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The effects of esketamine on postoperative delirium in older patients with fragile brain function during the non-acute phase following lung cancer surgery: a randomized controlled trial

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Abstract

Background Esketamine has been used in the prevention of postoperative neurocognitive disorders in trauma surgery, gastrointestinal surgery and other fields due to its significant anti-inflammatory effect. However, its effect on postoperative delirium (POD) in older patients with fragile brain function after lung cancer remains unclear. This study aims to evaluate the effect of low-dose esketamine on POD in older patients with fragile brain function following lung cancer surgery during the perioperative period.

Methods One hundred and eight older patients undergoing thoracoscopic radical lung cancer surgery were randomly assigned to the control group or the esketamine group. All patients received standardized anesthesia without pre-anesthesia medication. Esketamine group received esketamine 0.25 mg/kg during anesthesia induction and esketamine 0.1 mg/kg/h during anesthesia maintenance for 30 min. Control group received an equal volume of normal saline during both induction and maintenance of anesthesia. The Confusion Assessment Method (CAM) was used to evaluate the incidence(%) of POD at 24 h and 72 h post-surgery. Serum concentration of interleukin-6 (IL-6) and calcium-binding protein β(S100β)(mean ± SD) were measured intravenously before and one day after surgery to assess inflammation. Additionally, intraoperative dosages of propofol, sufentanil, and remifentani(mean ± SD)were recorded, along with postoperative extubation time, SpO_2 after extubation (mean ± SD), incidence (%) of vertigo, remedial analgesia, rates of nausea and vomiting, duration of recovery room stay, and total hospital stay (mean ± SD).

Results Compared with the control group, the incidence of POD was significantly lower in the esketamine group at 24 h post-operation (3.8% vs. 15.1%, $P=0.046$),but no difference at 72 h post-operation (0% vs. 7.5%, $P=0.126$). No significant difference in serum concentration of IL-6 and S100β was observed between the two groups on the day before surgery ($P>0.05$). However, one day post-operation serum concentration of IL-6 and S100β in the esketamine group were significantly lower than those in the control group (5.14 ± 1.70 vs. 6.03 ± 2.13, $P=0.019$;380.08 ± 204.01

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vs. 479.32 ± 213.07, $P = 0.016$). The consumption of sufentanil in the esketamine group was lower than those in the control group (28.06 ± 3.76 vs. 29.85 ± 4.21, $P = 0.023$). Extubation time, the rate of remedial analgesia, and recovery room stay duration were shorter in the esketamine group compared to the control group(27.08 ± 8.46 vs. 30.4.±7.72, $P = 0.035$; 5.7% vs. 18.9%, $P = 0.038$; 58.96 ± 16.98 vs. 65.83 ± 15.31, $P = 0.031$). After extubation, SpO_2 levels were higher in the esketamine group (98.02 ± 1.65 vs. 97.21 ± 1.56, $P = 0.011$), and total hospital stay was shorter than in the control group (8.75 ± 2.83 vs. 11 ± 5.96, $P = 0.015$).There was no significant difference in the incidence of postoperative dizziness, nausea, and vomiting between the two groups.

Conclusion Esketamine may reduce the incidence of early postoperative delirium in older patients with fragile brain function undergoing lung cancer surgery during the non-acute phase, appear to inhibit inflammation levels, and be associated with shortening postoperative recovery time.

Trial registration Chictr.org.cn identifier ChiCTR2400083811 (Date of registry: 05/05/2024, prospectively registered).

Keywords Esketamine, Fragile brain function, Inflammation, Postoperative delirium

Background

With the acceleration of the global aging process, the number of older patients undergoing surgical treatment is increasing. As one of the common malignancies, surgical resection remains an important treatment method for lung cancer. However, due to the decline in physiological functions, especially the decreased reserve function of the nervous system in older patients, perioperative management faces many challenges, and the incidence of postoperative complications is significantly higher than that in younger patient groups.

Non-acute fragile brain function is relatively common among the older population, covering patients with a history of cerebral hemorrhage, cerebral infarction, transient ischemic attack (TIA), cerebrovascular stenosis, parkinson's disease (PD), chronic headache and dizziness, but without definite recurrence and corresponding clinical symptoms within the past three months [1]. Although these patients are in a relatively stable disease state, their brain's self-regulation and adaptation abilities have been impaired. When facing stress factors such as surgical trauma, the effects of anesthetic drugs, and postoperative changes in the internal environment, their brain function is more likely to be disordered, thereby potentially increasing the risk of postoperative neuropsychiatric complications, among which postoperative delirium(POD) is a relatively common and severe one. Studies have shown that the incidence of POD significantly increases in patients with fragile brain function during the non-acute phase following surgery [2, 3].

POD is an acute brain dysfunction syndrome, manifested as fluctuations in the state of consciousness, inattention, confused thinking, and changes in cognitive function. It not only prolongs the hospital stay and increases medical costs but is also closely related to an increased postoperative mortality rate and the occurrence of long-term cognitive impairment. Multiple studies have confirmed that factors such as a history of cerebrovascular disease and advanced age are independent risk factors for POD in older patients [4, 5]. Moreover, older patients who develop POD are three times more likely to progress to permanent cognitive impairment or dementia [6]. Therefore, the prevention and treatment of POD in older patients with fragile brain function urgently need attention. Currently, the prevention and treatment measures for POD in older patients with lung cancer are limited. Traditional drug interventions often have problems such as unsatisfactory efficacy or significant side effects. Therefore, it is urgent to find safer and more effective prevention and treatment methods.

As a new type of anesthetic drug, esketamine has unique pharmacological properties. It not only has anesthetic and analgesic effects but also can regulate the neurotransmitter system of the brain, especially affecting glutamatergic neurotransmission, which plays a crucial role in the maintenance and regulation of brain function. Neuroinflammation induced by surgical anesthesia has been identified as one of the main mechanisms behind postoperative cognitive dysfunction(POCD) [7, 8]. Some recent studies suggest that esketamine may have a protective effect on the stress injury of the brain during the perioperative period through its neuroprotective effect and regulation of the inflammatory response, thus potentially reducing the risk of POD.Research indicates that esketamine can effectively reduce the incidence of POCD in older patients [9, 10]. However, its specific role in the prevention and treatment of POD in older patients with non-acute fragile brain function undergoing lung cancer surgery remains unclear and requires further in-depth research and exploration. This is precisely the important starting point and significance of this study, aiming to fill the gap in this clinical research field and provide new ideas and methods for improving the prognosis of older patients undergoing lung cancer surgery.

Methods

Study design

This study is a prospective, randomized controlled trial and was approved by the Ethics Committee of the Affiliated Li Huili Hospital of Ningbo University (Approval No.: KY2023SL381-01). The trial was registered at www.chictr.org.cn (ChiCTR2400083811) before participants were enrolled. A total of 108 older patients who underwent general anesthesia thoracoscopic lung cancer radical surgery at the Affiliated Li Huili Hospital of Ningbo University from May 2024 to November 2024 were enrolled after the patient or family agreed and signed an informed consent form.

Inclusion criteria: older patients with frailty brain function, including the following conditions

History of chronic stroke; transient ischemic attack; imaging-confirmed brain infarction (including lacunar infarction); moderate to severe cerebral vascular stenosis; parkinson's disease; **Age**: 65–80 years old; **American Society of Anesthesiologists (ASA) physical status classification**: ASA class II-III; **Body mass index(BMI)**: 18–30 kg/m^2;**Expected surgery duration**: 2–5 h.

Exclusion criteria

Long-term use of psychotropic drugs; Alcohol or drug dependency; Severe cardiac, pulmonary, or other major organ dysfunction; Need for a second surgery; Preoperative Mini-Mental State Examination (MMSE) score < 23.

Exclusion from study

Major intraoperative events, such as significant blood loss or severe arrhythmias; Unplanned transfer to the intensive care unit (ICU).

Randomization and blinding

Random number table method was used to randomly assign the enrolled patients into two groups: the control group and the esketamine group, with 54 patients in each group (Fig. 1). Patients, anesthesiologists, surgeons, nurses, postoperative follow-up personnel, and statistical analysts were all blinded to the study.

General anesthesia and analgesia protocol

Upon arrival in the operating room, all patients were monitored for pulse oxygen saturation (SpO2), heart rate (HR), electrocardiogram (ECG), body temperature, and Nacrotrend (Narcotrend-Compact, Germany) index(NTi).Under sedation, radial artery puncture was

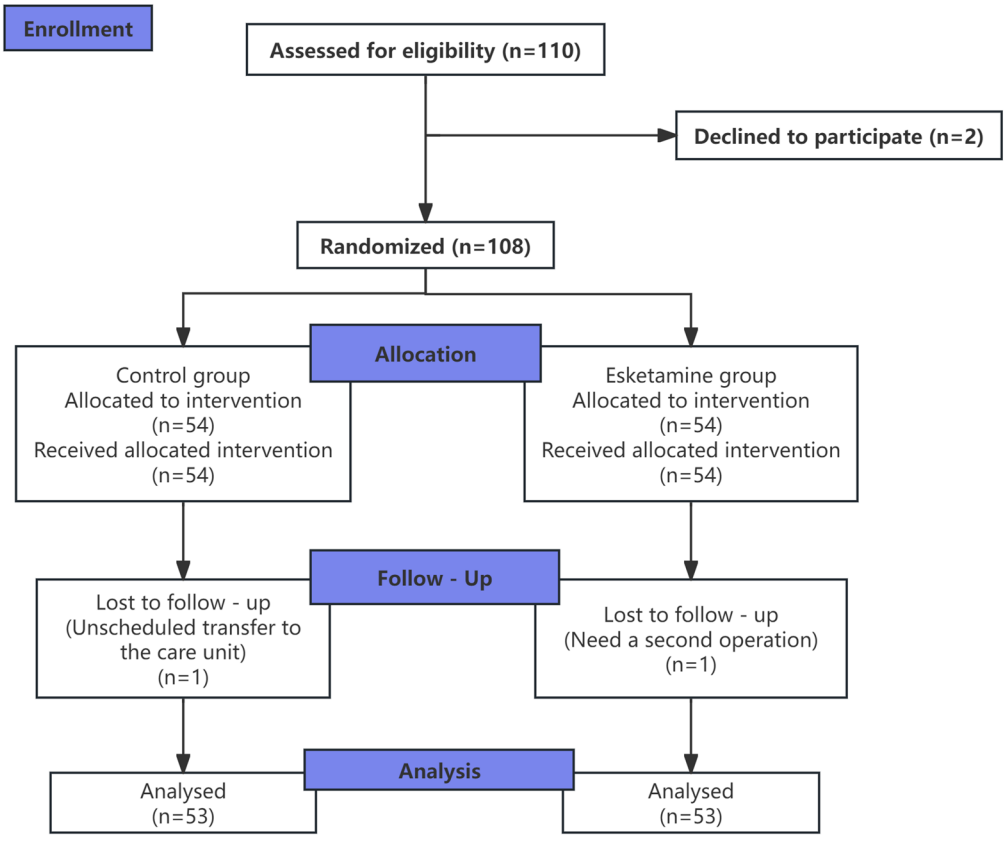

Fig. 1 Flow chart of the participants

performed to monitor invasive arterial blood pressure. Additionally, Pulse pressure variation (PPV) was monitored using a monitoring equipment (CARESCAPE Monitor B560, GE Healthcare, USA) to guide goal-directed fluid therapy. Prior to the trial, a selected group of anesthesiologists received training, which included drug protocols, intraoperative ventilation strategies, fluid management protocols, and postoperative analgesia, to minimize bias caused by individual operational differences. All patients received a standardized anesthesia protocol without preoperative medication.Midazolam (0.04–0.1 mg/kg), sufentanil (0.2–0.4 μg/kg), propofol (1–2 mg/kg), and rocuronium (0.6 mg/kg) were administered sequentially. After 2 min of mask ventilation with positive pressure and stabilization of circulation, endotracheal intubation was performed via oral route, and the endotracheal tube was connected to the anesthesia machine. End-tidal carbon dioxide waveform was monitored, and tube depth was confirmed by auscultation, followed by securing the tube.Tidal volume: 6–8 ml/kg, respiratory rate: 14–16 breaths/min, oxygen flow rate: 1.8 L/min, oxygen concentration:55%, maintain $PETCO_2$:35–45mmHg. Propofol was administered intravenously via pump at a rate of 50–150 μg/kg/min, and remifentanil at 0.1–0.4 μg/kg/min. Rocuronium 30 mg was administered intermittently to maintain muscle relaxation.

Patients in the esketamine group were injected esketamine (0.25 mg/kg) intravenously during induction, followed by continuous infusion at a rate of 0.1 mg/kg/h for 30 min.Patients in the control group received an equal volume of normal saline in place of esketamine during induction and maintenance of anesthesia.

Anesthesiologists adjusted the infusion rate of propofol and remifentanil based on NTi between 40 and 60. Blood pressure and heart rate were kept within 20% of baseline values. When mean arterial pressure (MAP) dropped more than 20% below baseline, small doses of norepinephrine or ephedrine were administered intravenously. If heart rate decreased by more than 20% from baseline, atropine 0.5 mg was administered intravenously.Goal-directed fluid therapy was used to maintain PPV ≤ 13%. Thirty minutes before the end of surgery, all patients received 50 mg of flurbiprofen axetil intravenously for analgesia. Under direct visualization by the surgeon, 20 ml of 0.25% ropivacaine was administered for paravertebral block.

Rescue analgesia was administered when the patient's Numerical Rating Scale (NRS) for pain was ≥ 4. In the recovery room, rescue analgesia was provided with intravenous sufentanil 5 μg. After returning to the ward, when the patient's NRS was ≥ 4, dezocine 5 mg was used for rescue analgesia.

Measurements

The primary outcome measure is the incidence of POD, diagnosed using the Confusion Assessment Method (CAM). Secondary outcome measures include the serum levels of interleukin-6 (IL-6) and S100β protein; intraoperative doses of propofol, sufentanil, and remifentanil; postoperative time to extubation, SpO_2 after extubation; recovery room stay duration; total hospital stay; the rate of rescue analgesia and the incidence of postoperative adverse events (dizziness, nausea, and vomiting).

The occurrence of POD at 24 h and 72 h after surgery was assessed using the CAM by an anesthesiologist who was specially trained and blinded to the trial group assignments.The CAM is a tool used for the rapid screening and diagnosis of acute delirium. It is a clinical assessment scale primarily aimed at identifying signs of delirium through the observation and evaluation of the patient's behavior.The diagnostic method of the CAM is based on the following four key features:1.Acute onset and fluctuating course 2.Attention deficits 3.Hallucinations or illusions 4.Disorganized thinking. If the patient meets the criteria of 1 and 2, plus either 3 or 4, a diagnosis of POD [11] can be made.

On the day before surgery and on the first day after surgery, 4 mL of venous blood was drawn from the patient and placed into a sterile tube and stand for 15 min, then centrifuged at 4000 rpm for 5 min. The serum was extracted and stored in a −80 °C biobank for subsequent analysis.The serum levels of IL-6 and S100β were measured by a professional biotechnology company(ADICON CLINICAL LABORATORIES, LTD.,Hangzhou, China) using the ELISA method.

In addition, intraoperative doses of propofol, sufentanil, and remifentanil; postoperative time to extubation; SpO_2 after extubation; recovery room stay duration; total hospital stay; the rate of rescue analgesia and the incidence of postoperative adverse events (dizziness, nausea, and vomiting). All clinical data collection personnel were unaware of the trial groupings.

Statistical analyses

Based on the reference literature [12–14], the expected incidence of POD in the esketamine group is 5%, while in the control group, it is 20%. The significance level (α) is set at 0.05, and the power (1-β) is set at 0.8. Using PASS 15 software(NCSS, LLC, Kaysville, Utah, USA), the required sample size for each group is calculated to be 50 participants. Accounting for an estimated dropout rate of 10%, 55 participants will be enrolled in each group, with a total of 110 participants across both groups.

Data analysis was conducted using SPSS 20.0 statistical software((IBM Corp., Armonk, New York, USA). The assessment of normality was carried out by means of the Kolmogorov-Smirnov test.Normally distributed

Table 1 Baseline and demographic characteristics

	Control group (*n* = 53)	Esketamine group (*n* = 53)	x^2/t	*P* Value
Gender			0.656	0.418
Male	32(60.4)	36(67.9)		
Female	21(39.6)	17(32.1)		
Age (years)	70.83 ± 3.791	70.00 ± 3.917	1.109	0.27
ASA			0.609	0.435
II	26(49.1)	22(41.5)		
III	27(50.9)	31(58.5)		
BMI(kg/m2)	23.54 ± 2.32	23.05 ± 3.02	0.948	0.345
MMSE Score(points)	27.6 ± 1.3	27.8 ± 1.7	−0.805	0.423

The data are represented as the mean ± SD or number (percentage)

ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination; n, number; SD, standard deviation; Continuous data were compared by Student's t-test; categorical data were compared using the chi-square (x^2) test

Table 2 Incidence of POD of the patients

	Control group (*n* = 53)	Esketamine group (*n* = 53)	x^2	*P* Value
POD within 24 h	8(15.1)	2(3.8)[a]	3.975	0.046
POD within 72 h	4(7.5)	0	2.338	0.126

The data are represented as a number (percentage); POD, postoperative delirium.Compared with the control group, [a]*P*<0.05. Data were compared using Fisher's exact test

continuous variables were expressed as mean ± standard deviation (± SD), and inter-group comparisons were performed using the independent two-sample t-test. Categorical variables were presented as percentages or proportions, and inter-group comparisons were made using the Chi-square test or Fisher's exact test, as appropriate. A *P*-value of < 0.05 was considered statistically significant.

Results

After screening, a total of 110 patients were recruited, of which two refused to participate in the trial. 108 patients were randomly assigned to either the control group or the esketamine group. One patient in the control group was excluded for unexpectedly transferred to the intensive care unit (ICU), one patient in the esketamine group required a second surgery and was excluded. Both patients were not included in further analysis. Ultimately, 53 patients from the control group or the esketamine group, completed the statistical analysis.The baseline and demographic characteristics were comparable between the two groups (Table 1).

Primary outcome

The incidence of POD within 24 h after surgery in the esketamine group was lower than that in the control group, and the difference was statistically significant ($P = 0.046$). There was no statistically significant difference in the incidence of POD at 72 h after surgery between the two groups ($P = 0.126$, Table 2).

Table 3 Intraoperative and postoperative conditions of the patients

	Control group (*n* = 53)	Esketamine group (*n* = 53)	x^2/t	*P* Value
Surgical Time	156.91 ± 41.71	166.13 ± 41.64	−1.140	0.257
Propofol Usage	1123.58 ± 359.03	1153.40 ± 330	−4.45	0.657
Sufentanil Usage	29.85 ± 4.21	28.06 ± 3.76[a]	2.31	0.023
Remifentanil Usage	1034.91 ± 364.08	952.83 ± 243.85	1.364	0.176
Extubation Time	30.43 ± 7.72	27.08 ± 8.46[a]	2.134	0.035
SPO_2 After Extubation	97.21 ± 1.56	98.02 ± 1.65[a]	−2.603	0.011
Recovery Room Stay	65.83 ± 15.31	58.96± 16.98[a]	2.187	0.031
Total Length of Hospital Stay postoperatively	11 ± 5.96	8.75 ± 2.83[a]	2.477	0.015
Rescue Analgesia	10(18.9)	3(5.7)[a]	4.296	0.038
Dizziness	5(9.4)	8(15.1)	0.789	0.374
PONV	7(13.2)	5(9.4)	0.376	0.54

The data are represented as the mean ± SD or number (percentage); PONV, postoperative nausea and vomiting.Compared with the control group, [a]*P*<0.05,Continuous data were compared by Student's t-test; categorical data were compared using the chi-square (χ2) test

Secondary outcomes

There were no statistically significant differences in surgical time, intraoperative propofol, and remifentanil consumption between the two groups ($P = 0.257$;$P = 0.657$;$P = 0.176$). The consumption of sufentanil in the esketamine group was lower than that the control group ($P = 0.023$). The esketamine group had shorter extubation time, recovery room stay time, and total hospital stay compared to the control group, and the difference was statistically significant ($P = 0.035$; $P = 0.031$; $P = 0.015$). The SpO_2 after extubation was higher in the esketamine group than in the control group($P = 0.011$). Compared with the control group, fewer patients in the esketamine group required rescue analgesia($P = 0.038$).There was no significant difference in the incidence of postoperative adverse reactions, such as dizziness, nausea, and vomiting, between the two groups ($P = 0.375$; $P = 0.54$, Table 3).

There was no significant difference in the serum concentrations of IL-6 and S100β between the two groups at baseline. ($P = 0.083$; $P = 0.742$). Moreover, the serum concentrations of IL-6 and S100β in both groups showed an upward trend compared to the baseline.Compared with the control group, the serum concentrations of IL-6 and S100β in the esketamine group were significantly decreased Post-op day 1 ($P = 0.019$; $P = 0.016$, Table 4).

Table 4 The serum concentrations of IL-1 and S100β of the patients

		Control group ($n=53$)	Esketamine group ($n=53$)	t	*P* Value
IL-6	Preoperative Day	4.39 ± 1.58	3.85 ± 1.61	1.750	0.083
	Postoperative Day 1	6.03 ± 2.13	5.14 ± 1.70[a]	2.386	0.019
S100β	Preoperative Day	282.92 ± 176.78	271.60 ± 176.18	0.330	0.742
	Postoperative Day 1	479.32 ± 213.07	380.08 ± 204.01[a]	2.449	0.016

The data are represented as the mean ± SD; Compared with the control group, [a]$P<0.05$;The data were compared by Student's t-test

Discussion

In this randomized controlled trial, we aimed to evaluate the effect of low-dose esketamine on POD in 108 older patients with fragile brain function undergoing thoracoscopic lung cancer surgery. Patients were randomly assigned to receive either esketamine (0.25 mg/kg during induction, 0.1 mg/kg/h for 30 min during maintenance) or normal saline. We found that the esketamine group had a significantly lower incidence of POD at 24 h postsurgery (3.8% vs. 15.1%, $P=0.046$) but not at 72 h. Serum levels of interleukin-6 and S100β, markers of inflammation, were significantly lower in the esketamine group on the first postoperative day. Additionally, esketamine use was associated with reduced sufentanil consumption, shorter extubation time, recovery room stay, and total hospital stay, as well as higher post-extubation SpO_2 and lower rescue analgesia rates, without increasing adverse events like dizziness or nausea. These findings highlight esketamine's potential to mitigate early POD, inhibit inflammation, and accelerate postoperative recovery in this vulnerable patient population.

Patients with fragile brain function are often complicated by a history of stroke, imaging-confirmed cerebral infarction, cerebral vascular stenosis, alzheimer's disease, parkinson's disease, and other conditions. These patients have weaker neural plasticity and recovery capabilities, making them more susceptible to the effects of surgical anesthesia, which leads to a higher incidence of POD. Therefore, this study focuses particularly on this special older population.

Research has shown that sub-anesthetic doses of esketamine may effectively reduce the incidence of delayed neurocognitive recovery and may improve early postoperative cognitive function in older patients undergoing gastrointestinal surgery [10]. Other studies have found that continuous intraoperative infusion of esketamine may help prevent sleep disorders after gynecological laparoscopic surgery, potentially reducing the risk of POD and cognitive dysfunction [15]. This study references the aforementioned literature and, based on preliminary trials, adopted an intravenous bolus dose of 0.25 mg/kg for esketamine and a continuous infusion at 0.1 mg/kg/h for 30 min during surgery.

POD is one of the common and serious complications in older patients, especially for those with fragile brain function, where the incidence and harm are more significant. In this study, compared with the control group, the incidence of POD in the esketamine group was significantly decreased 24 h after surgery, while there was no significant difference in the incidence of POD 72 h after surgery between the two groups. This suggests that a small dose of esketamine may have advantages in preventing early POD, though further research is needed to confirm this effect in broader patient populations. Esketamine may act on multiple receptors such as NMDA, γ-aminobutyric acid (GABA), cholinergic, opioid, and dopamine receptors [16], suggesting potential mechanisms for its effects. Its protective effect on the central nervous system may be a key factor. On the one hand, esketamine may regulate the neurotransmitter system, such as inhibiting the excessive release of excitatory amino acids and stabilizing the membrane potential of nerve cells, thereby reducing the damage and inflammatory response of nerve cells. Research has shown that esketamine may reduce neuroinflammation by regulating the activity of microglia and inhibiting their overactivation, thereby reducing damage to neurons and the release of inflammatory mediators [17], which helps to maintain the stability of brain function to a certain extent and reduce the risk of POD. On the other hand, the analgesic effect of esketamine may indirectly reduce the stress response caused by postoperative pain, and stress response is often an important factor in inducing POD.

Inflammatory response plays an important role in the occurrence and development of POD. Surgical trauma induces a systemic inflammatory response, and inflammatory cytokines can cross the blood-brain barrier and activate microglia, triggering neuroinflammation, which may induce POCD and POD [7] This study found that there was no statistically significant difference in the serum concentration of IL-6 and S100β between the two groups before surgery, but on the first postoperative day, both IL-6 and S100β in the esketamine group were significantly lower than those in the control group.This suggests that esketamine may effectively inhibit the excessive activation of postoperative inflammatory response, though further research is needed to confirm this potential effect. Research has shown [18] that esketamine significantly reduces inflammation levels by regulating the expression of multiple cytokines. As an important inflammatory mediator, IL-6 is released in large quantities after surgical trauma, triggering a systemic inflammatory response, which in turn affects brain function

and increases the incidence of delirium. S100β is a sensitive indicator reflecting brain damage and blood-brain barrier disruption. The decrease in its level indicates that esketamine may play a protective role in the microscopic structure of the brain, reducing brain damage caused by surgery and brain function disorders mediated by inflammation, which is consistent with the reduction in the incidence of POD, further revealing that the potential mechanism of esketamine in preventing POD may be closely related to inhibiting inflammatory response and reducing brain damage.

Research has found that esketamine can reduce the consumption of opioid medications during surgery [19]. The results of this study are consistent with previous reports. In this study, the use of sufentanil in the esketamine group and the rate of rescue analgesia in the recovery room were lower than those in the control group, and the esketamine group had a higher SpO_2 after extubation compared with the control group. The discrepancy in sufentanil usage between the two groups in this study may be attributed to two key mechanisms. First, during skin incision at the commencement of surgery, supplemental sufentanil (5–10 μg) was administered based on individual stress responses. Esketamine may antagonizes the N-methyl-D-aspartate (NMDA) receptor, possibly inhibits the activation and maintenance of the pain center, and also has a certain μ-receptor antagonistic effect, producing a strong analgesic effect mitigated stress reactions during incision in the esketamine group, thereby potentially reducing the need for sufentanil. Second, esketamine may alleviate postoperative hyperalgesia caused by remifentanil [20, 21], potentially reducing the need for rescue analgesia with sufentanil in the recovery room. Collectively, these factors contributed to lower overall perioperative sufentanil consumption in the esketamine group. In addition, esketamine may directly stimulate the respiratory center, thereby potentially counteracting the respiratory depression induced by opioids [22]. Research has also found that multi-component interventions can effectively reduce the incidence of POD [23], and multimodal analgesia is an important part of this approach. In this study, the esketamine group adopted a multimodal analgesia regimen with esketamine combined with non-steroidal anti-inflammatory drugs and paravertebral nerve block, which reduced the rate of rescue analgesia, decreased the consumption of opioids, and did not increase the incidence of adverse reactions. In terms of postoperative recovery indicators, the postoperative extubation time, recovery room stay time, and total hospital stay in the esketamine group were also shorter than those in the control group. These results suggest that esketamine may be beneficial to the early postoperative respiratory function recovery and rapid rehabilitation of patients and could potentially shorten the hospital stay by reducing postoperative pain and complications, reducing the economic burden on patients and the occupation of medical resources. Its rapid rehabilitation advantage may stem from its regulation of the overall stress response of the body and its effective control of postoperative pain and inflammation, thus creating a more favorable physiological and psychological state for patients' recovery.

However, this study also has certain limitations. Firstly, the sample size of this study is relatively limited. Although the results are statistically significant, larger-scale multicenter clinical trials are still needed to further verify its reliability and universality. Secondly, this study only observed the changes in short-term postoperative indicators, and the effects of esketamine on patients' long-term cognitive function and quality of life are still unclear. Future studies need to further extend the follow-up time to comprehensively evaluate its long-term efficacy and safety. In addition, "fragile brain function" is a conceptual framework rather than a reference to a specific metric, we did not develop a new score, this is a research gap. Future investigation could attempt to construct a integrated scoring systems that combine cognitive, imaging, and biological data to better characterize brain vulnerability. Such scores could enhance risk stratification and guide personalized perioperative care.

Conclusions

These findings suggest that esketamine may reduce the incidence of early postoperative delirium in older patients with fragile brain function undergoing lung cancer surgery during the non-acute phase, potentially inhibit inflammation levels, and be associated with shorter postoperative recovery time. However, these results require validation in larger, multicenter trials with longer follow-up to confirm their consistency and generalizability.

Abbreviations

ASA	America Society of Anesthesiologist
BMI	Body Mass Index
ECG	Electrocardiogram
HR	Heart Rate
SpO_2	Percutaneous Oxygen Saturation
MAP	Mean Arterial Pressure
PPV	Pulse Pressure Variation
CAM	Confusion Assessment Method
ELISA	Enzyme-Linked Immunosorbent Assay
ICU	Intensive Care Unit
IL-6	Interleukin-6
TIA	Transient Ischemic Attack
PD	Parkinson's Disease
POD	Postoperative Delirium
POCD	Postoperative Cognitive Dysfunction
PONV	Postoperative Nausea and Vomiting
SD	Standard Deviation
MMSE	Mini-Mental State Examination
NMDA	N-methyl-D-aspartic Acid
GABA	γ-aminobutyric acid

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Author contributions
Conceptualization, H.L and F.H; methodology, Z.X.; software, X.K.; validation, H.J. and Z.X.; formal analysis, F.H; investigation, H.J. and Z.X.; data curation, H.J; writing—original draft preparation, F.H; writing—review and editing, H.L.; visualization, F.H. All authors have read and agreed to the published version of the manuscript.

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Data availability
The data presented in this study are available on request from the corresponding author due to privacy and ethical restrictions.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of the Affiliated Li Huili Hospital of Ningbo University, China(KY2023SL381-01) and the protocol was registered at the Chinese Clinical Trial Registry (ChiCTR2400083811) (prospectively registered). The initial registration date was 05/05/2024. All procedures performed in this study involving human participants were in accordance with the Ethical Standards of the Institutional Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients signed written informed consent before surgery.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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