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# Esketamine and neurocognitive disorders in adult surgical patients: a meta-analysis

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## Abstract

**Background** Prior meta-analyses have established the potential of intravenous ketamine in safeguarding against neurocognitive impairment, but the efficacy of intravenous esketamine for the prevention of perioperative neurocognitive disorders (PND) remains uncertain. The primary aim of this meta-analysis was to conduct a comprehensive evaluation of the effects of esketamine on PND in adult surgical patients undergoing general anesthesia.

**Methods** We searched several electronic databases and clinical trial registries to find relevant trials. Randomized controlled trials of perioperative use of esketamine adjuvant were included in the analysis. The main outcome measured was the risk of postoperative delirium(POD) and postoperative cognitive dysfunction (POCD). Secondary outcomes included the assessment of postoperative cognitive status, pain scores (VAS/NRS), remifentanil consumption and the occurrence of postoperative nausea and vomiting (PONV).

**Results** Thirteen studies encompassing procedures such as abdominal, thoracoscopic lung, gastrointestinal, laparoscopic gynecological, spinal surgery, and modified radical mastectomy, were included in the analysis. A cohort comprising 1068 adult patients underwent general anesthesia, with 584 patients assigned to the esketamine group and 484 patients designated to the placebo group. The administration of general anesthesia was augmented by intravenous infusion of esketamine, and a comparative analysis was conducted in relation to alternative pharmacological interventions or a placebo. The application of esketamine during the perioperative period was observed to decrease the risk of POD ( RR 0.46; 95% CI: 0.32, 0.66, $p < 0.0001$, GRADE = High) and exhibited a protective influence on POCD (RR = 0.50; 95%CI: 0.30, 0.84, $p = 0.009$, $I^2 = 0\%$, GRADE = Moderate). Significant improvements were observed at 4, 24 and 48 h post-surgery when comparing esketamine to a placebo (4 h: SMD -0.78, 95% CI: -1.24, -0.32, $p = 0.0009$, $I^2 = 58\%$, GRADE = Low; 24 h: SMD -0.92, 95% CI: -1.40, -0.44, $p = 0.0002$, I2 = 86%, GRADE = Low; 48 h: SMD -0.9, 95% CI: -1.68, -0.12, $p = 0.02$, $I^2 = 89\%$, GRADE = Low), and intraoperative remifentanil consumption was significantly reduced in the esketamine group (SMD -0.56; 95%CI: − 0.86, − 0.27, $p = 0.0002$, $I^2 = 62\%$, GRADE = moderate). A notable reduction in the risk of PONV was observed in the esketamine group(RR = 0.64; 95%CI: 0.49, 0.84, $p = 0.001$, $I^2 = 0\%$, GRADE = High).

**Conclusion** The use of intravenous esketamine as an adjuvant in general anesthesia may represent a potentially beneficial strategy for reducing susceptibility to PND, with potential benefits for preventing POD and POCD. Furthermore, it can decrease intraoperative opioid consumption and alleviate postoperative pain intensity without increasing the incidence of PONV.

**Trial registration** This meta-analysis was registered on PROSPERO (CRD42023453714).

**Keywords** Esketamine, Perioperative neurocognitive disorders, Postoperative delirium, Meta-analysis

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## Introduction

Perioperative neurocognitive disorder (PND) poses a significant burden on a considerable proportion of surgical patients. In 2018, updated guidelines for naming cognitive alterations linked to anesthesia and surgery introduced the term PND to encompass various forms of cognitive decline observed during the perioperative period. These include acute postoperative delirium (POD), delayed neurocognitive recovery occurring within the initial 30-day recovery phase (dNCR), and postoperative neurocognitive dysfunction spanning from the expected recovery period of 30 days to 12 months (POCD) [1]. These various conditions have detrimental impacts on cognitive functions, including memory, sense of direction, and focus, following surgical procedures [1, 2]. PND not only prolongs the hospital stay but also elevates the likelihood of developing postoperative complications [3]. Moreover, there is a notable correlation between PND and the subsequent onset of dementia, along with a heightened risk of mortality in subsequent life phases [4]. As the aging of the population intensifies, surgeons and anesthesiologists confront a substantial challenge in effectively managing the pervasive consequences of PND. Therefore, exploring the pathogenesis and preventive measures of perioperative cognitive dysfunction has important clinical significance.

Esketamine, a non-competitive antagonist specific to the N-methyl-D-aspartate (NMDA) receptor, demonstrates an anesthetic potency twice as strong as racemic ketamine, while exhibiting a decreased likelihood of psychotropic adverse effects when administered at equipotent doses [5, 6]. In recent years, esketamine has attracted considerable attention from researchers in perioperative management due to its unique antidepressant properties [7]. In 2019, esketamine obtained approval from the U.S. Food and Drug Administration (FDA) for use in treating depression in the United States [8]. Moreover, mounting evidence suggests that S-ketamine demonstrates favorable safety and reliability when utilized as a part of multimodal analgesia protocol [9]. Research has further indicated that administering sub-anesthetic doses of esketamine during the perioperative phase can markedly decrease postoperative inflammatory indicators, highlighting its notable anti-inflammatory and neuroprotective characteristics [10]. Concurrently, the neuroprotective capabilities of ketamine and esketamine have attracted considerable interest in addressing both the prevention and management of PND.

Previous meta-analyses have explored the use of ketamine in addressing PND in adult surgical patients, demonstrating its protective effects against neurocognitive disorders [11, 12]. However, the current research findings regarding the specific impact of esketamine on PND remain inconsistent. Some studies have reported a positive preventive effect of esketamine on PND [10, 13, 14], while others have failed to observe significant effects [15]. This discrepancy may be attributed to various factors, including the type of surgery, sample size, administration route, dosage, and more. Consequently, it is imperative to conduct a meta-analysis to systematically assess the existing research evidence and clarify the influence of esketamine on perioperative cognitive dysfunction.

After conducting a literature search, it was found that studies primarily using PND as an indicator are relatively scarce. Most researchers continue to utilize the terms POCD and POD in their articles. For a comprehensive analysis of the included studies, this meta-analysis adopts the terms POCD and POD to describe the neurocognitive disorders that occur after surgery and anesthesia, aiming to provide valuable insights for future related research.

## Methods

### Literature retrieval and research selection

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our search was comprehensive, encompassing databases such as the Cochrane Library, PubMed, EMBASE, Web of Science, and EBSCO, covering all available records from their inception up to July 23, 2023. Subsequently, another search was conducted, concluding on October 3, 2024. Search queries, such as (S-ketamine OR esketamine) AND (perioperative neurocognitive disorders OR postoperative cognitive complications OR neurocognitive disorders OR postoperative delirium OR delirium), were employed. We conducted a We conducted a thorough examination of the reference lists of the full-text studies to uncover any additional trials deemed suitable for inclusion. Two authors, XL1 and XHX, independently screened the titles and abstracts of the retrieved articles.

### Inclusion and exclusion criteria

Inclusion criteria comprised: a. RCTs; b. administration of intravenous esketamine to participants; c. individuals aged 18 and above; d. surgeries induced by general anesthesia. Exclusion criteria encompassed: a. Clinical trials that remained unpublished; b. studies inaccessible in their entirety; c. case reports, conference abstracts, or review articles.

### Data extraction and quality assessment

XL[1], THZ and HMH, three researchers, independently collected the data and entered it into a customized Excel spreadsheet. The following information was extracted: the primary author's name, publication year, patient

count, age, gender, weight, American Society of Anesthesiologists (ASA) classification, surgical procedure type, specific techniques utilized in each group, and the outcome parameters measured. The primary findings of the study centered on the incidence of POD and POCD. Secondary outcomes encompassed the evaluation of postoperative cognitive status, pain intensity scores (measured using the Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS), ranging from 0-10), remifentanil consumption, and the incidence of postoperative nausea and vomiting (PONV). Previous research has established a correlation between the VAS and NRS, indicating their interchangeability [16]. To extrapolate data, we utilized WebPlotDigitizer, particularly for studies that presented information graphically without numerical values [17]. Furthermore, given the non-standard distribution of study results, we utilized an online calculator to convert data reported in the form of medians and interquartile ranges into mean ± standard deviation(SD) [18].

$XL^2$, HMH and JG, three investigators, independently reviewed the literature following the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions 5.0. The assessment of "risk of bias" involved the evaluation of concealment of allocations (indicative of selection bias), generation of random sequences (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), and incomplete outcome data (attrition bias). The level of certainty for the primary outcomes was assessed using GRADEpro software, taking into account various factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. In cases where potential disagreements emerged during the integration of research, data extraction, and assessment of literature quality, including issues pertaining to selective reporting (reporting bias) and other potential biases, discussions with a third assessor were conducted to resolve any discrepancies.

### Statistical analysis

The standardized mean difference (SMD) and mean difference (MD) for continuous data were evaluated, as well as the risk ratio (RR) for dichotomous data, all of which were accompanied by a 95% confidence interval (CI). For the statistical analysis of the aggregated data, Review Manager version 5.4.1 (RevMan, Cochrane Collaboration, 2020) was employed. When pooling data from the same measurement tool, SMD for datasets with distinct measurements were adopted. Statistical significance was determined by $P$ values below 0.05. Heterogeneity was assessed using I2 statistics, with a score exceeding 50% indicating substantial heterogeneity. A random effects model was employed to calculate the combined effect size when there was significant heterogeneity between studies ($P < 0.05$ or $I2 > 50$ %). Alternatively, a fixed effects model was utilized in cases of lower heterogeneity [19]. Subgroup analyses were performed, taking into account different administration periods (preoperative and intraoperative). To evaluate potential publication bias or small-study effects, funnel plots are constructed for outcomes with data from more than 10 studies. Additionally, sensitivity analyses are conducted to investigate the impact of individual studies on the overall results of the meta-analysis.

To avoid redundant sample size assessments in multi-arm studies, the count of participants is evenly distributed. In cases where there are two intervention groups and one control group, the number of patients in the control group is proportionally allocated to enable comparisons with each of the intervention groups. No adjustments are necessary for the mean and SD in cases of continuous outcomes. For dichotomous outcomes, the count of subjects experiencing the events is allocated proportionally [20].

## Results

### Eligible studies and the characteristics

Upon searching PubMed, EBSCO, Embase, Cochrane Library, and Web of Science, we identified a total of 2,588 relevant records (Fig. 1). A total of 1,261 duplicate articles were eliminated, resulting in 1,327 articles for initial screening. After reviewing their titles and abstracts, 1,284 records were excluded. The full texts of the remaining 43 reports were then carefully examined for eligibility. Of these, 28 reports were excluded due to various reasons: non-RCT design (2 reports), availability of only protocols (10 reports), inclusion of pediatric participants (15 reports), and absence of subjective PND data (3 reports). Ultimately, 13 studies met the inclusion criteria and were included in the meta-analysis.

Table 1 presents a summary of the characteristics of the 13 included studies [10, 13, 15, 21–30]. Table 2 summarizes the outcomes of 13 included studies, presenting a concise overview of their findings. These studies collectively included a total of 1,068 patients, with sample sizes varying between 39 and 140 patients. The age of the patients involved in the studies varied between 34 and 78 years. The majority of the studies (all 13 randomized controlled trials) recruited generally healthy patients (in terms of ASA physical status), while 7 out of the 13 studies included patients with ASA physical statuses III [13, 15, 21–23, 27, 28]. These patients underwent a variety of surgical procedures, including abdominal surgeries (such as colorectal surgery), cardiothoracic surgeries (such as lung resection and heart valve surgery), and non-thoracoabdominal surgeries (such as breast surgery and spinal

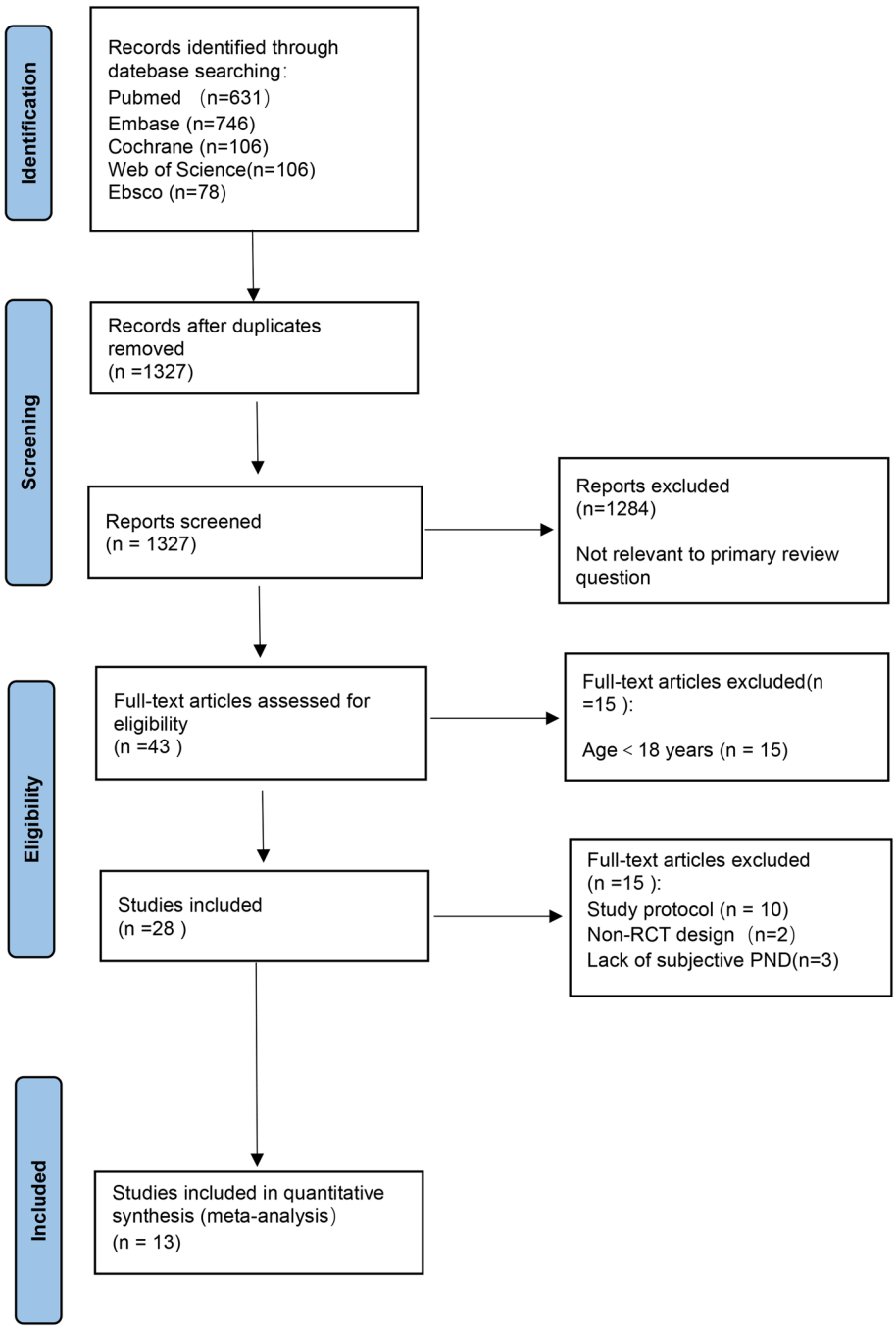


**Fig. 1** Flow diagram of study selection

surgery). Most of the studies administered esketamine during the surgical procedure, with a minority opting for preoperative or postoperative administration. The dosing protocols varied as well, with loading doses ranging from 0.125 mg/kg to 0.5 mg/kg and infusion rates between 0.1 mg/kg/h and 0.5 mg/kg/h. Only one study employed a postoperative dosing regimen for patient-controlled intravenous analgesia (PCIA), with a dose of 0.1 mg/kg. Postoperative cognitive status was adopted as the primary outcome, assessed using scales such as the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Confusion Assessment Method (CAM) or Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), Neuropsychological

**Table 1** Characteristics of the included trials

| No | First author | Year | Number (S/C) | Age,y (S/C) | Sex, male/ female (S/C) | BMI, kg/m$^2$ (S/C) | ASA I/II/III (S/C) | Surgical procedure | Primary anesthetic | Esketamine group | Control group |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Bornemann Cimenti | 2016 | 18/19/ 19 | 62.2 ± 9.8/ 58.4 ± 8.1/ 61.0 ± 12.4 | 9/9, 8/11, 8/11 | / | 1/5/12, 0/11/8, 3/8/8 | Open abdominal surgery | GA + PCIA (BA) | Low-dose group: 0.25 mg/kg IV bolus after induction of anesthesia + 0.125 mg/kg/h continuous IV infusion for 48 h Minimal-dose group:0.9% saline bolus after induction of anesthesia + 0.015 mg/kg/h continuous IV infusion for 48 h | Normal saline |
| 2 | Xiaodan Chen | 2022 | 37/37 | 57.14 ± 5.94/56.46 ± 6.07 | 19/17,17/20 | 22.81 ± 1.65/ 22.56 ± 1.46 | 13/21/3,15/18/4 | thoracoscopic radical lung cancer surgery | GA + TPVB + PCIA (BA) | 0.3 mg/kg IV during induction of anaesthesia + 0.2 mg/kg/h continuous IV infusion stopped 30 min before the end of surgery | / |
| 3 | Chao Han | 2023 | 33/34 | 70.60 ± 7.63/70.00 ± 6.25 | 18/15, 19/15 | 23.13 ± 3.42/ 23.21 ± 2.40 | / | gastrointestinal surgery | GA(TIVA) | 0.15 mg/kg IV before the initiation of surgery | normal saline |
| 4 | Tiantian Liu | 2023 | 20/19 | 46.25 ± 6.77/44.37 ± 9.74 | / | 22.68 ± 2.81/ 22.92 ± 2.60 | 3/17/0, 1/18/0 | laparoscopic gynecological surgery | GA | 0.125 mg/kg IV 30 min after the start of surgery | normal saline |
| No | First author | Year | Number (S/C) | Age,y (S/C) | Sex, m/f (S/C) | BMI,kg/m$^2$(S/C) | ASA I/II/III (S/C) | Surgical procedure | Primary anesthetic | Esketamine group | Control group |
| 5 | Jiamin Ma | 2023 | 31/31 | 69.45 ± 4.4/70.55 ± 4.2 | 24/7, 24/7 | 22.75 ± 2.76/ 23.64 ± 3.36 | 0/25/6, 0/24/7 | major abdominal surgery | GA | 0.25 mg/kg IV for induction + 0.125 mg/kg/h continuous IV infusion stopped 20 min before the end of surgery | normal saline |
| 6 | Junxia Zhang | 2023 | 40/40 | 52.6 ± 10.9/ 54.9 ± 9.9 | 0/40,0/40 | 23.3 (22.2–24.2), 23.7 (22.5–25.9) | 10/30/0, 8/32/0 | modified radical mastectomy | GA + PCIA (TIVA) | 0.5 mg/kg for induction + 0.5 mg/kg/h continuous IV infusion stopped 30 min before the end of surgery | sufentanil |

**Table 1** (continued)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | Jingjing Yuan | 2022 | 30/29/ 23 | 55 ± 11/ 56 ± 12/ 53 ± 12 | 9/21, 6/23, 7/16 | 23(22–25), 24(22–26), 24(21–25) | 20/10/0,19/10/0,13/10/0 | thoracoscopic lung surgery | GA + PCIA (TIVA) | Low-dose group: 0.15 mg/kg/h continuous IV infusion during surgery sub anesthesia-dose group: 0.25 mg/kg/h continuous IV infusion during surgery | normal saline |
| 8 | Wencai Tu | 2021 | 40/40 | 66.01 ± 5.4/65.27 ± 5.2 | 20/20, 22/18 | 22.39 ± 1.75, 22.16 ± 1.71 | / | Spinal Surgery | GA (TIVA) | 0.5 mg/kg for induction | sufentanil |
| 9 | Zhaojun Jing | 2024 | 44/43 | 69.2 ± 6.22/71.47 ± 6.2 | 30/14, 26/17 | 23.02 ± 2.19/23.54 ± 2.58 | 0/35/9, 0/34/9 | laparoscopic gastrointestinal tumor surgery | TAPB + GA + PCIA (TIVA) | 0.25 mg/kg IV after induction + 0.1 mg/kg/h continuous IV infusion stopped before the end of surgery | normal saline |
| No | First author | Year | Number (S/C) | Age,y (S/C) | Sex,m/f (S/C) | BMI,kg/m$^2$(S/C) | ASA I/II/III (S/C) | Surgical procedure | Primary anesthetic | Esketamine group | Control group |
| 10 | Tianyuan Luo | 2024 | 42/45/42 | 55.95 ± 9.1/55.2 ± 9.23/55.9 ± 10.6 | 19/23, 23/22, 22/20 | 23.48 ± 3.73/23.02 ± 3.31/23.59 ± 3 | 1/39/2,0/39/6,0/38/4 | non-cardiac thoracic surgery | GA + PCIA (TIVA) | Low-dose group: 0.2 mg/kg IV for induction High-dose group: 0.5 mg/kg IV for induction | normal saline |
| 11 | Yujia Wang | 2024 | 70/70 | 77.71 ± 7.57/76.9 ± 7.99 | 33/37, 38/32 | 26.01 ± 5.26/25.94 ± 4.18 | 10/35/25,12/32/26 | Thoracic surgery | GA | 0.5 mg/kg IV for induction | normal saline |
| 12 | Xinglong Xia | 2024 | 56/56 | 51.1 ± 9.9/ 51.6 ± 6.7 | 26/30, 26/30 | 22.9 ± 3.3/ 22.7 ± 4 | 0/14/42,0/13/43 | on-pump cardiac valve surgery | GA + PCIA (BA) | 0.5 mg/kg IV before anesthesia induction | normal saline |
| 13 | Jing Liu | 2024 | 30/30 | / | 21/9, 18/12 | / | / | / | GA + PCIA (TIVA) | 1 mg/kg for PCIA | normal saline |

**Table 2** Summary of outcomes: intraoperative esketamine administration compared with no esketamine

| No | First author | Primary outcomes | Outcome definition | Detection | Time frame | Secondary outcomes |
|---|---|---|---|---|---|---|
| 1 | Bornemann Cimenti | POD | ICDSC | I | 48 h after surgery | ①②③④ |
| 2 | Xiaodan Chen | POCD | MMSE | III | 1 day and 3 months after surgery | ②④⑤ |
| 3 | Chao Han | POCD | NPT | III | 7 days and 3 months after surgery | ②④⑤ |
| 4 | Tiantian Liu | POD and POCD | CAM-ICU and MMSE | II IV | 1 day after surgery | ④ |
| 5 | Jiamin Ma | POD and DNR | CAM-ICU and MMSE | II IV | CAM-ICU: 1, 2 and 3 days after surgery MMSE: 3 days after surgery | ②③④ |
| 6 | Junxia Zhang | POCD | MMSE | IV | 1 and 2 days after surgery | ①②③④⑤ |
| 7 | Jingjing Yuan | POD | - | - | PACU | ④⑤ |
| 8 | Wencai Tu | POCD | MoCA | IV | 24 h after surgery | ⑤ |
| 9 | Zhaojun Jing | POD | CAM | II | 1 and 3 days after surgery | ②③④⑤ |
| 10 | Tianyuan Luo | POD and POCD | CAM and MMSE | II IV | 1 and 3 days after surgery | ⑤ |
| 11 | Yujia Wang | POD and POCD | CAM and MoCA | II IV | CAM: after 7 days postoperatively MoCA: 7 days, 1 and 6 months after surgery | ② |
| 12 | Xinglong Xia | POD | CAM or CAM-ICU | II | Twice daily within 7 days after surgery | - |
| 13 | Jing Liu | POD | CAM | II | 1 and 3 days after surgery | ①②③⑤ |

*ICDSC* Intensive Care Delirium Screening Checklist, *CAM-ICU* Confusion Assessment Method for the ICU, *CAM* Confusion Assessment Method, *MMSE* Mini-mental state examination, *MoCA* Montreal Cognitive Assessment, *NPT* Neuropsychological Testing, *PONV* Postoperative nausea and vomiting

I: Delirium if ICDSC ≥ 4, II: CAM or CAM-ICU (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, (4) altered level of consciousness. A patient was considered to have delirium if criteria 1 and 2 are met, along with either criterion 3 or 4. III: a Z-score ≤ − 1.96 on at least 2 different tests, IV:MMSE or MoCA: a decline of ≥ 2 points from baseline

①Postoperative pain intensity at 4 h after surgery, ②Postoperative pain intensity at 24 h after surgery, ③Postoperative pain intensity at 48 h after surgery, ④remifentanil consumption; ⑤PONV

Test(NPT), and Intensive Care Delirium Screening Checklist (ICDSC). Follow-up durations ranged from 1 day to 6 month postoperatively. A total of 12 studies were conducted in China, while the remaining one study was conducted in Austria [21].

### Quality assessment of the selected studies

As depicted in Fig. 2, based on the Cochrane Collaboration tool, the combined risks of bias were categorized as either "low risk" or "unclear risk." A total of 6 studies [13, 23–25, 28, 30] are characterized by an overall low risk of bias, which signifies reliability in both methodology and outcomes. Seven studies [10, 15, 21, 22, 26, 27, 29] exhibit an unclear overall risk of bias, indicating that the reliability of their results cannot be adequately assessed based on the information provided. Notably, none of the studies demonstrate a high overall risk of bias.

Additionally, Table 3 provides an overview of the level of certainty associated with both primary and seondary outcomes. The quality of evidence for the incidence of POD, as assessed by the GRADE system, is considered high. In contrast, the quality of evidence for the incidence of POCD is deemed moderate. Regarding MMSE or MoCA scores, the quality of evidence is rated as low at 1 day post-surgery, moderate at 3 days, and moderate at both 1 and 3 months after surgery. For pain scores, the quality of evidence is low at 4, 24, and 48 h post-surgery, remaining consistent across these time points. The quality of evidence for remifentanil consumption is considered moderate. Lastly, the quality of evidence for the incidence of PONV is rated as high.

### Effect of interventions

#### *Effects of esketamine on POD*

POD was reported in 8 trials (Fig 3) [13, 21, 23–25, 27–29]. Outcome assessment was performed using CAM or CAM-ICU in 7 trials and according to ICDSC in 1 trial. In 1 trial reporting delirium as a continuous outcome (mean ICDSC score), we have obtained detailed data from a previous meta-analysis, (ICDSC≥4 yes/no) [27].

8 studies reported on the incidence of POD (Fig. 3) [13, 21, 23–25, 27–29]. Upon assessment, the results demonstrated a notably lower incidence of POD in the esketamine group compared to the control group [RR = 0.46; 95%CI: 0.32, 0.66, $p < 0.0001$, $I^2 = 0\%$, GRADE = High (Fig. 3)].

#### *Effects of esketamine on POCD*

Currently, the clinical diagnosis of POCD primarily relies on a combination of neuropsychological test batteries (NPT), MoCA, and MMSE [31–33]. By utilizing at least two different neuropsychological tests (employing the

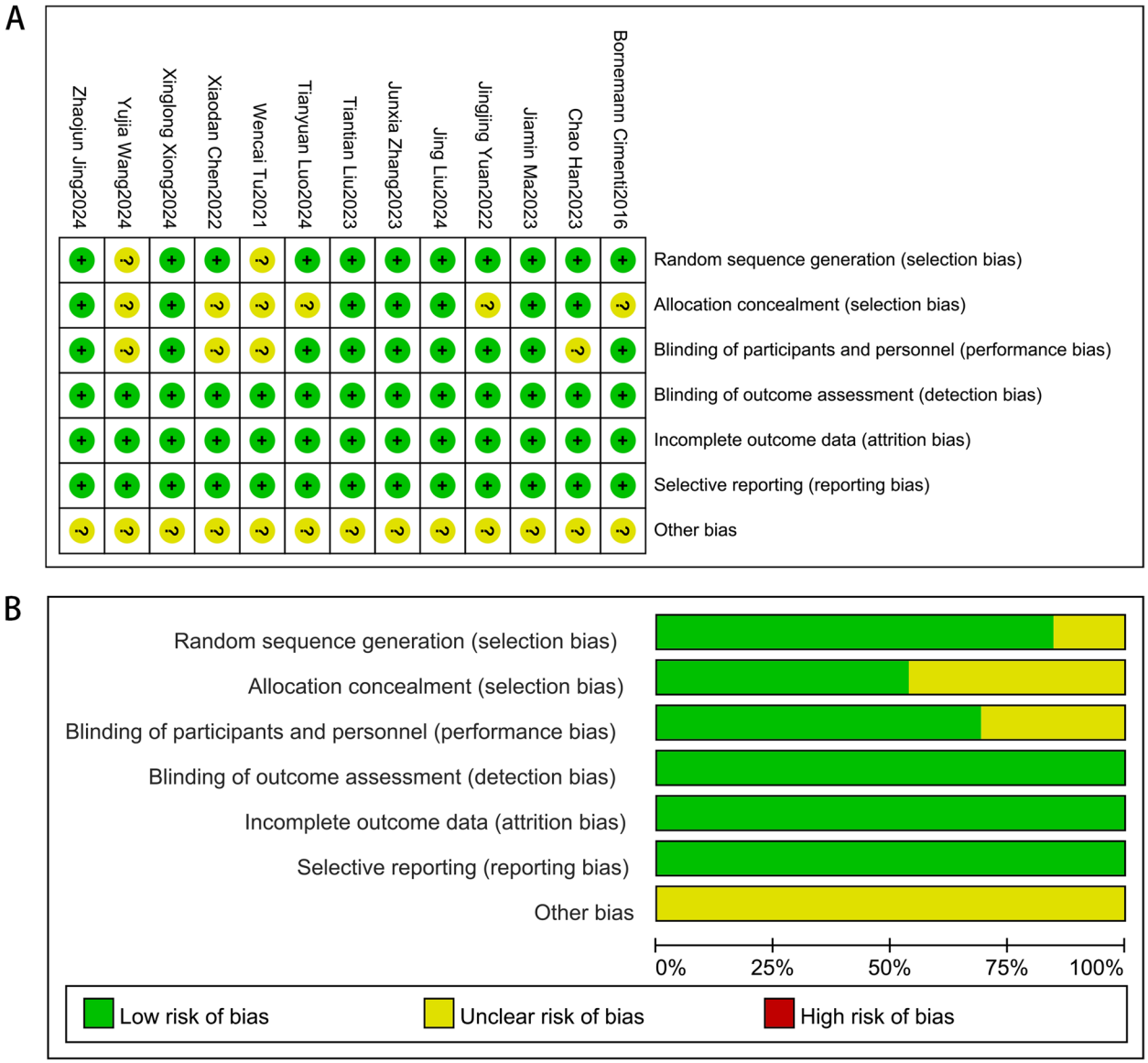


**Fig. 2** Bias Assessment. **A** Tabular overview presenting the review authors' evaluations on each risk of bias aspect for every study. **B** Graphical representation illustrating the distribution of review authors' assessments across studies for each risk of bias element. "+" denotes a low risk of bias; "?" indicates an unclear risk of bias; "–" signifies a high risk of bias

"Z-score method") or assessing with the MMSE score (where a postoperative score decrease of at least 2 points compared to the preoperative score is observed), clinicians can determine whether a patient has developed POCD. While NPT can be time-consuming and may face challenges in patient cooperation, MoCA is well-suited for screening patients with mild cognitive impairments. Conversely, MMSE demonstrates greater sensitivity to moderate to severe cognitive impairments.

POCD was reported in 3 trials (Fig. 4) [10, 22, 27]. When assessing the incidence of POCD, the results indicated that the esketamine group had a significantly lower occurrence compared to the control group [RR = 0.50; 95%CI: 0.30, 0.84, $p = 0.009$, $I^2 = 0\%$, GRADE = moderate (Fig. 4)].

### *MMSE*

In our meta-analysis, postoperative cognitive assessments were conducted using the MMSE in six trials (with MMSE score data unavailable for one of these trials), the MoCA in two trials, and the NPT in one trial. However, due to the limited number of trials utilizing NPT and

**Table 3** The GRADE level of certainty for main outcome

| Outcomes | No of studies | Quality assessment | | | | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Relative (95% CI) | Absolute (95% CI) | | |
| The incidence of POD | 9 | No serious | No serious | No serious | No serious | None | RR 0.46 (0.32,0.66) | 124 fewer per 1,000 (from 157 to 78 fewer) | ⊕⊕⊕⊕ High | Critical |
| The incidence of POCD | 3 | No serious | Serious[a] | No serious | No serious | None | RR 0.5 (0.30,0.84) | 121 fewer per 1,000 (from 169 to 39 fewer) | ⊕⊕⊕◯ Moderate | Critical |
| MMSE or MoCA score at 1 day after surgery | 5 | No serious | Serious[a] | No serious | Serious[b] | None | - | SMD 0.74 (-0.48, 1.95) | ⊕⊕◯◯ Low | Critical |
| MMSE or MoCA score at 3 day after surgery | 3 | No serious | Serious[a] | No serious | No serious | None | - | SMD 0.25 (-0.37, 0.88) | ⊕⊕⊕◯ Moderate | Criticalv |
| MMSE or MoCA score at 1 month after surgery | 2 | No serious | Serious[a] | No serious | No serious | None | - | SMD 0.47 (-0.22, 0.72) | ⊕⊕⊕◯ Moderate | Critical |
| MMSE or MoCA score at 3 months after surgery | 2 | No serious | Serious[a] | No serious | No serious | None | - | SMD 0.13 (-0.15, 0.42) | ⊕⊕⊕◯ Moderate | Critical |
| The incidence of PONV | 10 | No serious | No serious | No serious | Serious[b] | None | RR 0.64 (0.49,0.84) | 100 fewer per 1,000 (from 141 to 44 fewer) | ⊕⊕⊕⊕ High | Critical |
| Pain scores at 4 h after surgery | 3 | No serious | Serious[a] | No serious | Serious[b] | None | - | SMD -0.78 (-1.24, -0.32) | ⊕⊕◯◯ Low | Critical |
| Pain scores at 24 h after surgery | 7 | No serious | Serious[a] | No serious | Serious[b] | None | - | SMD -0.92 (-1.4, -0.44) | ⊕⊕◯◯ Low | Critical |
| Pain scores at 48 h after surgery | 4 | No serious | Serious[a] | No serious | Serious[b] | None | - | SMD -0.9 (-1.68, -0.12) | ⊕⊕◯◯ Low | Critical |
| Remifentanil consumption | 10 | No serious | No serious | No serious | Serious[b] | None | - | SMD -0.56 (-0.86, -0.27) | ⊕⊕⊕◯ Moderate | Critical |

*CI* Confidence interval, *MD* Mean difference, *RR* Risk ratio, *PND* Perioperative neurocognitive disorders, *MMSE* Mini-mental state examination, *PONV* Postoperative nausea and vomiting

[a] Quality was rated down for imprecision due to total population size is less than 400

[b] Quality was rated down for inconsistency because $I^2 > 50\%$

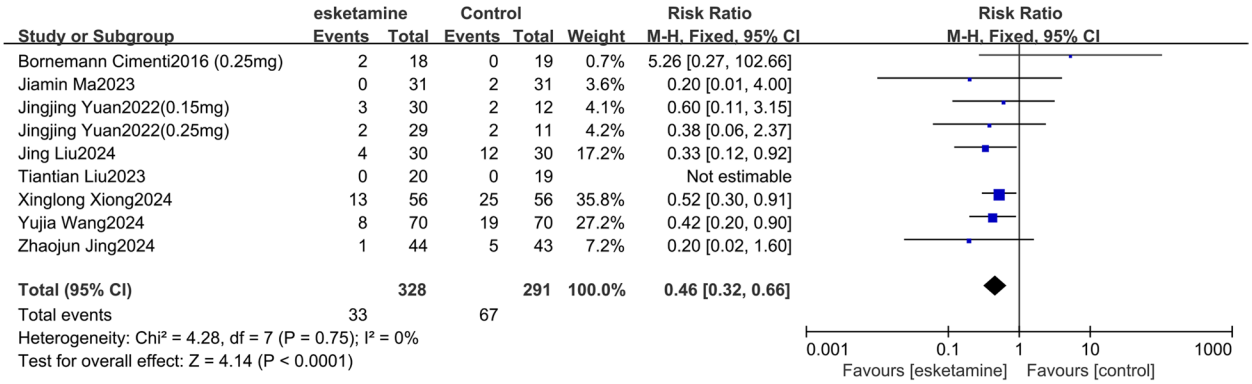


**Fig. 3** Forest plot of the incidence of postoperative delirium

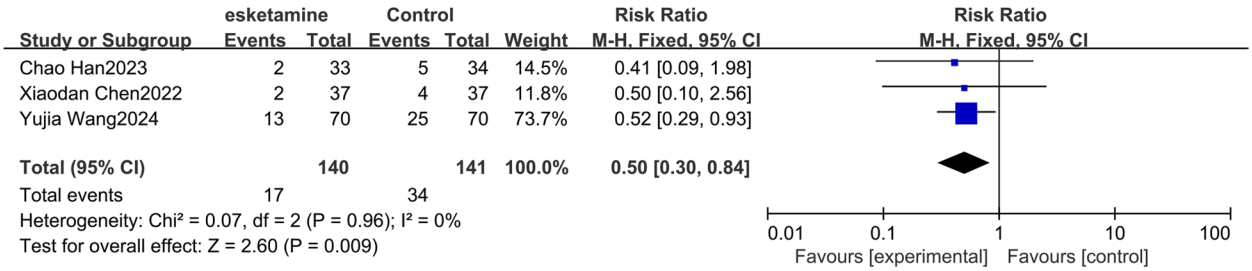


**Fig. 4** Forest plot of the incidence of postoperative cognitive dysfunction

the lack of specific scoring data, a statistically significant combination could not be formed. Therefore, we only analyzed studies that assessed postoperative cognition using the MMSE and MoCA.

No statistically significant differences in overall MMSE scores were observed between the two groups at 1 day, 3 days, and 3 months post-surgery [SMD 0.74, 95% CI: -0.48, 1.95, $p = 0.23$, I2 = 95% (Fig. 5A); SMD 0.25, 95% CI: -0.37, 0.88, $p = 0.43$, I2 = 0% (Fig. 5B) ; SMD 0.13, 95% CI: -0.15, 0.42, $p = 0.02$, I2 = 0% (Fig. 5C)]. A random effects model was employed for the analysis. However, a notable difference in the overall MMSE scores was observed between the two groups at 1 month post-surgery.

Pooling the postoperative cognitive score data at 1 day after surgery using a random-effects model revealed a significant difference between the two groups. Our meta-analysis evaluated the data at 3 day, 1 month and 3 months after surgery and determined that there was no significant heterogeneity among the studies at these time points ($I^2 < 50\%$). Consequently, we employed a fixed-effects model to calculate the pooled effect size.

### *Postoperative pain scores*

A meta-analysis evaluated pain scores at 4, 24, and 48 hours postoperatively and identified significant heterogeneity among studies at each of these time points ($I^2 > 50\%$). Consequently, we employed a random-effects model to calculate the pooled effect sizes. When comparing the S-ketamine group to the placebo group, there was a notable improvement in pain scores (VAS/NRS 0-10) at 4, 24, and 48 hours[4 h: SMD -0.78, 95% CI: -1.24, -0.32, $p = 0.0009$, $I^2 = 58\%$, GRADE = Low (* MERGEFORMAT Fig. 6A); 24 h: SMD -0.92, 95% CI: -1.40, -0.44, $p = 0.0002$, $I^2 = 86\%$, GRADE = Low (Fig. 6B) ; 48 h: SMD -0.9, 95% CI: -1.68, -0.12, $p = 0.02$, $I^2 = 89\%$, GRADE = Low (Fig. 6C)].

### *Remifentanil consumption*

Intraoperative remifentanil consumption was significantly reduced in the esketamine group [SMD -0.56; 95%CI: −0.86, −0.27, $p$=0.0002, $I^2$ = 62%, GRADE = Moderate (Fig. 7)]. A random effects model was used. The random effect model of data synthesis shows that there are significant differences between studies.

### *Incidence of PONV*

A fixed effects model for data synthesis revealed no significant difference among the studies. The esketamine group exhibited a significantly reduced incidence of

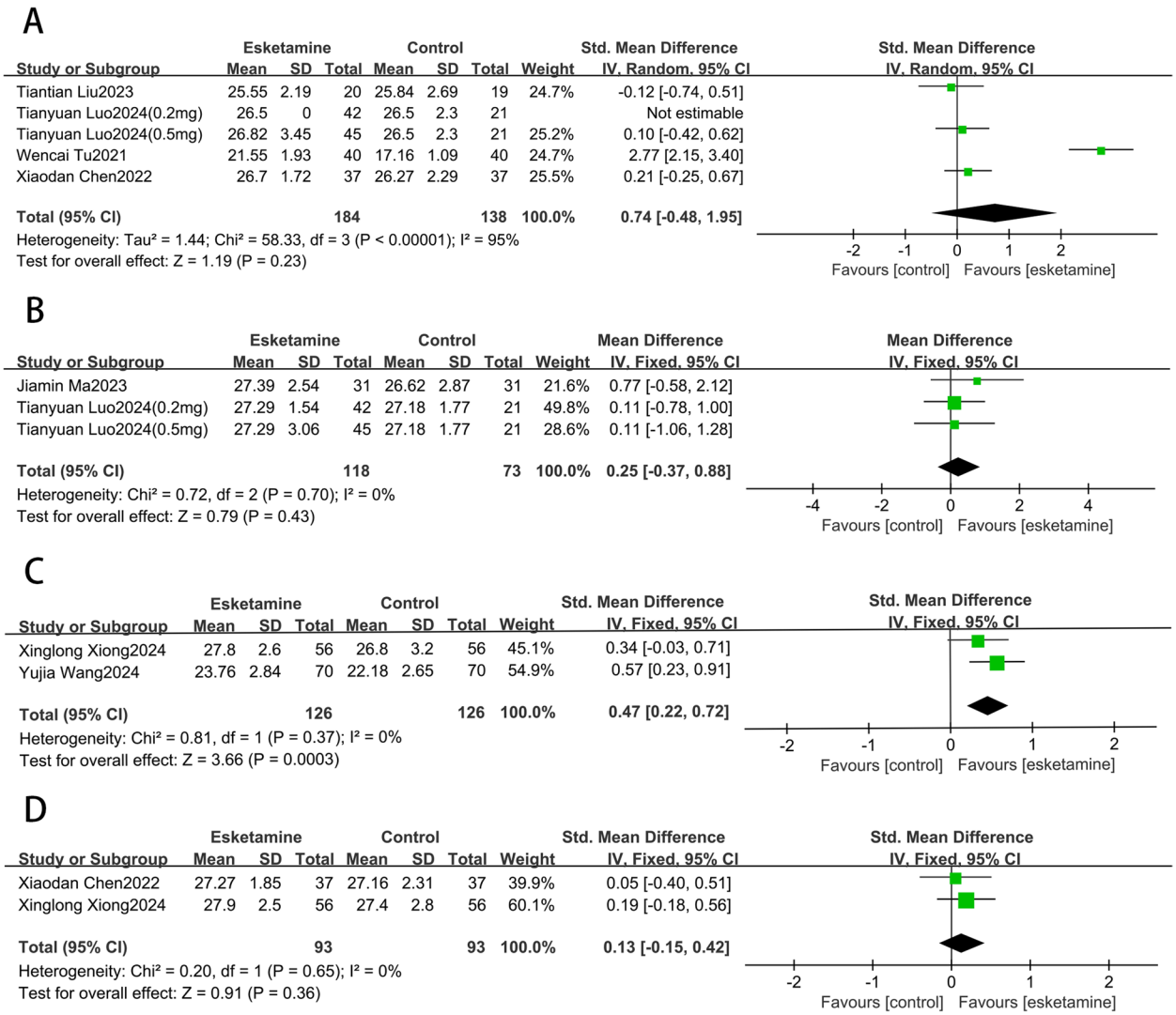


**Fig. 5** Forest plot of postoperative cognitive function assessed by MMSE or MoCA. **A** MMSE or MoCA scores at 1 day after surgery. **B** MMSE or MoCA scores at 3 days after surgery. **C** MMSE or MoCA scores at 1 month after surgery. **D** MMSE or MoCA scores at 3 months after surgery

PONV [RR = 0.64; 95%CI: 0.49, 0.84, $p = 0.001$, $I^2 = 0\%$, GRADE = High (Fig. 8)].

### Subgroup analysis

Our intention to examine subgroups for investigating the impact of these factors on neurocognitive outcomes was hindered by the limited number of trials and the heterogeneous nature of the data, preventing any meaningful statistical combination.

### Sensitivity analysis and publication bias

Sensitivity analyses were performed by systematically omitting one study at each iteration to identify the potential sources of heterogeneity. Notably, the exclusion of the study authored by Junxia Zhang [30] significantly impacted the heterogeneity of the pooled results related to the consumption of remifentanil, indicating that this particular study was a major determinant in identifying the heterogeneity. Similarly, the exclusion of the study by Xiaodan Chen [22] markedly affected the heterogeneity of the collective outcomes associated with the 24-h postoperative pain score, suggesting that this specific study was a primary factor in determining the heterogeneity. While the exclusion of the study authored by Tucai Wen [26] did not significantly alter the pooled results related to MMSE or MoCA scores one day after surgery, it notably reduced the heterogeneity associated with these results.

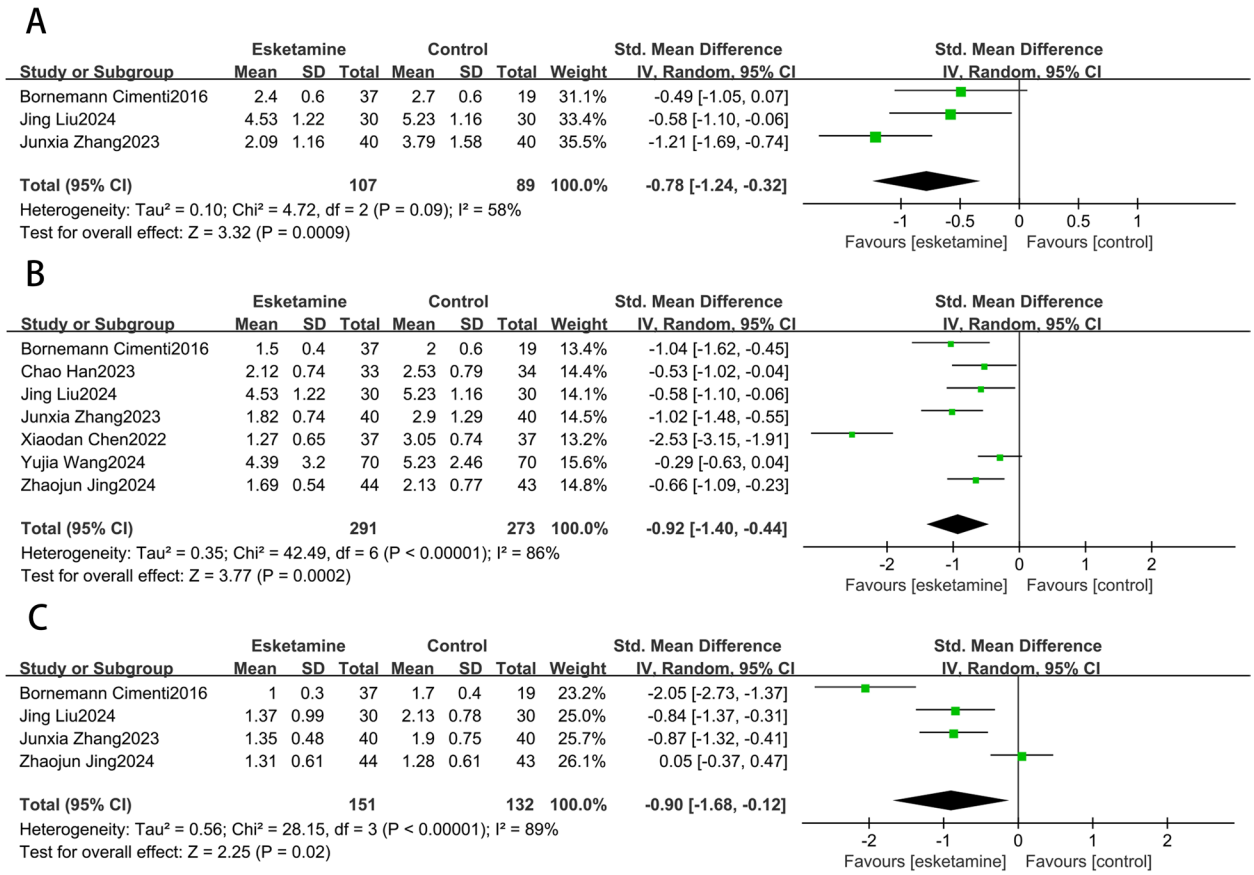


**Fig. 6** Forest plot of postoperative pain scores after surgery. **A** Pain scores at 4 h after surgery. **B** Pain scores at 24 h after surgery. **C** Pain scores at 48 h after surgery

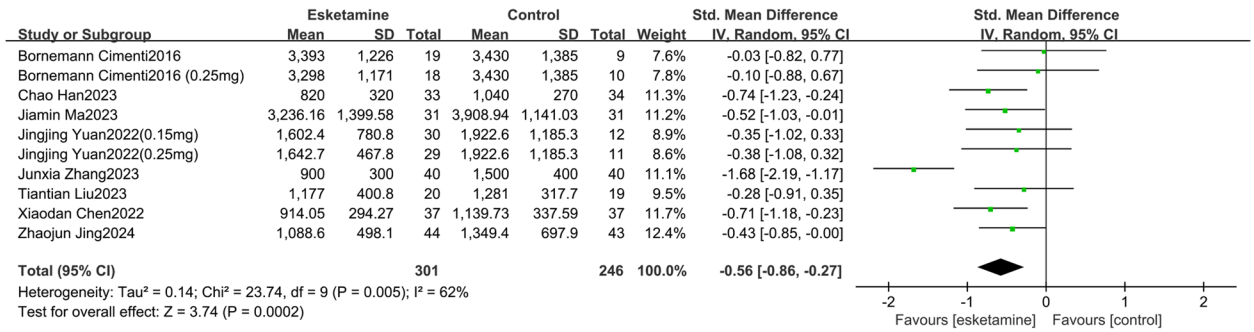


**Fig. 7** Forest plot of remifentanil consumption

No evident publication bias was detected upon examination of the funnel plots (see Supplementary Fig. 1 and Supplementary Fig. 2).

## Discussion

In this meta-analysis, we systematically evaluated the impact of low-dose esketamine on PND in adult patients undergoing general anesthesia. This meta analysis employed three recognized delirium assessment tools: CAM, CAM-ICU, or ICDSC, alongside three established cognitive assessment methods: MMSE, MoCA, or NPT, for postoperative neurocognitive evaluations. Convincing evidence has been provided herein, demonstrating the favorable impact of esketamine on reducing the incidence of POD within one week and POCD one month after surgery,

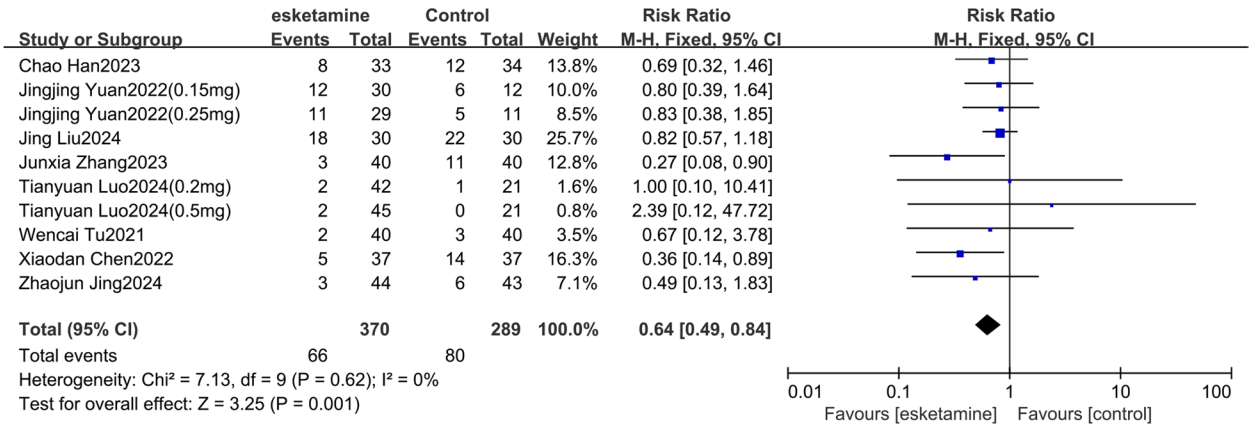


**Fig. 8** Forest plot of the incidence of PONV

collectively termed as PND, among adult surgical patients undergoing general anesthesia. Furthermore, this aligns with the forest plot of MMSE scores one month postoperatively, which shows higher MMSE scores in the esketamine group compared to the placebo group. This meta-analysis also revealed that the use of esketamine was associated with a reduction in postoperative pain intensity at 4, 24, and 48 h after surgical intervention, despite the presence of considerable heterogeneity. Notably, perioperative administration of esketamine significantly prolonged the duration of analgesic efficacy. Furthermore, it was found that the application of perioperative esketamine could reduce the dosage of opioids such as remifentanil administered intraoperatively. It is worth mentioning that intravenous administration of esketamine during the perioperative period does not increase the likelihood of PONV.

POD and POCD are common central nervous system complications following surgical anesthesia, and in 2018, they were renamed as components of PND [1]. Despite extensive researches on PND, the specific underlying mechanisms remain inconclusive. Currently, it is believed that neuroinflammation, neuroendocrine dysregulation, oxidative stress, disruption of blood–brain barrier integrity, synaptic dysfunction, mitochondrial dysfunction, neuronal apoptosis, ferroptosis and pyroptosis, as well as certain preoperative complications (such as Alzheimer's disease and senile dementia) and postoperative complications (such as sleep disorders, pain, and opioid use) are closely associated with the occurrence of PND [34].

Esketamine, a non-competitive antagonist of the NMDA receptor [10], has shown potential in recent basic research and clinical studies to reduce the incidence of PND. Due to their anti-inflammatory and neuroprotective effects, ketamine and esketamine have emerged as potential drugs for preventing PND. However, the impact of esketamine on PND remains controversial. Therefore, we conducted this meta-analysis to comprehensively assess the effect of esketamine on PND in surgical patients undergoing general anesthesia.

Esketamine, also referred to as "S-ketamine," represents the D-isomer of Ketamine. ketamine could be implicated in diverse psychiatric manifestations, potentially stemming from the overstimulation of NMDA receptor [35]. Despite some research efforts, the effect of ketamine on POD remains uncertain, as the ketamine group showed an increased incidence of hallucinations [11, 12]. Previous studies have explored the use of ketamine in addressing PND in adult surgical patients, demonstrating its protective effects against neurocognitive disorders [36, 37]. However, these findings stand in stark contrast to a recent meta-analysis by Viderman et al. [11], which found no statistically significant difference in the incidence of POD between the ketamine group and the control group. This discrepancy may stem from differences in the surgical populations studied. The meta-analysis conducted by Hovaguimian et al. [12] yielded some differing findings compared to their results. Although they did not find that ketamine could reduce the incidence of POD, they did uncover a protective effect of ketamine on POCD in surgical patients undergoing general anesthesia. While no comprehensive meta-analysis has been undertaken to date regarding esketamine, its pharmacological effects exhibit comparability to those of ketamine, thereby rendering it a pertinent reference for the purpose of juxtaposition with our study findings.

Simultaneously, esketamine has also been demonstrated to exhibit neuroprotective effects, as evidenced by increased autophagy and decreased oxidative stress [38, 39]. Furthermore, its administration has been observed to enhance the anti-inflammatory function of

the immune system while concurrently mitigating cognitive impairment [40]. These assertions are substantiated by clinical investigations that illustrate the effectiveness of esketamine in enhancing postoperative cognition, mitigating inflammatory factors such as interleukin-6 (IL-6), and confirming its anti-inflammatory and neuroprotective attributes [10]. These findings align with our meta-analysis results, indicating that esketamine can significantly reduce the incidence of POD and improve POCD in adult patients undergoing surgery, further suggesting its potential ne uroprotective effects.

However, it is noteworthy to mention a meta-analysis that contradicted the findings of a clinical study, which indicated that intranasal esketamine adversely affected cognitive performance in healthy individuals, indicating an associated decline in cognitive function [41]. This contradiction stands in stark contrast to the neuroprotective evidence observed in pediatric populations, where esketamine has been found to decrease the likelihood of emergence agitation in children undergoing tonsillectomy [42].

A recently published meta-analysis [9] has demonstrated that intravenous esketamine, as an adjunct to general anesthesia, can effectively reduce pain intensity and opioid requirements in the short term after surgery, aligning with the findings of our meta-analysis. Although the pain relief effect is transient, its significance in the early postoperative period, particularly within the first 48 h, is noteworthy for promoting early mobility and enhancing patient comfort. Our findings are consistent with those of Jing et al. [23], as there were fewer patients requiring additional analgesics in the esketamine group and a reduction in intraoperative opioid consumption, such as remifentanil.

It is well-established that PONV are among the most common complications following general anesthesia. Our research findings resonate with those elucidated by Brinck et al., emphasizing the correlation between ketamine administration and a reduction in the incidence of PONV. Some studies have shown that esketamine or S-ketamine does not induce PONV. However, Wang et al. [9] found that varying doses of esketamine did not decrease the occurrence of PONV. The research conducted by Yu Qi et al. [43] revealed that intravenous administration of S-ketamine during anesthesia induction, intraoperative maintenance, and postoperative analgesia can effectively reduce the incidence of PONV in patients undergoing thoracic surgery by decreasing opioid consumption. In our study, the results of our meta-analysis indicate that perioperative intravenous esketamine does not increase the likelihood of PONV. We attribute the decreased incidence of PONV in the S-ketamine group to two significant factors. This may be associated with the reduction in perioperative opioid consumption and the stability of hemodynamics during anesthesia [44]. Potential mechanisms may involve decreased mean arterial pressure during surgery, leading to intermittent hypoperfusion of the brainstem and vestibular system. This, in turn, may trigger the release of cytokines, histamine, and serotonin. These substances can stimulate histamine and serotonin receptors in the chemoreceptor trigger zone, potentially causing PONV [43]. Our findings resonate with those elucidated by Brinck et al. [45], underscoring an association between ketamine administration and a diminished occurrence of PONV.

As of now, this represents the first meta-analysis dedicated to assessing the efficacy and safety of esketamine in relation to neurocognitive outcomes among surgical patients. Following a meticulous review of a diverse range of research-related articles, incorporating stringent criteria for inclusion and exclusion, we utilized established methodologies, including the GRADE and Cochrane criteria, to evaluate the overall level of confidence and the risk of bias. A sensitivity analysis was performed to pinpoint the source of heterogeneity.

Nevertheless, we acknowledge several limitations that require acknowledgment. Firstly, the pronounced heterogeneity in certain analyses may be ascribed to varied study designs, diverse surgical techniques, and differences in esketamine administration methods, dosages, and duration. Additional influencing factors could also impact the outcomes. Despite our comprehensive search across multiple databases, there remains a possibility that relevant experiments on esketamine use, which we intend to examine, may have gone unnoticed. Secondly, the included studies were only from some countries and the limited size of the study sample could potentially result in an overestimation of the therapeutic impact of esketamine on neuroprotection. Thirdly, our assessment revealed that the quality of the evidence was not high. A comprehensive analysis of all available data on this crucial issue was conducted, indicating that the use of esketamine for preventing neurological issues was supported by low-quality evidence. Finally, our meta-analysis encompassed patients aged between 40 and 80, with an ASA grade I to III, and a body mass index ranging from 18 to 30. While these inclusion criteria allowed for the observation of esketamine efficacy within this specific patient cohort, they may not entirely capture the neuroprotective effectiveness of esketamine in other populations.

It is recommended that forthcoming research endeavors explore the administration of diverse doses of esketamine within heterogeneous patient populations. Through such endeavors, we aim to acquire a thorough comprehension of the efficacy of esketamine and establish recommended safe dosage parameters tailored to specific demographic groups. Despite inherent limitations, our

meta-analysis contributes substantive insights into the merits of employing esketamine as an adjunct to perioperative general anesthesia for the prevention of PND. There is an imperative need to conduct additional mechanistic studies and expansive clinical trials to enhance the precision of perioperative anesthesia protocols, elucidate the neuroprotective attributes of esketamine, and extend its applicability to morea broader array of patients in varied surgical contexts.

## Conclusion

In summary, our meta-analysis indicates that perioperative administration of esketamine can effectively reduce the risk of POD within one week and POCD one month after surgery. The underlying mechanisms may be associated with esketamine's anti-neuroinflammatory and neuroprotective effects. Additionally, the use of esketamine can reduce perioperative opioid consumption and decrease postoperative pain intensity without increasing the incidence of PONV.

### Abbreviations

| | |
|---|---|
| PND | Perioperative neurocognitive disorders |
| POD | Postoperative delirium |
| POCD | Postoperative Cognitive Dysfunction |
| NMDA | N-methyl-D-aspartate |
| NMDAR | N-methyl-D-aspartic acid receptor |
| RCTs | Randomized controlled trials |
| ASA | American Society of Anesthesiologists |
| VAS | Visual Analogue Scale |
| NRS | Numerical Rating Scale |
| PONV | Postoperative nausea and vomiting |
| SMD | Standardized mean difference |
| MD | Mean difference |
| RR | Risk ratio |
| CI | Confidence Interval |
| MoCA | Montreal Cognitive Assessment |
| MMSE | Mini-Mental State Examination |
| TPVB | Thoracic paravertebral block |
| TAPB | Transversus abdominis plane block |
| PCIA | Patient-controlled intravenous analgesia |
| ICDSC | Intensive Care Delirium Screening Checklist |
| NPT | Neuropsychological Testing |
| CAM | Confusion Assessment Method |

## Supplementary Information

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Supplementary Material 1.

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### Authors' contributions

XL1: Roles/Writing—original draft, Writing—review & editing, Data curation; XL2: Methodology, Supervision, Validation; HMH: Resources, Software, Validation, Data curation; XHX: Investigation, Data curation, Project administration; THZ: Visualization, Data curation, Formal analysis; JG: Formal analysis, Conceptualization, Validation, Funding acquisition. All authors reviewed the manuscript.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

Approval from an ethics committee and consent to participate were not required, as the analysis solely involved published research data.

### Consent for publication

Not available.

### Competing interests

The authors declare no competing interests.

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## Publisher's Note