and the trial design received approval from the Ethics Committee of Liaoning Cancer Hospital & Institute (Ethics Approval No.

KT20240301). It was registered with the Chinese Clinical Trial Registry (ChiCTR2400092239). The study followed the principles of the Declaration of Helsinki, and all participants or their legal representatives provided informed consent.

Patients

Patients were recruited between November 2024 and April 2025, and all provided written informed consent in accordance with the CONSORT guidelines.

The inclusion criteria included (1) patients undergoing thoracoscopic lobectomy for lung cancer; (2) patients aged ≥65 years; (3) body mass index (BMI) between 18.5–30.0 kg/m^2 and classified as American Society of Anesthesiologists (ASA) II or III; (4) Mini-Mental State Examination (MMSE) score ≥26; (5) patients without a history of surgery in the past three months. Those who met all inclusion criteria were enrolled in the study. The exclusion criteria included (1) patients allergic to the anesthesia drugs used in this study; (2) patients with a history of alcohol, sedative-analgesic drugs, psychotropic drugs, or substance abuse and addiction; (3) patients unable to cooperate in completing the MMSE or scoring below specified thresholds (illiterate ≤ 17, primary school level ≤ 20, secondary school level ≤ 22, and university level ≤ 23), or suffering from psychiatric disorders; (4) patients with any of the following characteristics: severe cardiac, hepatic, pulmonary, and renal insufficiencies (left ventricular ejection fraction < 30%, creatinine > 176 μmol/L, blood urea nitrogen > 7.1 mmol/L, albumin < 30 g/L, Forced Expiratory Volume in 1 second < 50%); (5) patients with long-term opioid treatment; (6) patients undergoing lithium treatment or with contraindications to the use of LiDCO; (7) patients refusing to participate in the study. Withdrawal criteria included (1) patients voluntarily withdrew from the study or the study data were incomplete; (2) patients who needed to be converted from thoracoscopic surgery to open thoracic surgery; (3) intraoperative blood loss of more than 800 mL or needed transfusion therapy; (4) other serious cardiovascular events (such as malignant arrhythmia, acute myocardial ischemia, anaphylaxis).

Randomization and Blinding

A computerized randomization program was used to generate a sequence with permuted blocks of 4 and 6, maintaining a 1:1 allocation ratio. Allocation concealment was ensured by keeping the sequence hidden from both the researchers and participants. While the anesthesiologist, responsible for administering the anesthetic agents, was aware of the group assignment to administer the appropriate treatment, all patients, follow-up staff, and investigators involved in data collection and outcome assessment remained blinded to the group allocation throughout the study. Cognitive function and postoperative assessments were performed by blinded investigators to minimize any potential bias in the outcome evaluation.

Study Procedures

On the day before surgery, researchers measured the noninvasive blood pressure and heart rate (HR) for patients in stress-free, pain-free, and awake states. Additionally, the MMSE scale was used to assess patients' cognitive function and a preoperative Simple Reaction Time Score (SRT) was performed using Benchmark software to assess neurobehavioral status. No patient received premedication.

Patients were fasted for 8 hours and abstained from drinking for 2 hours preoperatively. Upon entering the anesthesia preparation room, baseline mean arterial pressure (MAP), HR, and blood oxygen saturation (SpO2) were monitored and recorded. Under local anesthesia, a paravertebral nerve block (PVB) was performed by administering 0.5% ropivacaine 20 mL into the thoracic paravertebral space (T4-T6). After the block, a needle test was performed to assess the blockade level and ensure the correct surgical anesthesia plane. These patients were then transferred to the operating room in a supine position, and venous access to the upper limb was established. Before the induction of anesthesia, radial artery puncture cannulation was performed under local anesthesia for continuous arterial blood pressure monitoring, and the results were calibrated with noninvasive cuff blood pressure (NIBP). The electrocardiogram (ECG), MAP, peripheral capillary oxygen saturation (SpO_2), and bispectral index (BIS) were monitored continuously. Relevant data were collected every minute by the monitoring equipment. In addition, a LiDCO hemodynamic monitor (LiDCO rapidV3) was connected to record cardiac output (CO),stroke volume (SV), stroke volume variation (SVV), and systemic vascular resistance index (SVRI). All procedures were performed by the same surgical team under general anesthesia.

The induction of anesthesia involved the intravenous administration of sufentanil at a dose of 0.2–0.4 μg·kg^{-1} for Group C, esketamine at a dose of 0.4 mg·kg^{-1} for Group F, and propofol at a dose of 1.5–2.0 mg·kg^{-1} for both groups. The administration persisted for over 30 seconds. When the eyelash reflex disappeared and adequate anesthetic depth was achieved, rocuronium bromide was injected at 0.6 mg·kg^{-1}. Then, double-lumen endotracheal intubation was performed when the drugs had taken full effect, and the tube's precise positioning was confirmed by fiberoptic bronchoscopy.

Mechanical ventilation was conducted in volume-controlled ventilation mode. Tidal volume settings were adjusted to 6–8 mL·kg^{-1} for two-lung ventilation and 4–6 mL·kg^{-1} for one-lung ventilation based on ideal body weight. The airway pressure was maintained below 30 cmH2O, and the fraction of inspired oxygen was initially set at 100% and adjusted according to patient oxygenation. The respiratory rate, inspiratory-expiratory time ratio, and positive end-expiratory pressure were adjusted individually to maintain the partial pressure of arterial carbon dioxide ($PaCO_2$) level within 35–45 mmHg.

The maintenance of anesthesia was achieved through total intravenous anesthesia (TIVA). Group F received esketamine at 0.1–0.15 mg·kg^{-1}·h^{-1} and propofol at 4–10 mg·kg^{-1}·h^{-1} by continuous intravenous infusion. Group C received remifentanil 5–10 μg·kg^{-1}·h^{-1} and propofol 4–10 mg·kg^{-1}·h^{-1} by continuous intravenous infusion. The administration rate was adjusted based on hemodynamic parameters and clinical signs to maintain adequate anesthetic depth. When the intraoperative Surgical Pleth Index exceeded 50, Group F received esketamine 0.25 mg·kg^{-1} as a single intravenous bolus injection, while Group C received sufentanil 10 μg intravenously for enhanced analgesia. Rocuronium bromide was administered intermittently to maintain muscle relaxation. In the first hour of surgery, 6 mL·kg^{-1} of normal saline was infused, thereafter reduced to 2.5 mL·kg^{-1} per hour. All surgical procedures were performed via thoracoscopic approach through the fourth or fifth intercostal space anterolaterally. Before the completion of surgery, patients were given 40 mg parecoxib by intravenous injection and 100 mg acetaminophen through a 30-minute intravenous infusion. At the conclusion of the procedure, 10 mg azasetron was administered to reduce the risk of postoperative nausea and vomiting.

In case of hypotension (when MAP was less than 80% of baseline blood pressure for more than 5 minutes), norepinephrine was administered at 0.05–0.10 μg·kg^{-1}·min^{-1} until MAP exceeded 80% of baseline. Conversely, urapidil (12.5 mg) was administered in case of hypertension (when MAP exceeded 120% of baseline for more than 5 minutes). When HR was below 40 bpm, atropine 0.3 mg was injected intravenously; when HR exceeded 100 bpm, esmolol 10 mg was administered. Colloid infusion was considered when SVV >13% and patients showed signs of hypovolemia.

The infusion of intravenous anesthetics was stopped at the end of the procedure. Subsequently, patients were transferred to the Post-Anesthesia Care Unit (PACU). When the train-of-four ratio of patients reached ≥0.9, neostigmine was administered at a dose of 0.04 mg/kg if needed. The tracheal tube was removed once patients could open their eyes, breathe spontaneously, have adequate tidal volume, and achieve circulatory stability. Patients were assessed using the Ramsay sedation score and Bruggrmann comfort scale in the PACU. The follow-up evaluation was conducted for patients in the ward at 1 and 3 days after surgery.

Outcome Measures

The primary outcome was the incidence of POCD within three days after surgery. POCD was defined as meeting either of the following criteria: (1) MoCA score < 26,[20] or (2) SRT exceeding 20%[21] of the preoperative baseline value. Secondary outcomes included MoCA scores and SRT scores at 24 and 72 hours postoperatively, intraoperative hemodynamic parameters, postoperative pain scores, time to first analgesic request after extubation, anesthetic consumption, and fluid management requirements. Additionally, a detailed analysis was conducted to explore the correlation between the occurrence of POCD and the factors associated with hemodynamic stability.

Patient demographic and clinical characteristics including age, gender, BMI, education level, ASA classification, paravertebral block (PVB) side, location of resection, preoperative comorbidities (hypertension, diabetes, coronary artery disease), alcohol consumption, smoking history, duration of operation, duration of anesthesia, and hospital stay were recorded. The baseline MAP and HR of patients were determined at T0 timepoint (before anesthesia induction) when patients were in a conscious and resting state. Preoperative CO and hemoglobin levels were also measured. Preoperative cognitive function was assessed using the MMSE scale to ensure baseline cognitive competency, and baseline SRT was measured using Benchmark software to establish individual neurobehavioral baselines. Safety analysis was performed on

the full ITT population (n=92). No significant differences were observed between groups in the incidence of major cardiovascular events, respiratory complications, or other serious adverse events.

Hemodynamic parameters including MAP, HR, CO, cardiac index (CI), SV, SVV, and SVRI were continuously monitored throughout the procedure. For each hemodynamic parameter, both mean values across all measurement timepoints and variation ranges (calculated as the difference between maximum and minimum values) were calculated and analyzed to assess cardiovascular stability.

Cognitive function was evaluated using validated assessment tools at predetermined intervals. The MoCA was administered preoperatively and at 24 and 72 hours postoperatively to assess global cognitive function. SRT testing was performed using standardized software protocols at matching timepoints to evaluate neurocognitive processing speed and attention.

Postoperative pain was evaluated using Visual Analog Scale (VAS) scores at 24 and 72 hours after surgery. Time to first analgesic request after extubation was recorded to assess the duration of perioperative analgesic efficacy. Total consumption of anesthetic agents was recorded, including propofol dosage (mg), esketamine dosage in the OFA group (mg), remifentanil and sufentanil consumption in the control group (μg), and vasoactive drug usage such as norepinephrine (μg). Fluid management parameters included total crystalloid and colloid administration volumes (mL). Additionally, both groups had similar postoperative complications, as well as comparable total analgesic consumption at the 24-hour and 72-hour time points (converted to morphine equivalent dose, MED) (Table 1S).

Comprehensive physiological monitoring was performed at predefined timepoints throughout the perioperative period. The observation timepoints from T0 to T5 were established as follows: T0: before anesthesia induction (baseline); T1: at the time of endotracheal intubation; T2: 15 minutes after surgical incision; T3: 45 minutes after surgical incision; T4: 60 minutes after surgical incision; T5: during lung recruitment maneuver and immediately before completion of surgery. At each timepoint, hemodynamic parameters were systematically recorded and analyzed.

Sample Size Calculation

The sample size required for this study was calculated based on the pre-test results of a POCD incidence of 40%[22] in the control group and a POCD incidence of 10% in the opioid-free anesthesia group based on preliminary study results where one out of ten patients developed POCD, with a detection rate of 80% and a two-sided significance level of 0.05. With the aid of G*Power 3.1 software (Heinrich-Heine-Universität Düsseldorf, Germany), it was determined that each group should consist of 34 subjects, totaling 68 subjects for the study. Given that approximately 20% of patients were excluded, the total number of participants was determined to be 80, with 40 patients allocated to each group.

Statistical Analysis

Statistical analysis was conducted using SPSS 26.0 and R software (version 4.3.0). The normality of continuous variables was evaluated using the Shapiro–Wilk test and visual inspection of histograms. Normally distributed variables are expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared with independent samples t-tests. Non-normally distributed variables are presented as medians with interquartile ranges [M(P25, P75)] and compared using the Mann–Whitney *U*-test. Categorical data are presented as frequencies and percentages and compared using chi-square tests or Fisher's exact test when expected cell counts were below 5.

For repeated hemodynamic measurements across multiple timepoints, repeated-measures ANOVA was used to assess time effects, group effects, and time-group interaction effects. Non-normally distributed longitudinal data were analyzed using generalized linear mixed models.

A two-stage variable selection approach was used to identify independent risk factors for POCD. First, univariate logistic regression analysis was performed on all potential predictors, with variables having $P < 0.1$ selected for further analysis. Next, the Least Absolute Shrinkage and Selection Operator (LASSO) regularization method with 10-fold cross-validation, using the glmnet package in R, was applied to the pre-selected variables. The optimal lambda value was determined to select the final predictors. Variables selected by LASSO were then included in multivariate logistic regression models to calculate odds ratios (OR) with 95% CI.

Two sensitivity analyses were conducted to evaluate model robustness by sequentially adding covariates to the core model. The first included duration of anesthesia, propofol consumption, and mean cardiac output. The second added preoperative simple reaction time and body mass index. Model performance was assessed using the area under the receiver operating characteristic curve (AUC), McFadden's pseudo-R^2, and the Hosmer-Lemeshow goodness-of-fit test. Multicollinearity was assessed using variance inflation factors (VIF), with VIF > 5 indicating potential concerns.

All continuous variables were standardized using z-score normalization prior to logistic regression analysis. The events per variable ratio was calculated for reliable modeling. All statistical tests were two-sided, with $P < 0.05$ considered statistically significant.

Results

From November 2024 to April 2025, a total of 137 patients were assessed for eligibility. After exclusions, 92 patients were randomized into Group F (n=46) and Group C (n=46). Of these, 12 patients were dropped from the analysis due to various reasons, including 4 with surgical plan modifications, 3 who refused to participate, 1 who was converted to open thoracic surgery, and 4 lost to follow-up. Thus, the final analysis included data from 80 patients (40 from each group). Detailed information on these participants is shown in Figure 1.

Participant Characteristics

Baseline characteristics are shown in Table 1. The data on baseline and demographic characteristics were well balanced between the two groups.

Primary Outcome

The overall incidence of POCD in this trial was 31.3%, including 8 (20%) patients in Group F and 17 (42.5%) patients in Group C (RD, −22.5%; 95% CI, −44.8% to −0.2%; P = 0.054) (Table 2).

Secondary Outcomes

No significant differences were observed in MoCA scores between groups at either 1 day (28 (26, 29) vs 28 (26, 29), P = 0.898) or 3 days (28 (27, 29) vs 28 (27, 29), P = 0.902) after surgery. However, patients in Group F demonstrated significantly faster simple reaction times compared to Group C at both 1 day (539.5 (486.75, 582.5) vs 579 (530, 652), P = 0.031) and 3 days (510 (450.5, 543) vs 544.5 (511.25, 580.5), P = 0.020) postoperatively.

No significant differences were observed in baseline hemodynamic parameters between the two groups. During the surgical period (T1–T5), Group F demonstrated significantly higher values for mean MAP (104.16 ± 5.11 vs 79.60 ± 3.81, P < 0.001), HR (84.91 ± 4.06 vs 64.78 ± 4.00, P < 0.001), CO (5.98 ± 0.61 vs 3.73 ± 0.48, P < 0.001), CI (5.3 ± 0.41 vs 3.3 ± 0.38, P < 0.001), SV (69.84 ± 3.64 vs 55.81 ± 3.71, P < 0.001), and SVRI (1890.06 ± 112.96 vs 1289.02 ± 94.87, P < 0.001) compared to Group C. Moreover, Group F exhibited smaller hemodynamic fluctuations, with reduced variations in MAP (15.35 ± 5.62 vs 39.28 ± 6.46, P < 0.05), CO (1.53 ± 0.51 vs 2.8 ± 0.58, P < 0.001), and SV (6.38 ± 3.23 vs 21.35 ± 4.01, P < 0.001). No significant differences were observed in SVV-related parameters between the groups (Figure 2).

In terms of postoperative pain management, VAS scores were comparable between groups at both 1 day and 3 days after surgery. Time to first analgesic request was similar between groups (176.22 ± 11.90 vs 171.75 ± 10.34, P = 0.077). Regarding perioperative resource utilization, patients in Group C required significantly more colloid administration (0 (0, 25) vs 395.00 (330, 412.5), P < 0.001), while Group F consumed significantly more propofol (626.05 ± 108.39 vs 484.59 ± 78.94, P < 0.001). Crystalloid administration was similar between groups (619.50 ± 102.03 vs 580.23 ± 96.38, P = 0.081) (Table 2).

Variable Selection for Logistic Regression

Univariate analysis identified several variables associated with POCD development with $P < 0.1$: older age (69 (68, 70) vs 67 (66, 68), P = 0.001), preoperative SRT (508.40 ± 52.82 vs 481.33 ± 58.26, P = 0.051), sufentanil consumption (0 (0, 25) vs 25 (0, 25), P = 0.031), colloid administration (360 (250, 400) vs 150 (0, 335), P = 0.009), MAP range (37 (28, 42) vs 20 (13.5, 35.5), P = 0.002), CO range (2.7 (2.3, 2.9) vs 1.8 (1.3, 2.3), P < 0.001), SV range (20 (10, 23) vs 11 (5, 20), P = 0.018), SVV

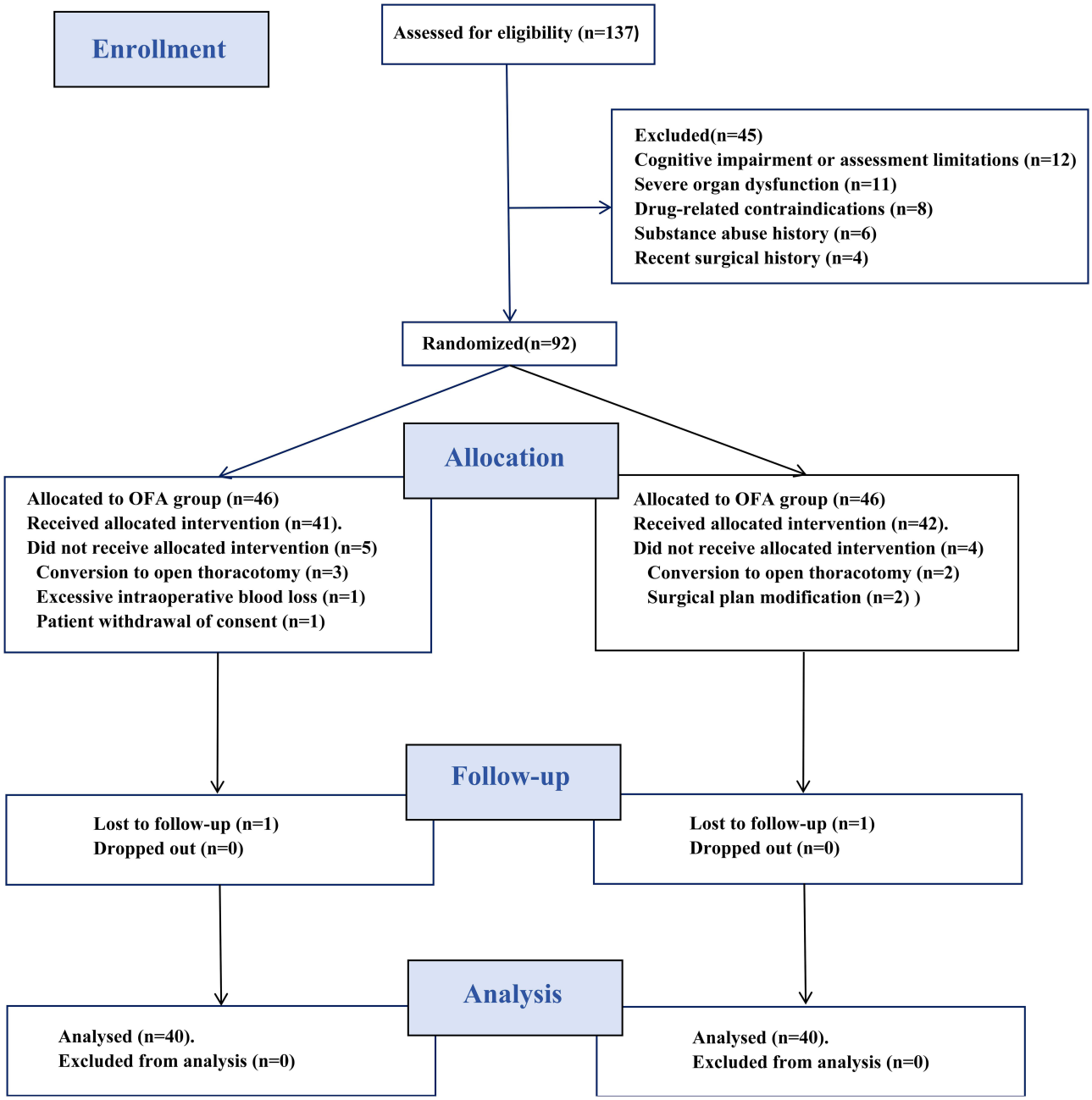

Figure 1 CONSORT diagram describing each stage of the randomized trial.

range (5 (3, 5) vs 4 (3, 5), P = 0.022), SVRI range (463 (368, 1051) vs 1056 (446, 1158), P = 0.018), VAS score at 3 days (3 (2, 3) vs 2 (2, 3), P = 0.028), and time to first analgesic request (169.40 ± 10.19 vs 176.07 ± 11.25, P = 0.013) (Table 3).

Subsequently, LASSO regularization with 10-fold cross-validation was applied to these variables. Using the optimal lambda value (λ = 0.126), three variables were ultimately selected for inclusion in the multivariate logistic regression model: age, CO variation range and time to first analgesic request.

Logistic Regression and Sensitivity Analysis

Multivariate logistic regression analysis of the three LASSO-selected variables revealed that age (OR=2.738, 95% CI 1.37–6.30, P = 0.008) and cardiac output variation range (OR=4.673, 95% CI 2.25–11.82, P < 0.001) were independent risk factors for

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Table 1 Demographic Characteristics and Intraoperative Data

	Group F (n=40)	Group C (n=40)	P value
Age, (y)	67.83±1.68	67.58±1.58	0.495
Male, n (%)	28/40 (70.0)	21/40 (52.5)	0.108
BMI, (kg/m2)	21.56±1.66	21.45±1.58	0.763
Education level, n (%)			0.854
Illiterates	14 (35)	14 (35	
Primary school	14 (35.0)	16 (60)	
Junior high school or higher	12 (30)	10 (25)	
MMSE	29 (28, 30)	29 (28, 30)	0.147
ASA classification, (II/III)%	24/16	23/17	0.82
PVB side			0.108
Left	10 (25)	19 (47.5)	
Right	29 (72.5)	20 (50)	
Bilateral	1 (2.5)	1 (2.5)	
Location of resection			0.973
Upper	21 (52.5)	22 (55)	
Middle	3 (7.5)	3 (7.5)	
Lower	16 (40)	15 (37.5)	
Preoperative comorbidities, n (%)			
Hypertension	11 (27.5)	13 (32.5)	0.626
Diabetes	12 (30)	10 (25)	0.617
Coronary artery disease	14 (35.0)	10 (25.0)	0.329
Preoperative CO, (L/min)	5.50±0.36	5.52±0.44	0.848
Preoperative Hb, (g/dL)	13.49±0.97	13.34±1.07	0.51
Preoperative SRT, (ms)	493.90±61.51	485.68±54.05	0.527
Alcohol consumption, n (%)	20 (50)	17 (42.5)	0.501
Smoking history, n (%)	32 (80.0)	34 (85.0)	0.556
Duration of operation, (min)	100 (90, 110)	97.5 (91.25, 108.75)	0.957
Duration of anesthesia, (min)	122.5 (115, 135)	121 (115, 134.75)	0.981
Hospital stay, (days)	6 (5, 7)	6 (6, 7)	0.718

Notes: Data are presented as mean ± SD, median (interquartile range), or number of patients (%). P-values were calculated using independent t-tests for continuous variables and Chi-square tests for categorical variables to compare the esketamine-based opioid-free anesthesia group (Group F) and the control group (Group C). A P-value of < 0.05 was considered statistically significant.

Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination; ASA, American Society of Anesthesiologists; PVB, paravertebral block; CO, cardiac output; Hb, hemoglobin; SRT, simple reaction time.

Table 2 Primary Outcome and Secondary Outcomes

	Group F (n=40)	Group C (n=40)	P value
Primary Outcome			
POCD, n (%)	8 (20%)	17 (42.5%)	0.054
Secondary Outcomes			
MoCA scores			
1 day after surgery	28 (26, 29)	28 (26, 29)	0.898
3 days after surgery	28 (27, 29)	28 (27, 29)	0.902
SRT (ms)			
1 day after surgery	539.5 (486.75, 582.5)	579 (530, 652)	0.031
3 days after surgery	510 (450.5, 543)	544.5 (511.25, 580.5)	0.020
MAP-related indicators			
Mean, (mmHg)	104.16±5.11	79.60±3.81	< 0.001
Range,(mmHg)	15.35±5.62	39.28±6.46	< 0.05
HR-related indicators			
Mean, (bpm)	84.91±4.06	64.78±4.00	< 0.001
Range,(bpm)	25.9±5.66	14.95±5.05	< 0.001
CO-related indicators			
Mean,(L/min)	5.98 ± 0.61	3.73 ± 0.48	< 0.001
Range,(L/min)	1.53 ± 0.51	2.8 ± 0.58	< 0.001
CI-related indicators			
Mean, ($L/min/m^2$)	5.3 ± 0.41	3.3 ± 0.38	< 0.001
Range, ($L/min/m^2$)	3.31 ± 0.54	0.75 ± 0.23	< 0.001
SV-related indicators			
Mean,(mL)	69.84 ± 3.64	55.81 ± 3.71	< 0.001
Range,(mL)	6.38 ± 3.23	21.35 ± 4.01	< 0.001
SVV-related indicators			
Mean,(%)	11.39 ± 1.03	11.41 ± 1.48	0.942
Range,(%)	4.22 ± 1.54	4.22 ± 1.54	0.309
SVRI-related indicators			
Mean,($dyn \cdot s \cdot cm^{-5} \cdot m^2$)	1890.06 ± 112.96	1289.02 ± 94.87	< 0.001
Range, ($dyn \cdot s \cdot cm^{-5} \cdot m^2$)	1149.55 ± 96.94	420.1 ± 74.98	< 0.001
VAS			
1 day after surgery	3 (2, 3)	3 (2, 3)	0.090
3 days after surgery	3 (2, 3)	2.5 (2, 3)	0.199

(*Continued*)

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Table 2 (Continued).

	Group F (n=40)	Group C (n=40)	P value
Time to First AnalgesicReques, (min)	176.22±11.90	171.75±10.34	0.077
Colloid, (mL)	0 (0, 25)	395.00 (330,412.5)	< 0.001
Crystalloid, (mL)	619.50 ± 102.03	580.23 ± 96.38	0.081
Propofol, (mg)	626.05 ± 108.39	484.59 ± 78.94	< 0.001

Notes: Data are presented as mean ± standard deviation, median (interquartile range), or number of patients (%). P-values were calculated using independent t-tests for continuous variables and Chi-square tests for categorical variables to compare the esketamine-based opioid-free anesthesia group (Group F) and the conventional opioid anesthesia control group (Group C). A P-value of < 0.05 was considered statistically significant. Hemodynamic parameters: Mean values represent the average of all intraoperative measurements from T0 to T5 timepoints. Range values represent the difference between maximum and minimum values recorded during the surgical procedure for each parameter. Time to First Analgesic Request: Measured from the time of tracheal extubation to the first patient request for additional analgesic medication. POCD was defined as either MoCA score < 26 or SRT exceeding 20% of preoperative baseline within 3 days after surgery.

Abbreviations: POCD, postoperative cognitive dysfunction; SRT, simple reaction time; MoCA, Montreal Cognitive Assessment; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; CI, cardiac index; SV, stroke volume; SVV, stroke volume variation; SVRI, systemic vascular resistance index; VAS, visual analog scale.

POCD development. Conversely, longer time to first analgesic request was identified as a protective factor (OR=0.399, 95% CI 0.18–0.76, P = 0.01). The model demonstrated good discriminative ability with the AUC of 0.880 (Figure 3A).

Two sensitivity analyses were conducted by sequentially adding covariates to the core three-variable model. The first sensitivity analysis incorporated duration of anesthesia, propofol consumption, and mean CO, yielding consistent results with age (OR=2.6, 95% CI 1.27–6.13, P = 0.016), CO variation range (OR=6.68, 95% CI 2.36–26.06, P = 0.002), and time to first analgesic request (OR=0.36, 95% CI 0.16–0.71, P = 0.007) maintaining statistical significance. The second sensitivity analysis additionally included preoperative SRT and BMI, with similar findings: age (OR=2.39, 95% CI 1.12–5.86, P = 0.036), CO variation range (OR=9.49, 95% CI 2.96–43.11, P < 0.001), and time to first analgesic request (OR=0.35, 95% CI 0.15–0.72, P = 0.008) remained significant predictors. The newly added variables in both sensitivity analyses did not achieve statistical significance (Table 4 and Figure 3B).

Discussion

This study demonstrated that esketamine-based OFA did not significantly reduce the incidence of early POCD in elderly patients undergoing thoracoscopic surgery, although a 22.5% reduction in POCD incidence was observed. The OFA group showed significantly faster reaction times at 24 and 72 hours postoperatively. Intraoperative fluctuations in mean MAP, CO, and SV were significantly smaller in the OFA group compared with the control group. Multivariate analysis identified age and intraoperative CO fluctuations as independent risk factors for POCD, while delayed first request for analgesia was a protective factor.

The OFA group showed higher MAP, HR, and CO, along with smaller ranges of values, indicating that the esketamine-based OFA protocol resulted in smaller hemodynamic fluctuations during surgery and caused less cardiovascular suppression. This finding differs from previous studies by Zhang et al[23] likely due to a broader patient population that included younger individuals, and the fact that esketamine was only used during the maintenance phase in their study. A study[23] on elderly patients undergoing hip joint surgery reported similar results to ours. However, while that study primarily focused on blood pressure and heart rate, we expanded our analysis by incorporating additional hemodynamic parameters, such as CO, CI, SV, SVV, and SVRI. Furthermore, to assess hemodynamic fluctuations, we calculated the range of values at different time points and overall variability. Importantly, we selected thoracic surgery as the procedure, which has a greater impact on hemodynamic stability. The reduced hemodynamic fluctuations in the OFA group may be attributed to esketamine's unique pharmacological properties. As an NMDA receptor antagonist, esketamine selectively blocks pain transmission pathways and reduces excessive sympathetic activation caused by nociceptive stimuli, thereby maintaining cardiovascular stability.[24,25] Moreover, esketamine has

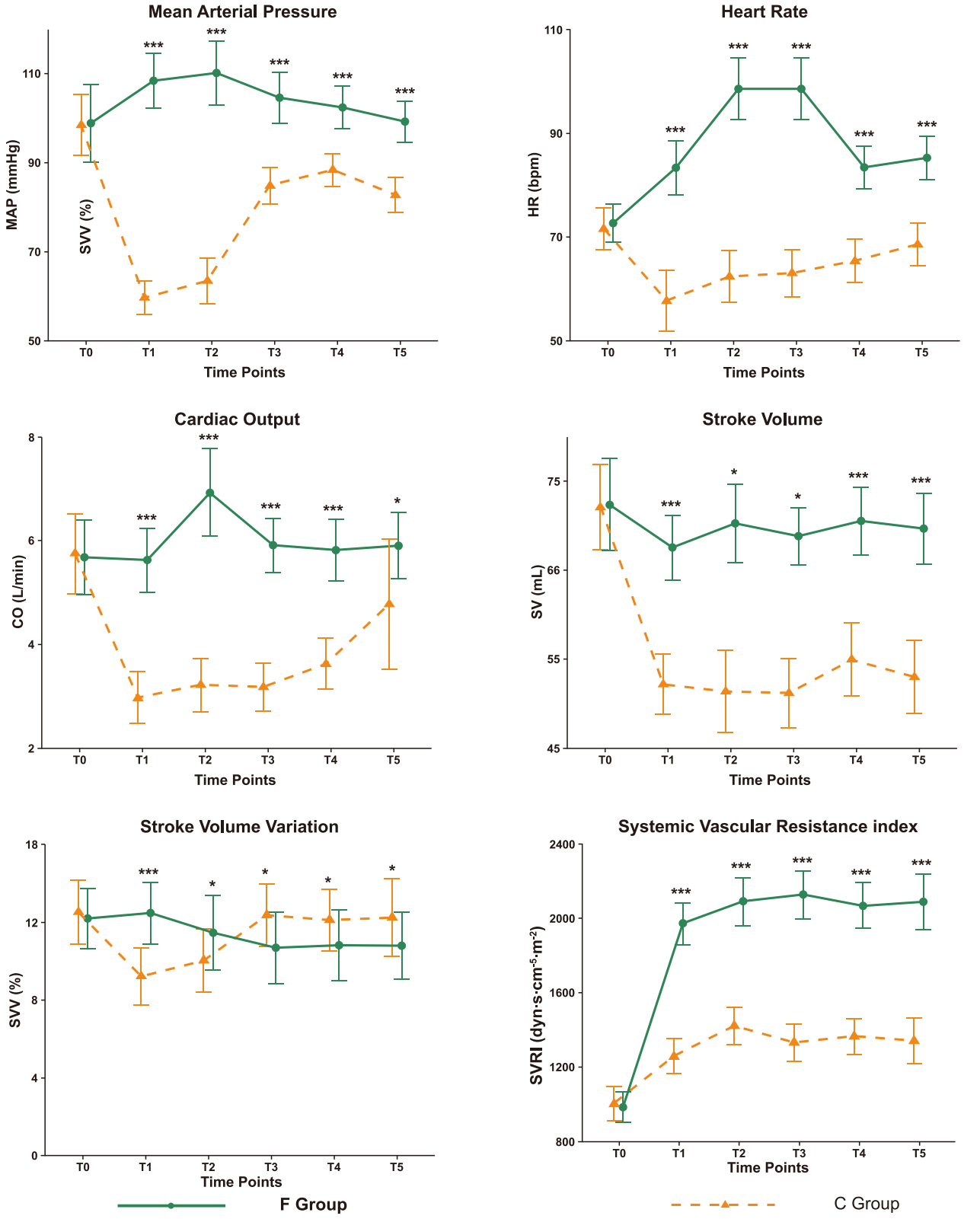

Figure 2 Hemodynamic Parameters Throughout the Perioperative Period.

Notes: Statistical comparisons between groups at each time point were performed using independent samples t-tests for normally distributed data or Mann–Whitney *U*-tests for non-normally distributed data. *P < 0.05, ***P < 0.001 compared with Group C at the corresponding time point. Time points: T0, before anesthesia induction (baseline); T1, at endotracheal intubation; T2, 15 minutes after surgical incision; T3, 45 minutes after surgical incision; T4, 60 minutes after surgical incision; T5, during lung recruitment maneuver before surgery completion.

Abbreviations: MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; SV, stroke volume; SVV, stroke volume variation; SVRI, systemic vascular resistance index.

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Table 3 Comparison of Baseline and Perioperative Characteristics Between POCD and Non-POCD Patients

	POCD (n=29)	NPOCD (n=51)	*P*-value
Age, (y)	69 (68, 70)	67 (66, 68)	0.001
Male, n (%)	14 (56.0%)	35 (63.6%)	0.687
BMI, (kg/m^2)	21.17 ± 1.69	21.65 ± 1.57	0.217
Preoperative MMSE	29 (28, 30)	29 (28, 30)	0.534
ASA classification, n (%)			> 0.99
II	15 (60.0)	32 (58.2)	
II	10 (40.0)	23 (41.8)	
Education level, n (%)			0.243
Illiterates	9 (36.0)	19 (34.5)	
Primary school	12 (48.0)	18 (32.7)	
Junior high school or higher	4 (16.0)	18 (32.7)	
Preoperative comorbidities, n (%)			
Hypertension	10 (40.0)	14 (25.5)	0.292
Diabetes	10 (40.0)	12 (21.8)	0.156
Cardiovascular disease	8 (32.0)	16 (29.1)	> 0.99
Lesion laterality			0.322
Left	12 (48.0)	36 (65.5)	
Right	12 (48.0)	18 (32.7)	
Bilateral	1 (4.0)	1 (1.8)	
Lobectomy site			0.543
Upper	12 (48.0)	31 (56.4)	
Middle	3 (12.0)	3 (5.5)	
Lower	10 (40.0)	21 (38.2)	
Alcohol, n (%)	12 (48.0)	25 (45.5)	> 0.99
Smoking, n (%)	21 (84.0)	45 (81.8)	> 0.99
Preoperative SRT, (ms)	508.40 ± 52.82	481.33 ± 58.26	0.051
Preoperative CO, (L/min)	5.57 ± 0.39	5.48 ± 0.41	0.367
Preoperative hemoglobin, (g/L)	13.55 ± 1.07	13.31 ± 0.98	0.328
Duration of anesthesia, (min)	122.00 (115, 131)	120 (115, 135)	0.774
Propofol, (mg)	530.82 ± 131.72	566.45 ± 110.83	0.213
Sufentanil, (μg)	0 (0, 25)	25 (0, 25)	0.031
Remifentanil, (μg)	0 (0, 482.09)	377.21 (0, 498.36)	0.156
Norepinephrine, (μg)	0 (0, 34.97)	0 (0, 0)	0.278

(*Continued*)

Table 3 (Continued).

	POCD (n=29)	NPOCD (n=51)	*P*-value
Colloid, (mL)	360 (250, 400)	150 (0, 335)	0.009
Crystalloid (mL)	579.56 ± 100.05	609.09 ± 100.36	0.226
MAP-related indicators			
Mean, (mmHg)	83 (78.5, 102.2)	95.20 (81, 102.8)	0.327
Range,(mmHg)	37 (28, 42)	20 (13.5, 35.5)	0.002
HR-related indicators			
Mean, (bpm)	67.7 (64.7, 83.5)	81.20 (65.85, 84.15)	0.264
Range,(bpm)	22 (13, 28)	19 (14, 26)	0.905
CO-related indicators			
Mean,(L/min)	4.2 (3.6, 5.8)	5.3 (3.8, 5.9)	0.226
Range,(L/min)	2.7 (2.3, 2.9)	1.8 (1.3, 2.3)	<0.001
CI-related indicators			
Mean, ($L/min/m^2$)	3.60 (3.20, 5.20)	4.8 (3.4, 5.25)	0.244
Range, ($L/min/m^2$)	0.80 (0.69, 3.20)	2.65 (0.74, 3.25)	0.255
SV-related indicators			
Mean,(mL)	59.30 (55.30, 67.80)	65.5 (56.35, 69.5)	0.249
Range,(mL)	20 (10, 23)	11 (5, 20)	0.018
SVV-related indicators			
Mean,(%)	11.56 ± 1.27	11.33 ± 1.28	0.451
Range,(%)	5 (3, 5)	4 (3, 5)	0.022
SVRI-related indicators			
Mean,($dyn \cdot s \cdot cm^{-5} \cdot m^2$)	1379.5 (1254.7, 1862.2)	1746.3 (1323.2, 1890.5)	0.267
Range, ($dyn \cdot s \cdot cm^{-5} \cdot m^2$)	463 (368, 1051)	1056 (446, 1158)	0.018
VAS			
1 day after surgery	3 (2, 3)	3 (2, 3)	0.156
3 days after surgery	3 (2, 3)	2 (2, 3)	0.028
TimetoFirstAnalgesicReques, (min)	169.40 ± 10.19	176.07 ± 11.25	0.013

Notes: Data presented as mean ± standard deviation, median (interquartile range), or number of patients (percentage). POCD was defined as Montreal Cognitive Assessment (MoCA) score < 26 or Simple Reaction Time (SRT) exceeding 20% of preoperative baseline within 3 days after surgery. Variables with P < 0.1 were considered for inclusion in multivariate analysis.

Abbreviations: BMI, body mass index; MMSE, Mini-Mental State Examination; ASA, American Society of Anesthesiologists; SRT, Simple Reaction Time; CO, cardiac output; MAP, mean arterial pressure; HR, heart rate; CI, cardiac index; SV, stroke volume; SVV, stroke volume variation; SVRI, systemic vascular resistance index; VAS, Visual Analog Scale.

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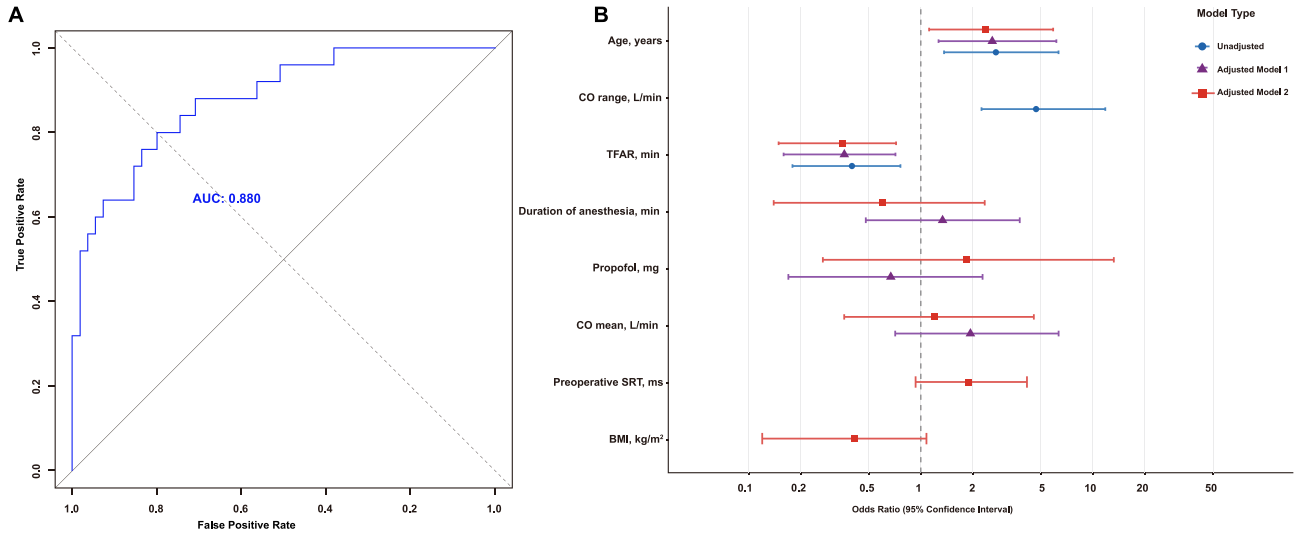

Figure 3 Receiver Operating Characteristic Curve and Forest Plot of Multivariate Logistic Regression for POCD.
Notes: (**A**) Receiver operating characteristic (ROC) curve of the multivariate logistic regression model for postoperative cognitive dysfunction (POCD) in elderly patients undergoing thoracoscopic surgery. The area under the curve (AUC) is displayed. (**B**) Forest plot depicting odds ratios (ORs) and 95% confidence intervals (CIs) for risk factors associated with POCD, as estimated by three logistic regression models: unadjusted, adjusted model.
Abbreviations: CO, cardiac output; TFAR. TimetoFirstAnalgesicReques.

sympathomimetic properties that activate noradrenergic and dopaminergic systems, enhancing myocardial contractility and heart rate, which helps maintain adequate tissue perfusion pressure.[26,27] However, we cannot entirely attribute the improved blood pressure stability to esketamine alone. As this study examines esketamine as an opioid-free anesthesia alternative, part of the reduced hemodynamic fluctuations can also be attributed to the reduction in opioid use. Opioids have been shown in numerous studies to exert suppressive effects on the cardiovascular system.[10]

Regarding postoperative analgesia, there were no significant differences in time to first analgesic request or postoperative VAS scores between groups, suggesting that esketamine-based OFA provides comparable analgesia to traditional opioid-based techniques. As an NMDA receptor antagonist, esketamine effectively blocks central sensitization and hyperalgesia, contributing to its analgesic properties.[28] However, propofol consumption was significantly higher in the

Table 4 Multivariate Logistic Regression Analyses of Risk Factors for Postoperative Cognitive Dysfunction (POCD)

	Unadjusted			Adjusted 1			Adjusted 2		
	P	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI
Age	0.008	2.738	(1.37, 6.30)	0.016	2.6	(1.27, 6.13)	0.036	2.39	(1.12, 5.86)
Co, range, (L/min)	< 0.001	4.673	(2.25, 11.82)	0.002	6.68	(2.36, 26.06)	< 0.001	9.49	(2.96, 43.11)
TFAR, min	0.01	0.399	(0.18, 0.76)	0.007	0.36	(0.16, 0.71)	0.008	0.35	(0.15, 0.72)
Duration of anesthesia, min	N/A	N/A	N/A	0.579	1.34	(0.48, 3.77)	0.474	0.6	(0.14, 2.36)
Propofol, mg	N/A	N/A	N/A	0.542	0.67	(0.17, 2.29)	0.527	1.84	(0.27, 13.22)
Co, mean, (L/min)	N/A	N/A	N/A	0.220	1.94	(0.71, 6.32)	0.773	1.2	(0.36, 4.54)
Preoperative SRT, (ms)	N/A	N/A	N/A	N/A	N/A	N/A	0.089	1.89	(0.93, 4.13)
BMI, (kg/m2)	N/A	N/A	N/A	N/A	N/A	N/A	0.097	0.41	(0.12, 1.08)

Notes: Adjusted model 1 (additionally adjusted for duration of anesthesia, propofol consumption, and mean cardiac output), and adjusted model 2 (further adjusted for preoperative simple reaction time and body mass index). Odds ratios (ORs) and 95% confidence intervals (CIs) are shown for each variable. N/A indicates variables not included in the respective model.
Abbreviations: OR, odds ratio; CI, confidence interval; CO, cardiac output; TFAR, time to first analgesic request; SRT, simple reaction time; BMI, body mass index.

OFA group, indicating that esketamine has limited propofol-sparing effects. To achieve adequate surgical anesthesia comparable to opioid-based techniques, higher doses of hypnotic agents may be required. Most studies currently compare the analgesic effects of esketamine based on postoperative analgesic consumption. However, we believe that the time to first request for analgesia can capture the dynamic time course of analgesic failure, revealing the critical moment when patients transition from effective pain relief to breakthrough pain under postoperative control conditions. This mechanistic result is directly related to esketamine's NMDA receptor antagonism and its impact on central sensitization.

Multiple studies have shown that NMDA receptor antagonists can improve postoperative cognitive function, particularly executive function and information processing speed. The significant improvement in SRT observed in this study supports the beneficial effects of esketamine on cognitive processing speed. This selective cognitive protection may result from several mechanisms: first, esketamine blocks NMDA receptors on GABAergic interneurons, leading to cortical disinhibition and indirectly promoting dopamine and norepinephrine release, which helps maintain psychomotor function in the basal ganglia-thalamus-cortex circuit.[26,29] Second, unlike opioids that cause generalized central nervous system depression, esketamine preserves reticular activating system function, maintaining cortical arousal and attention.[30,31] The domain-specific nature of this cognitive enhancement has been previously demonstrated across different clinical contexts. Lan et al[32] reported preferential improvements in psychomotor tasks and processing speed in adolescent patients with major depressive disorder treated with esketamine. Although their study focused on therapeutic rather than anesthetic applications, the consistent pattern of selective cognitive enhancement—favoring psychomotor function over global cognitive measures—aligns with our perioperative findings and suggests that esketamine's domain-specific neuroprotective effects are independent of clinical context. However, MoCA scores showed no significant improvement, and overall POCD incidence was not markedly reduced. This may be because POCD diagnosis requires comprehensive assessment across multiple cognitive domains (memory, attention, executive function, language),[33] while esketamine's neuroprotective effects appear to be domain-specific, primarily affecting cognitive processing speed.[34]

To identify factors affecting cognitive function, we performed multivariate logistic regression analysis. Results showed that hemodynamic fluctuations, pain management, and intraoperative drug selection were important factors influencing postoperative cognitive function. Intraoperative CO fluctuations were identified as an independent risk factor for POCD. Studies have shown that elderly patients often have impaired cerebral autoregulation, making them more vulnerable to hemodynamic changes.[35] Large CO fluctuations may lead to cerebral hypoperfusion or hyperperfusion, causing endothelial and microcirculatory damage that ultimately affects cognitive function.[36,37] This finding differs from most literature that emphasizes MAP maintenance.[38] While MAP and CO reflect different aspects of cerebral oxygenation, cerebral blood flow (CBF) depends on cerebral perfusion pressure (CPP = MAP - ICP). When CO decreases, even if MAP is maintained through compensatory vasoconstriction, absolute cerebral blood flow may still be reduced.[39] In thoracoscopic surgery, positional changes, one-lung ventilation, and intrathoracic pressure variations can affect intracranial pressure (ICP). Since ICP is not routinely monitored, MAP alone may not accurately reflect CPP.[40] In low-output states, compensatory peripheral vasoconstriction may maintain "normal" MAP while masking tissue hypoperfusion.

This study also showed that prolonged time to first analgesic request was protective for cognitive function, suggesting that effective pain management positively affects cognitive outcomes. Pain stress activates the hypothalamic-pituitary-adrenal axis, increasing cortisol levels and triggering inflammatory responses that impair cognitive function.[41,42] The causal relationship between adequate analgesia and cognitive preservation has been demonstrated experimentally, with animal studies showing that effective postoperative pain control significantly reduces neuroinflammatory responses and subsequently improves cognitive outcomes.[43]

Additionally, propofol consumption was higher in the OFA group. Previous studies have shown that propofol's effects on cognitive function are dose-dependent. At standard doses, propofol does not significantly affect early POCD, but higher doses can severely impair cognitive function.[44] Clinical studies suggest that an infusion rate of 10 $mg \cdot kg^{-1} \cdot h^{-1}$ is generally considered the upper limit for propofol dosing.[45] Exceeding this dose may excessively suppress GABA receptor-mediated neural activity, reducing cortical-subcortical pathway excitability and potentially impairing cerebral autoregulation, thereby increasing POCD risk.[46,47] Although propofol dose was higher in the OFA group, it remained

below the threshold dose, and its effect on postoperative cognitive function was minimal. Our regression analysis confirmed that propofol at standard doses is not a risk factor for POCD.

This study has several limitations. First, the relatively small sample size and single-center design may limit generalizability, and larger multicenter studies are needed for validation. Second, this study focused only on early postoperative cognitive changes. Future research could incorporate longer follow-up periods with more time points for a more comprehensive evaluation. Third, we did not directly monitor cerebral oxygen saturation, cerebral blood flow, or neurobiological markers, which limits understanding of underlying mechanisms.Future studies should consider more precise brain function monitoring techniques, such as near-infrared spectroscopy or functional magnetic resonance imaging, to better understand esketamine's neuroprotective mechanisms. Fourth, POCD definitions and assessment tools require further validation in larger samples to determine sensitivity and specificity. Additionally, hemodynamic parameters are influenced by numerous confounding factors, and we cannot exclude the potential residual confounding from unmeasured variables. Therefore, the findings of this study should be considered exploratory. Additionally, esketamine has not been approved for clinical use in some countries, and its cost is higher compared to opioid anesthetics.

Future research could explore opioid alternatives, using different combinations of analgesic agents and dosages, tailored to various surgical procedures and patient populations. This would further advance the (Enhanced Recovery After Surgery) ERAS concept and help develop personalized anesthesia protocols to enhance surgical safety and improve postoperative cognitive function. Additionally, future studies could adopt the more recent and precise nomenclature for cognitive decline following surgery, as defined by the 2018 standards for Postoperative Neurocognitive Disorder (PND), to ensure consistency in clinical research and clinical practice.

Conclusion

In summary, compared to conventional opioid-based anesthesia, esketamine-based opioid-free anesthesia did not significantly reduce the incidence of POCD in elderly patients undergoing thoracoscopic lung cancer surgery. However, the observed trend toward a decrease in POCD incidence is clinically meaningful. Additionally, esketamine-based opioid-free anesthesia provides equivalent analgesic efficacy to opioid-based anesthesia while promoting faster postoperative reaction function recovery and reducing hemodynamic fluctuations.

Data Sharing Statement

All anonymized individual participant data and other study-related documents will be made available to qualified researchers upon request. The specific data that will be shared include anonymized individual participant data, including demographic, clinical, and outcome measures, as well as other relevant study documents such as the study protocol and statistical analysis plan. Data will be available upon reasonable request from interested parties by contacting the corresponding author (wanglingfei.good@163.com). The data will be available starting from the online publication date of this article and will remain accessible for a period of 5 years thereafter.

Acknowledgment

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR.

The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (https://www.parinc.com).

Disclosure

The authors report no conflicts of interest in this work.

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