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Efficacy and safety of esketamine in preventing perioperative neurocognitive disorders: a meta-analysis of randomized controlled studies

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Abstract

Background Perioperative neurocognitive disorders (POND) are common in older adults and are associated with adverse outcomes. This meta-analysis aimed to evaluate the efficacy and safety of esketamine for the prophylaxis of POND.

Methods Electronic databases were comprehensively searched from inception to April 1, 2024, to identify randomized controlled trials (RCTs) exploring the impact of perioperative esketamine on POND in adult patients. The primary outcomes were the incidence of POND and the level of postoperative cognitive function. The secondary outcomes included recovery characteristics (i.e., respiratory depression, extubation time, agitation, hallucinations, and nightmares) and inflammatory markers. Subgroup and meta-regression analyses were conducted to investigate the heterogeneity and effect of esketamine dosage.

Results A total of 24 RCTs ($n = 2,130$ patients), all conducted in China with relatively short follow-up periods (≤ 3 months), were included. Esketamine was found to significantly reduce the risk of POND (risk ratio:0.53, 95%confidence interval [CI]: 0.43–0.67) and improved cognitive function on postoperative day 1 (standardized mean difference [SMD]:1.22, 95%CI:0.85–1.59) and day 3 (SMD:0.94, 95%CI: 0.46–1.43) compared with controls, without impacting recovery characteristics. Furthermore, esketamine was associated with lower pain scores, reduced risk of postoperative nausea/vomiting, and decreased levels of inflammatory markers (IL-6, TNF-α, and S100β). Subgroup and meta-regression analyses revealed that age, quality of studies, type of esketamine administration, and esketamine dosage did not have a significant impact on cognitive outcomes. The evidence showed moderate certainty for POND risk, low certainty for POD 1 cognitive function and several complications (agitation, hallucinations, PONV, respiratory issues, nightmares) and biomarkers (TNF-α, s100β), and very low certainty for POD 3 cognition, extubation time, pain, and IL-6 levels.

Conclusion Perioperative esketamine is potentially effective in reducing the risk of POND and improving cognitive function in adult patients, regardless of age and dosage. Nevertheless, the certainty of evidence was low to very low for several outcomes (e.g., cognitive function on POD 3). Given that all included studies were conducted in China

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with relatively short follow-up periods, further high-quality RCTs with diverse populations and longer follow-up are warranted to validate these findings.

Keywords Perioperative neurocognitive disorders, Esketamine, Postoperative, Inflammatory markers, Cognitive function

Introduction

Postoperative delirium or delayed cognitive recovery within 30 days, also known as perioperative neurocognitive disorders (POND) [1, 2], is common in older adults (≥ 65 years). Although the exact pathophysiology remains unclear, several mechanisms have been suggested, including neuroinflammation, neuroendocrine activation, neuronal aging, and neurotransmitter imbalances [1, 3–5]. POND (e.g., postoperative delirium) is associated with long-term cognitive and functional deterioration, increased postoperative complications and mortality, heightened risk of developing dementia, and increased healthcare costs within 1 year [6, 7], rendering it a major public health concern. There has been increasing interest in recent years in identifying pharmacological strategies for the prevention of POND [8–10]. Because a single pharmacological strategy may not be suitable for every patient, the continuous exploration of various medications to enhance patient safety remains a justifiable and necessary approach.

Esketamine, the S-enantiomer of ketamine, doubles the anesthetic potency of ketamine owing to its high affinity for the N-methyl-D-aspartate (NMDA) receptor [11]. The incidence of adverse events associated with esketamine is lower than that associated with ketamine, making the former a more favorable alternative [11]. Several randomized controlled trials (RCTs) have reported convincing evidence of the efficacy of esketamine in reducing postoperative delirium or cognitive dysfunction in patients undergoing cardiac or non-cardiac surgery [12–15]. Although these initial findings are promising, a knowledge gap or uncertainty remains regarding its application in preventing cognitive dysfunction. For example, a recent meta-analysis revealed that ketamine, a racemic mixture composed of two optical isomers, namely, S(+)-ketamine (esketamine) and R(−)-ketamine, failed to prevent the occurrence of postoperative delirium and neurocognitive disorders [16]. Additionally, numerous studies have been conducted in Chinese populations [12–15]; therefore, the generalizability of these findings to other ethnic groups remains uncertain, given potential differences in drug metabolism and healthcare practices. Esketamine is increasingly recognized for its diverse perioperative applications, including postoperative pain management and depression prevention [17–22]. Exploring its potential role in preventing cognitive dysfunction could further enhance clinicians' understanding of its broader clinical utility. However, no systematic investigation has comprehensively evaluated its effectiveness and safety in POND prevention across different populations and surgical settings. Therefore, this meta-analysis aimed to evaluate the efficacy and safety of esketamine in POND prophylaxis by analyzing data from RCTs.

Method

The study was previously registered in PROSPERO (CRD42024530517). It also adhered to the standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [23].

Search strategy and data sources

A comprehensive search strategy was employed to identify RCTs that investigated the effects of perioperative esketamine on POND. Electronic databases, including Medline, Embase, Cochrane Central Register of Controlled Trials, and Google Scholar, were searched from inception to April 1, 2024, without language restrictions. MeSH terms and free-text keywords related to "esketamine," "surgery," "postoperative cognitive dysfunction," and "randomized controlled trials" were used in the search. The aforementioned terms were combined using the Boolean operators "AND " and "OR." The detailed search strategy for MEDLINE is provided in Supplemental Table 1. To ensure comprehensive coverage, the reference lists of relevant articles and reviews were manually screened to identify additional studies. In addition, the China National Knowledge Infrastructure (CNKI) database was searched for eligible studies that were not identified in the major databases.

Study selection and inclusion/exclusion criteria

The selection process was conducted in accordance with the PRISMA guidelines. Two independent reviewers screened the titles and abstracts of all records retrieved from the databases. Articles that met the inclusion criteria were selected for full-text review. The full texts of the selected articles were independently evaluated by the same reviewers to determine their eligibility for inclusion in the meta-analysis.

The inclusion criteria were as follows: (1) studies involving adult patients (aged 18 years or older)

undergoing elective surgery with general anesthesia, (2) administration of intravenous esketamine prior to the end of surgery (such as during anesthetic induction or via intraoperative infusion), (3) use of a placebo or standard care as a comparator, (4) reporting of cognitive function outcomes (e.g., Mini-Mental State Examination [MMSE]) or incidence of POND, and (5) an RCT design.

The exclusion criteria were as follows: (1) non-randomized trials, observational studies, case reports, or reviews; (2) studies involving obstetric patients or those undergoing intracranial surgery; (3) studies including patients undergoing sedation procedures; (4) the use of esketamine in combination with other drugs that might reduce the incidence of POND, such as dexmedetomidine; (5) the use of regional anesthesia without general anesthesia; and (6) studies involving the administration of esketamine postoperatively. We excluded obstetric patients and sedation procedures due to their distinct physiological states and anesthetic protocols that could confound assessment of esketamine's cognitive effects. These exclusions helped maintain clinical homogeneity and focused the analysis on standard general anesthesia for elective surgeries.

If the two reviewers had any disagreements during the study selection process, they were resolved through discussion and reaching a consensus. In cases where consensus was not achievable, a third senior reviewer was consulted to make the final decision.

Data collection

A standardized data extraction form was used to collect relevant information from the included studies. Two independent reviewers extracted data on study characteristics (i.e., first author's name, publication year, country, sample size, study design, and follow-up duration), patient characteristics (age, sex, American Society of Anesthesiologists [ASA] physical status, body mass index), intervention details (i.e., esketamine dose), outcome measures (i.e., incidence of POND and diagnostic criteria), adverse events (e.g., hallucinations and nightmares), details on surgery (i.e., type and duration of surgery), recovery characteristics (i.e., extubation time, agitation, incidence of postoperative nausea and vomiting [PONV], incidence of respiratory depression, and pain score), and inflammatory markers (e.g., interleukin 6 [IL-6]). In case of missing or unclear data, the corresponding authors were contacted via email.

Outcomes and definitions

In the current meta-analysis, POND was defined as postoperative delirium or delayed cognitive recovery within 30 days of surgery. The dual primary outcomes were the incidence of POND and level of cognitive function in patients who received perioperative esketamine compared to those who did not, with the diagnosis of POND based on the criteria used in each study. Cognitive function (assessed using MMSE or other scales reported in the included studies) on postoperative days (PODs) 1 and 3 was compared between the groups. The secondary outcomes included extubation time, postoperative pain score, postoperative recovery characteristics (i.e., agitation, hallucinations, PONV, respiratory depression, and nightmares), and levels of inflammatory markers on POD 1 (i.e., IL-6, TNF-α, S100β).

Quality assessment for the included studies

Two independent reviewers evaluated the methodological soundness and potential bias of the included studies using the Cochrane risk of bias (RoB) tool 2.0. Five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result) were evaluated and judged as having a low risk of bias, some concerns, or a high risk of bias. For example, in the domain of missing outcome data, a study was assessed as having a high risk of bias due to a dropout rate exceeding 20%. This high attrition rate could impact the validity of the study's findings by introducing potential systematic differences between groups, ultimately affecting the reliability of the results. The overall risk of bias for each study was determined based on the judgments for each domain, with studies classified as having a low risk of bias (low risk in all domains), some concerns (some concerns in at least one domain but not high risk in any domain), or a high risk of bias (high risk in at least one domain or some concerns in multiple domains).

Certainty of evidence

To evaluate the certainty of evidence for each outcome in this meta-analysis, we employed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. We systematically downgraded evidence quality based on: risk of bias (when $\geq 50\%$ of studies had high risk or some concerns in key domains), inconsistency (unexplained heterogeneity, $I^2 > 75\%$), indirectness (differences in populations, interventions, or outcomes), imprecision (wide confidence intervals), and publication bias (assessed through funnel plots). Based on these evaluations, we categorized the overall certainty of the evidence for each outcome as high, moderate, low, or very low.

Statistical analyses

Data synthesis and analysis were conducted using Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and Comprehensive

Meta-Analysis version 4 (Biostat, Englewood, NJ, USA). Dichotomous outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Continuous outcomes were expressed as mean differences or standardized mean differences (SMDs) with 95% CIs, depending on whether the outcome measures were reported using the same or different scales across the studies. A random-effects model was used for the analyses, considering the anticipated clinical and methodological heterogeneities among the included studies.

Heterogeneity was evaluated using Cochran's Q test ($p < 0.10$ indicating significant heterogeneity) and quantified using the I^2 statistic, with I^2 values of 25%, 50%, and 75% indicating low, moderate, and high heterogeneity, respectively. Subgroup analyses were conducted on the primary outcomes to explore the potential sources of heterogeneity and evaluate the effect of esketamine in specific populations. The prespecified subgroups included age (i.e., > 65 years vs. ≤ 65 years), quality of studies (low risk of bias vs. some concerns to high risk of bias), and type of esketamine administration (bolus only vs. bolus plus infusion). A meta-regression analysis was conducted to explore the association between esketamine dosage and the risk of POND. The total dosage of esketamine was determined using a formula that considered the actual surgical duration. For instance, if the protocol for esketamine administration includes a bolus dose of 0.5 mg/kg and an infusion rate of 0.1 mg/kg per hour, the total dosage for a procedure lasting 2 h would be 0.7 mg/kg.

Sensitivity analyses were conducted to assess the robustness of the findings by sequentially omitting one study at a time and recalculating the pooled effect estimates. Publication bias was evaluated using funnel plots and Egger's regression test when at least ten studies/datasets were available for an outcome. Trial sequential analysis (TSA) was conducted to control for type I and II errors and determine whether the cumulative evidence was sufficient to draw firm conclusions. The TSA software version 0.9.5.10 beta (Copenhagen Trial Unit, Copenhagen, Denmark) was used with a significance level of 5%, power of 80%, and relative risk reduction of 20%. $P < 0.05$ was considered to indicate statistical significance for all analyses, except for the test of heterogeneity, where $P < 0.10$ was used to determine statistical significance.

Results

Study selection and characteristics

A total of 1,241 records were identified through database searches. After removing 232 duplicate records, 1,009 were screened by title and abstract, leading to the exclusion of 447 records. The remaining 36 reports were sought for retrieval, of which 26 were excluded for various reasons (Fig. 1). Ten RCTs identified from the major databases were included. After searching the CNKI database, 21 additional records were identified. After excluding studies that did not meet the eligibility criteria, 14 studies were ultimately selected for inclusion (Fig. 1). Overall, the meta-analysis included 24 RCTs [12–15, 24–43], all published between 2021 and 2024.

The main characteristics of the 24 included trials, involving 2,130 patients, are summarized in Table 1. The included studies used various study designs, with 19 and 5 studies using two- and three-arm designs, respectively. The mean age of the participants ranged from 40 to 73 years, with the proportion of male patients varying from 0 to 77%. A total of 16 studies focused on the elderly population (i.e., mean age > 65 years) [13, 14, 24, 25, 27, 33–40, 42, 43], whereas eight included relatively young patients (aged ≤ 65 years) [12, 15, 26, 28–32]. The surgical procedures and diagnostic criteria for POND varied among the included studies (Supplemental Table 2). The mean surgical duration ranged from 51 to 269 min, and the estimated dosage of esketamine, which was administered before anesthetic induction or intraoperatively, ranged from 0.1 to 1.1 mg/kg (Supplemental Table 3). Fifteen studies reported the incidence of POND as an outcome [12–14, 24–26, 29, 30, 32, 34, 36, 38, 42, 43], and 19 studies assessed cognitive function using two measurement tools (i.e., MMSE or Montreal Cognitive Assessment) (Table 1) [13, 14, 26–29, 31–40, 42, 43]. The follow-up periods also differed across the studies, ranging from 1 day to 3 months postoperatively. All 24 studies were conducted in China.

Risk of bias

In the 24 included studies (Fig. 2), notable concerns were identified in eight trials regarding the randomization process, mainly because of insufficient details on the concealment of the allocation sequence. In the examination of bias from missing outcome data, one study [13] was categorized as high-risk, as more than 20% of the participants dropped out, and another study [29] raised concerns with a dropout rate exceeding 10%. In terms of outcome measurement, the risk of bias in the two studies [29, 30] that evaluated the occurrence of POND within POD 1 was considered to have some concerns attributed to the short follow-up period. Overall, the risk of bias was deemed low in seven studies, presented some concerns in 16, and was high in one.

Outcomes

Primary outcome: risk of POND

The cumulative incidences of POND were 13.3% (93/698) and 22.9% (147/642) in the esketamine and control groups, respectively. The esketamine group had a 47%

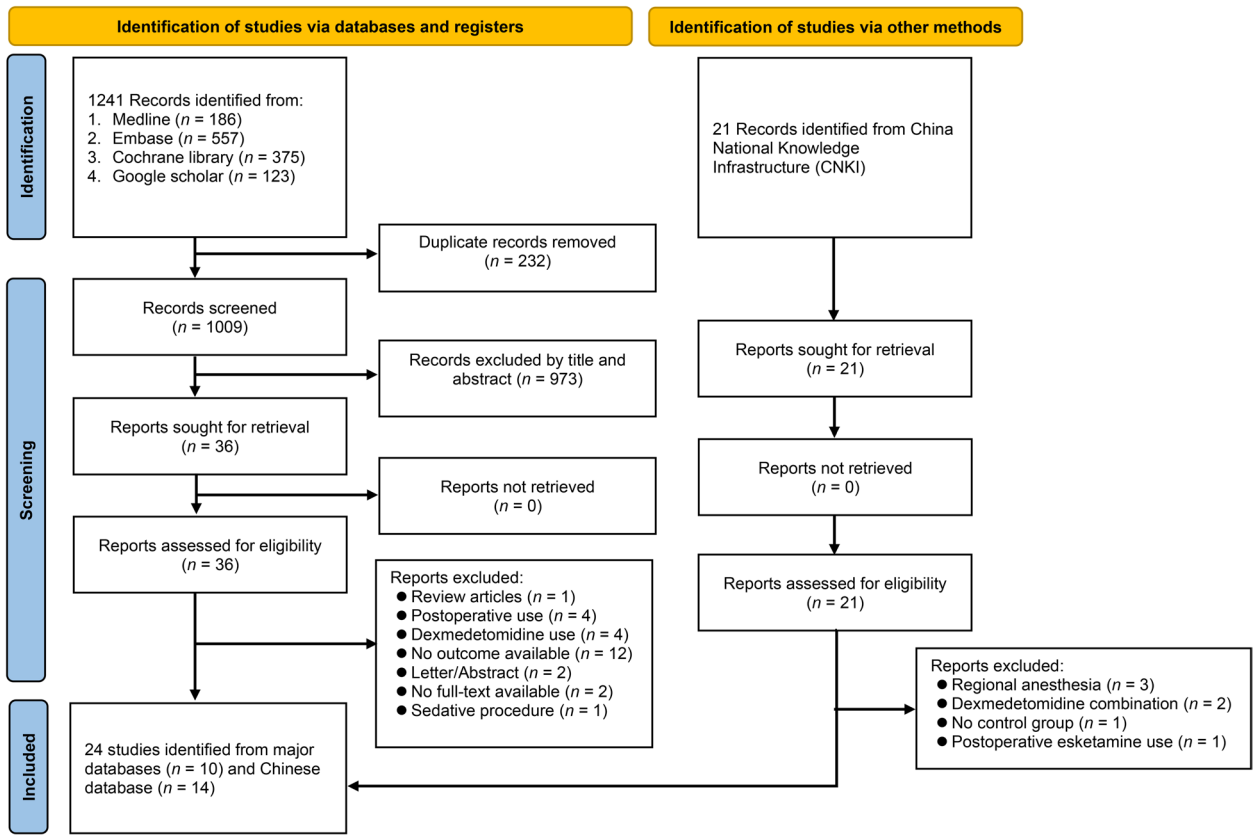

Fig. 1 Flow chart of the study selection process

lower risk of developing POND than the control group (RR: 0.53, 95% CI: 0.43–0.67, $P<0.00001$, $I^2=0\%$) (Fig. 3) [12–15, 24–26, 29, 30, 32, 34, 36, 38, 42, 43]. Sensitivity analysis using the leave-one-out approach revealed consistent findings, indicating the robustness of the overall result. In the subgroup analysis by age, the RRs for POND in participants aged > 65 years and ≤ 65 years were 0.43 (95% CI: 0.31–0.6; $P<0.00001$, $I^2=0\%$) and 0.64 (95% CI: 0.47–0.86; $P=0.003$, $I^2=0\%$), respectively (subgroup difference, $P=0.09$) (Supplemental Fig. 1). This finding indicates a greater risk reduction in the older age group, despite the absence of a statistically significant difference.

In the subgroup analysis by study quality, the pooled relative risk (RR) was 0.6 (95% CI: 0.45–0.82, $p=0.001$, $I^2=0\%$) for studies with a low risk of bias and 0.46 (95% CI: 0.33–0.64, $p<0.00001$, $I^2=0\%$) for studies with some concerns to high risk of bias, with no significant subgroup differences ($P=0.24$) (Supplemental Fig. 2). Subgroup analysis based on esketamine administration type also showed no significant difference between bolus only (RR: 0.56, 95% CI: 0.44–0.7; $P<0.00001$, $I^2=0\%$) and bolus plus infusion doses (RR: 0.36, 95% CI: 0.18–0.73; $P=0.005$, $I^2=0\%$) (subgroup difference: $P=0.26$) (Supplemental Fig. 3).

Primary outcome: cognitive function measurement

On POD 1, the pooled data indicated that the esketamine group had significantly better postoperative cognitive function than the control group (SMD: 1.22, 95% CI: 0.85–1.59; $P<0.00001$, $I^2=91\%$) (Fig. 4) [13, 14, 26–29, 31–40, 42, 43]. Sensitivity analysis revealed consistent findings, confirming the robustness of the overall result. Subgroup analysis by age revealed that the cognitive benefit of esketamine was also more pronounced in older participants (aged > 65 years) (SMD: 1.34, 95% CI: 0.9–1.77; $P<0.00001$) than in younger participants (aged ≤ 65 years) (SMD: 0.95, 95% CI: 0.23–1.66; $P=0.010$), although the difference between the two subgroups was not statistically significant (Supplemental Fig. 4). In the subgroup analysis by quality of studies, the pooled effect size was 1.15 (95% CI: 0.56–2.45, $I^2=92\%$) for studies with a low risk of bias and 1.14 (95% CI: 0.74–1.55, $I^2=91\%$) for studies with some concerns to high risk of bias (subgroup differences: $P=0.49$) (Supplemental Fig. 5). No significant difference was observed between

Table 1 Summary of characteristics for 24 randomized controlled studies

Outcome	Study design	Mean age (years)	Mean BMI (kg/m^2)	Male (%)	ASA	*N*	Mean surgical time	Total dosage estimated (mg/kg)†	Control group	follow-up (days)	Outcomes	Country
Chen 2022 [26]	3-arm	57/59/56	23/22/23	51/42/46	I-III	120	145	0.78	NB/placebo	3 m	①②	China
Han 2023 [13]	2-arm	70/70	23/23	55/56	I-III	67	165	0.15	NS	3 m	①②	China
Jing 2024 [24]	2-arm	69/71	23/24	68/61	II-III	87	183	0.56	NS	3	①	China
Li 2022 [25]	2-arm	69/69	26/26	28/23	II-III	80	105	0.2	NS	3	①	China
Li 2023 [41]	2-arm	69/66	na	57/49	I-III	115	91	0.3	placebo	1	②	China
Liu 2022 [30]	2-arm	45/46	25/25	0	I-II	80	98	0.5	fetanyl	2	①	China
Liu 2023 (1) [29]	2-arm	46/44	23/23	0	I-II	38	100	0.125	ns	1	①②	China
Liu 2023 (2) [39]	2-arm	65/66	22/22	53/50	I-II	60	94	0.5	sufentanil	1	②	China
Lu 2021 [31]	2-arm	59/59	22/22	56/59	I-II	68	156	0.5	NS	2	②	China
Luo 2024 [12]	3-arm	56/55/56	23/23/24	45/51/52	I-III	129	145/162	0.2/0.5	NS	3	①	China
Ma 2023 [14]	2-arm	69/71	23/24	77/77	II-III	62	269	0.8	NS	3	①②	China
Mao 2023 [32]	2-arm	45/44	24/24	0	I-II	104	86	0.5	NS	7	①②	China
Shi 2024 [33]	2-arm	70/70	24/24	48/47	I-II	120	143	0.1	NS	3	②	China
Sun 2023 [34]	2-arm	68/68	na	42/44	I-III	90	na	0.375	placebo	5	①②	China
Tang 2023 [35]	3-arm	69/68/68	na	45/40/50	I-III	120	na	0.25/0.5	NS	5	②	China
Tu 2021 [27]	2-arm	66/65	22/22	50/55	I-III	80	na	0.5	sufentanil	1	②	China
Wang 2023 [42]	2-arm	68/69	25/24	47/55	II-III	102	115	0.25	NS	7	①②	China
Wu 2021 [36]	2-arm	69/68	na	0	I-II	80	na	0.25	NS	3	①②	China
Xiong 2024 [15]	2-arm	53/52	23/23	46/46	II-III	112	246§	0.25	NS	7	①	China
Yu 2023 [43]	3-arm	70/70/70	22/22/22	59/57/52	II-III	138	215/218	0.25/0.5	NS	7	①②	China
Zhang 2023 [40]	2-arm	69/69	22/22	38/41	II-III	68	85	0.24	NS	2	②	China
Zhao 2023 [37]	2-arm	67/67	26/26	0	I-II	60	100	0.27	NS	1	②	China
Zhao 2024 [28]	3-arm	40/40/39	22/23/23	53/47/50	I-II	90	52/51	0.6/0.7	NS	1	②	China
Zhu 2023 [38]	2-arm	72/73	24/24	53/57	II-III	60	90	1.1	NS	5	①②	China

①incidence of perioperative neurocognitive disorders (POND) (15 studies)

②cognitive function measurement (19 studies); *m* months, *na* not available

† Estimated from the bolus dosage and the product of the infusion dosage and surgical time; *NB* nerve block

§ cardiac surgery, *BMI*:body mass index, *ASA* merican Society of Anesthesiologists physical status, *NS* normal saline

◀ **Fig. 2** Risk of bias for 24 studies. Each study is assessed across six domains, with risk levels indicated by color coding: Green (+): Low risk of bias; Yellow (?): Some concerns; Red (−): High risk of bias. Two independent reviewers assessed the quality of the studies, resolving any disagreements through discussion or by consulting a third reviewer if needed

studies using only bolus doses (SMD: 1.21, 95% CI: 0.8–1.63; $P<0.00001$, $I^2=88\%$) and those using a combination of bolus and infusion doses (SMD: 1.23, 95% CI: 0.53–1.92; $P=0.0005$, $I^2=94\%$) (subgroup difference: $P=0.97$) (Supplemental Fig. 6).

The beneficial effect of esketamine on cognitive function was also observed on POD 3 (SMD: 0.94, 95% CI: 0.46–1.43; $P=0.0001$, $I^2=90\%$, sensitivity analysis: consistent) (Fig. 5) [14, 32, 33, 35, 36, 38, 42, 43]. Subgroup analysis revealed that age (subgroup difference: $P=0.42$) (Supplemental Fig. 7), quality of studies (subgroup difference: $P=0.14$) (Supplemental Fig. 8), and type of esketamine administration (subgroup difference: $P=0.11$) (Supplemental Fig. 9) had no impact on the beneficial effect of esketamine.

Secondary outcome: recovery characteristics and inflammatory markers

To avoid bias, we excluded three studies [27, 30, 39] that used opioids in the control group when assessing the impact of esketamine on pain scores, risk of PONV, and respiratory depression. The use of esketamine was associated with a lower pain score (SMD: −0.81, 95% CI: −1.17 to −0.45; $P<0.0001$, $I^2=84\%$, sensitivity analysis: consistent) (Fig. 6) and risks of PONV (RR: 0.67, 95% CI: 0.47 to 0.94; $P=0.02$, $I^2=12\%$, sensitivity analysis: inconsistent) (Fig. 7). No differences were observed in other outcomes, including respiratory depression (RR: 0.35, 95% CI: 0.09–1.46; $P=0.15$, $I^2=32\%$, sensitivity analysis: inconsistent) (Fig. 8), extubation time (SMD: −0.51, 95% CI: −1.14 to 0.12; $P=0.11$, $I^2=93\%$, sensitivity analysis: consistent) (Supplemental Fig. 10), risks of agitation (RR: 0.76, 95% CI: 0.37–1.55; $P=0.45$, $I^2=0\%$, sensitivity analysis: consistent) (Supplemental Fig. 11), hallucinations (RR: 1.86, 95% CI: 0.53–6.52; $P=0.33$, $I^2=0\%$, sensitivity analysis: consistent) (Supplemental Fig. 12), and nightmares (RR: 2.93, 95% CI: 0.61–13.92; $P=0.18$, $I^2=0\%$, sensitivity analysis: consistent) (Supplemental Fig. 13) between the groups. Sensitivity analysis of PONV and respiratory depression revealed inconsistent findings, indicating that the evidence is not robust.

This meta-analysis showed that the levels of inflammatory markers IL-6 (SMD: −1.64, 95% CI: −2.34 to −0.93; $P<0.00001$, $I^2=95\%$) (Fig. 9), TNF-α (SMD: −1.68, 95% CI: −2.45 to −0.91; $P<0.0001$, $I^2=94\%$) (Fig. 10), and S100β (SMD: −1.59, 95% CI: −2.13 to −1.04; $P<0.00001$,

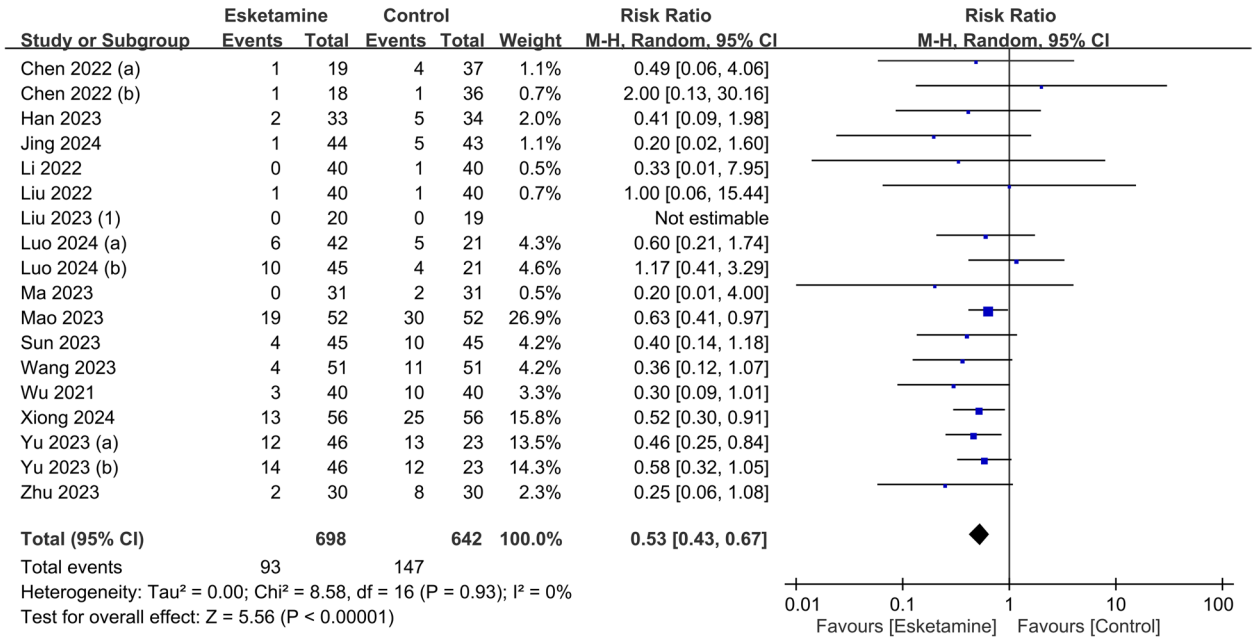

Fig. 3 Forest plot showing the risk of perioperative neurocognitive disorders (POND). (**a**) (**b**) denote different datasets within the same study. The diamond (◆) represents the overall pooled effect estimate, while the squares (■) indicate the weight of individual studies, with the size of each square proportional to the study's contribution to the meta-analysis. CI, confidence interval; M-H, Mantel–Haenszel method

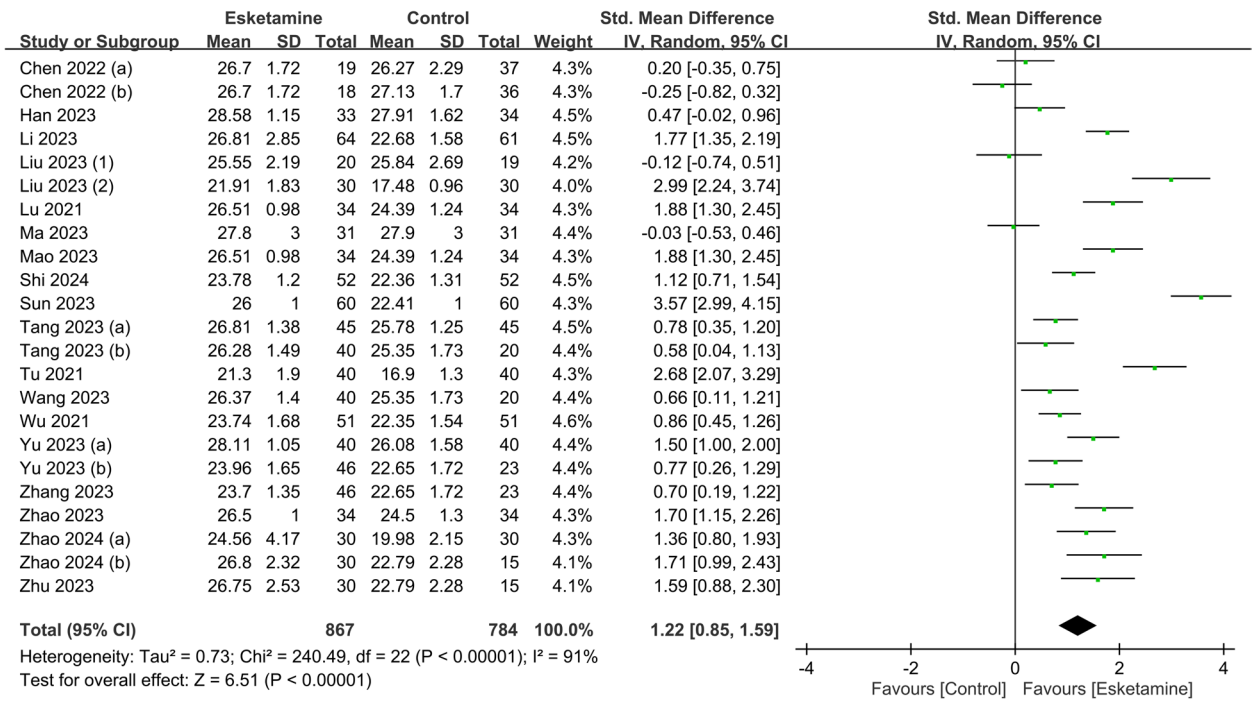

Fig. 4 Forest plot showing the difference in cognitive function between the groups on postoperative day 1. (**a**) (**b**) denote different datasets within the same study, whereas (1) (2) denote different studies. The diamond (◆) represents the overall pooled effect estimate, while the squares (■) indicate the weight of individual studies, with the size of each square proportional to the study's contribution to the meta-analysis. CI, confidence interval; Std., standardized; IV: invariance

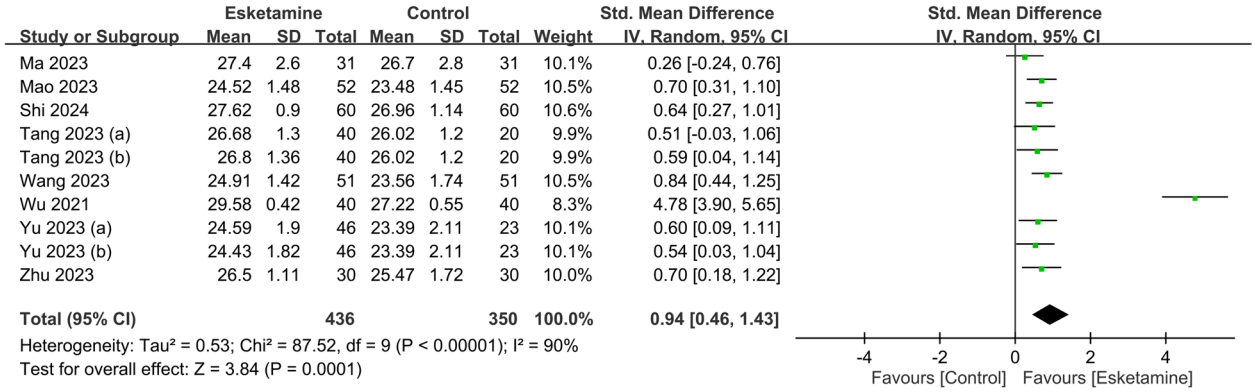

Fig. 5 Forest plot showing the difference in cognitive function between the groups on postoperative day 3. (**a**) (**b**) denote different datasets within the same study. The diamond (◆) represents the overall pooled effect estimate, while the squares (■) indicate the weight of individual studies, with the size of each square proportional to the study's contribution to the meta-analysis. CI, confidence interval; Std., standardized; IV: invariance

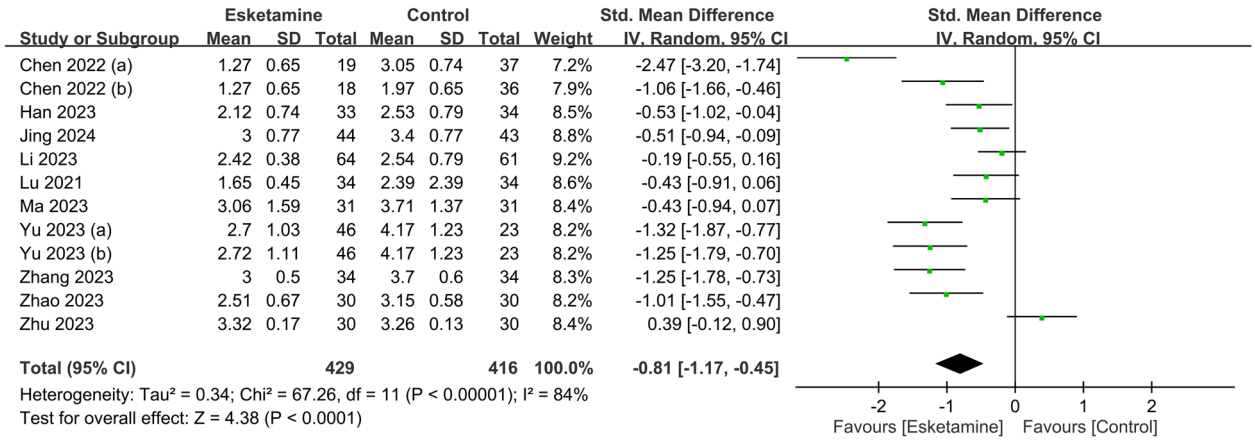

Fig. 6 Forest plot showing the difference in pain score between the groups. (**a**) (**b**) denote different datasets within the same study. The diamond (◆) represents the overall pooled effect estimate, while the squares (■) indicate the weight of individual studies, with the size of each square proportional to the study's contribution to the meta-analysis. CI, confidence interval; Std., standardized; IV: invariance

I^2 = 89%) (Fig. 11) were significantly lower in the esketamine group than in the control group. Sensitivity analyses revealed consistent findings for these three outcomes.

Meta-regression analysis

Meta-regression analyses investigating the risk of POND and level of cognitive function revealed that esketamine dosage had no impact on the risk of POND (Fig. 12a) or level of cognitive function (Fig. 12b–12c).

Trial sequential analysis

For the risk of POND, TSA showed that the z-curve crossed the required information size, indicating that the evidence is adequate to support the finding (Fig. 13). Because of the presentation of the effect size as SMD, it was not feasible to conduct TSA for cognitive function owing to software limitations.

Publication bias

Funnel plots were used for four outcomes, each involving more than 10 datasets. The symmetry observed in these funnel plots suggested a low risk of publication bias for the outcomes: risk of POND (Egger's test: P=0.27) (Supplemental Fig. 14), cognitive function on POD 1 (Egger's test: P=0.19) (Supplemental Fig. 15), and PONV (Egger's test: P=0.19) (Supplemental Fig. 16). However, three outcomes demonstrated a risk of publication bias, namely, cognitive function on POD 3 (Egger's test: P=0.04) (Supplemental Fig. 17), pain scores (Egger's test: P=0.005) (Supplemental Fig. 18), and IL-6 levels (Egger's test: P=0.006) (Supplemental Fig. 19).

Certainty of evidence

The certainty of the evidence is summarized in Table 2. The evidence indicated moderate certainty regarding the

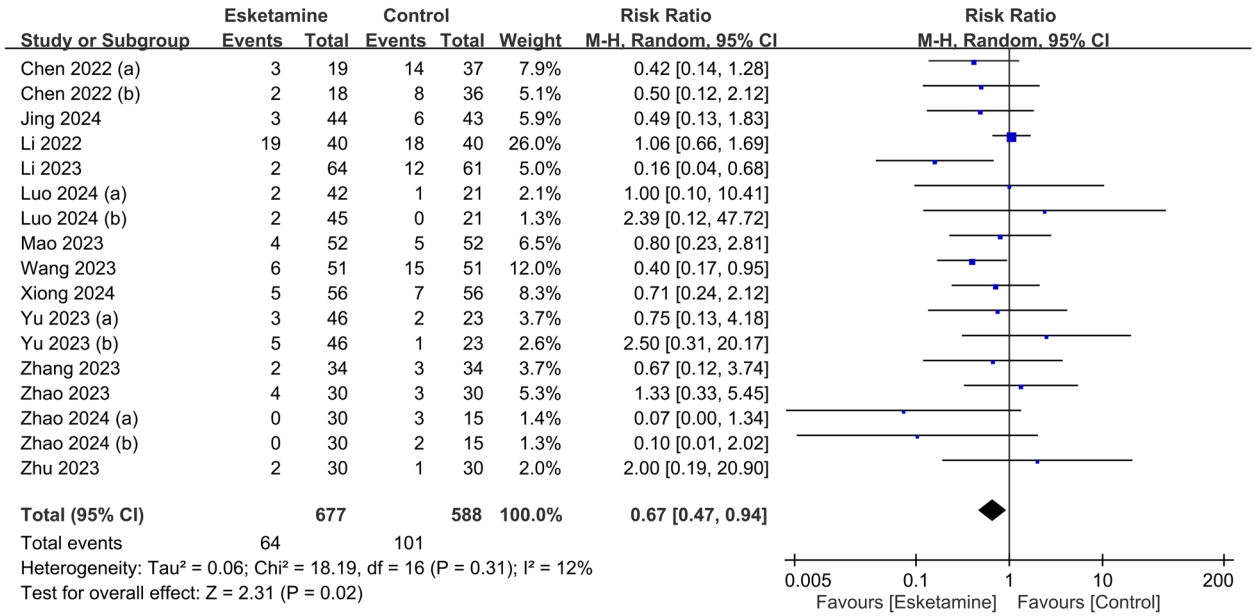

Fig. 7 Forest plot showing the risk of postoperative nausea and vomiting (PONV) between the groups. (**a**) (**b**) denote different datasets within the same study. The diamond (◆) represents the overall pooled effect estimate, while the squares (■) indicate the weight of individual studies, with the size of each square proportional to the study's contribution to the meta-analysis. CI, confidence interval; M-H, Mantel–Haenszel method

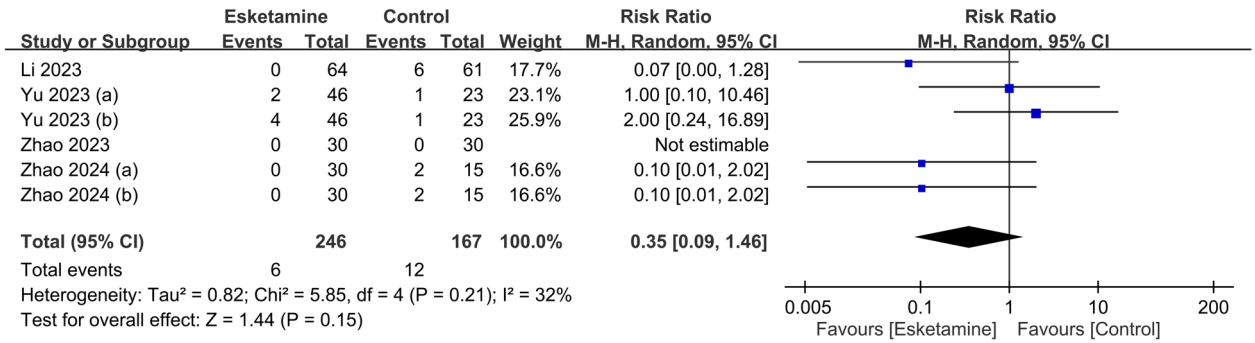

Fig. 8 Forest plot showing the risk of respiratory depression between the groups. (**a**) (**b**) denote different datasets within the same study. The diamond (◆) represents the overall pooled effect estimate, while the squares (■) indicate the weight of individual studies, with the size of each square proportional to the study's contribution to the meta-analysis. CI, confidence interval; M-H, Mantel–Haenszel method

risk of POND. However, the certainty of evidence was deemed low for cognitive function on POD 1, risks of agitation, hallucinations, PONV, respiratory depression, nightmares, and TNF-α and s100β levels. The certainty of evidence was considered very low for cognitive function on POD 3, extubation time, pain scores, and IL-6 levels.

Discussion

This meta-analysis revealed that the esketamine group had a lower risk of POND (RR: 0.53) and better postoperative cognitive function on POD 1 (SMD: 1.22) and 3 (SMD: 0.94) than the control group did. Esketamine was also found to be associated with lower pain scores, and reduced risks of PONV as well as decreased levels of inflammatory markers (IL-6, TNF-α, and S100β). In addition, the use of esketamine did not have a negative impact on the other recovery characteristics (i.e., respiratory depression, extubation time, agitation, hallucinations, and nightmares). Subgroup analyses revealed that patient age, study quality, and type of esketamine administration did not affect the beneficial effects of esketamine. Moreover, meta-regression analysis revealed that esketamine dosage did not have an impact on the risk of POND or cognitive function. TSA supported the beneficial effect of esketamine in POND prevention.

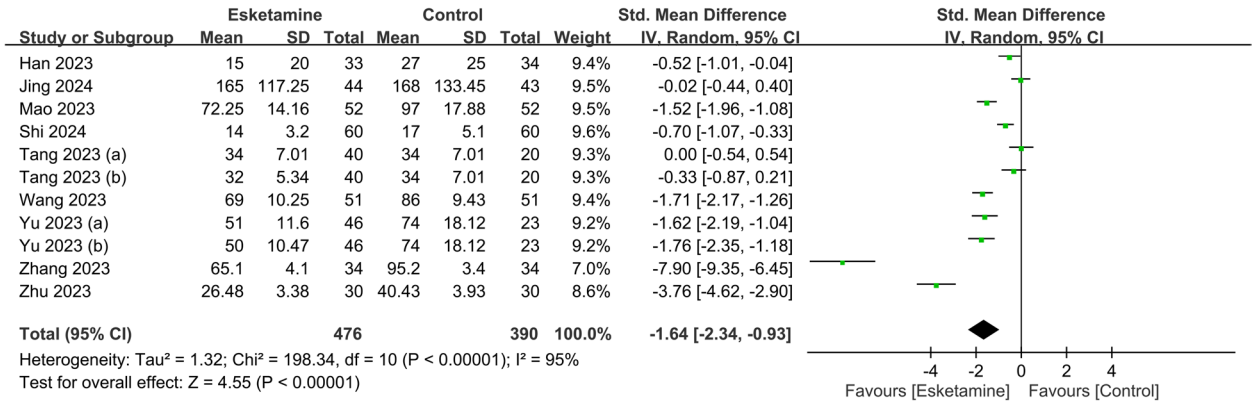

Fig. 9 Forest plot showing the levels of IL-6 between the groups. (**a**) (**b**) denote different datasets within the same study. The diamond (◆) represents the overall pooled effect estimate, while the squares (■) indicate the weight of individual studies, with the size of each square proportional to the study's contribution to the meta-analysis. CI, confidence interval; Std., standardized; IV: invariance

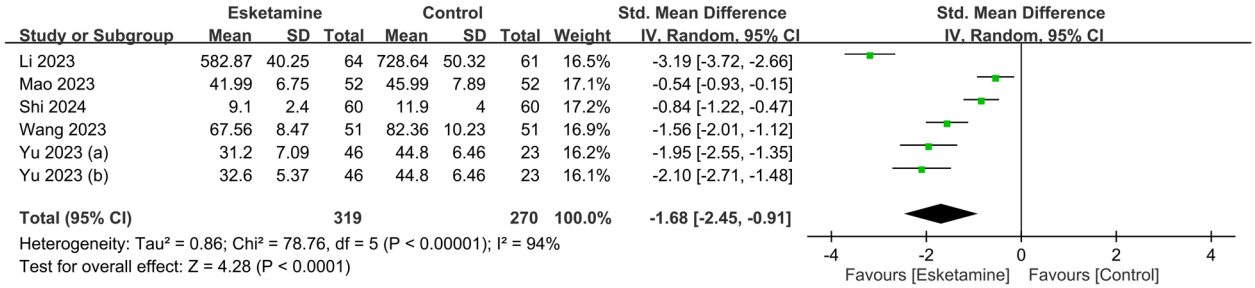

Fig. 10 Forest plot showing the levels of TNF-α between the groups. (**a**) (**b**) denote different datasets within the same study. The diamond (◆) represents the overall pooled effect estimate, while the squares (■) indicate the weight of individual studies, with the size of each square proportional to the study's contribution to the meta-analysis. CI, confidence interval; Std., standardized; IV: invariance

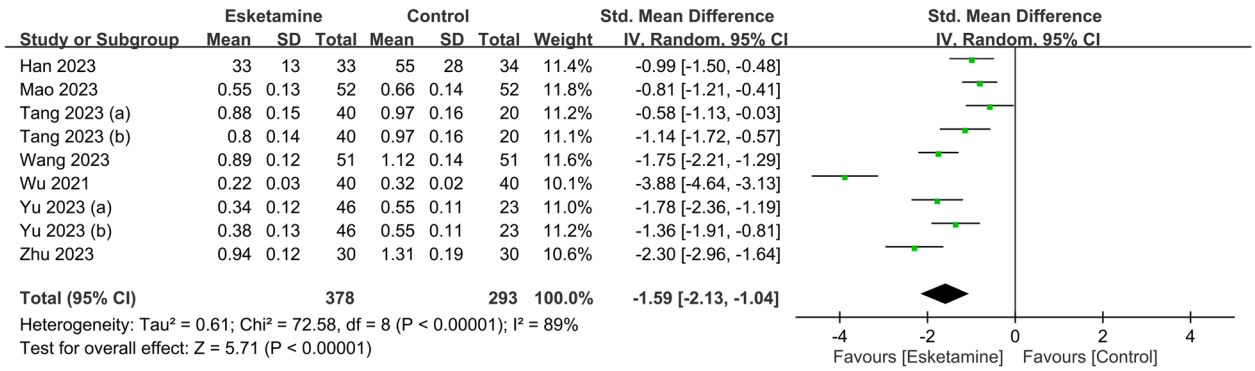

Fig. 11 Forest plot showing the levels of S100β between the groups. (**a**) (**b**) denote different datasets within the same study. The diamond (◆) represents the overall pooled effect estimate, while the squares (■) indicate the weight of individual studies, with the size of each square proportional to the study's contribution to the meta-analysis. CI, confidence interval; Std., standardized; IV: invariance

Various underlying mechanisms, including neuroinflammation, neuroendocrine system activation, neuronal aging, and neurotransmitter imbalance, are believed to play a role in the development of POND [1, 3–5]. Clinically, nonmodified predictors for POND include advanced age, preexisting cognitive impairment, preoperative frailty, ASA physical status > 2, and preexisting psychiatric disorders [44–47]. In contrast, adjusted predictors may encompass preoperative factors such as poor sleep quality and depression, along with postoperative

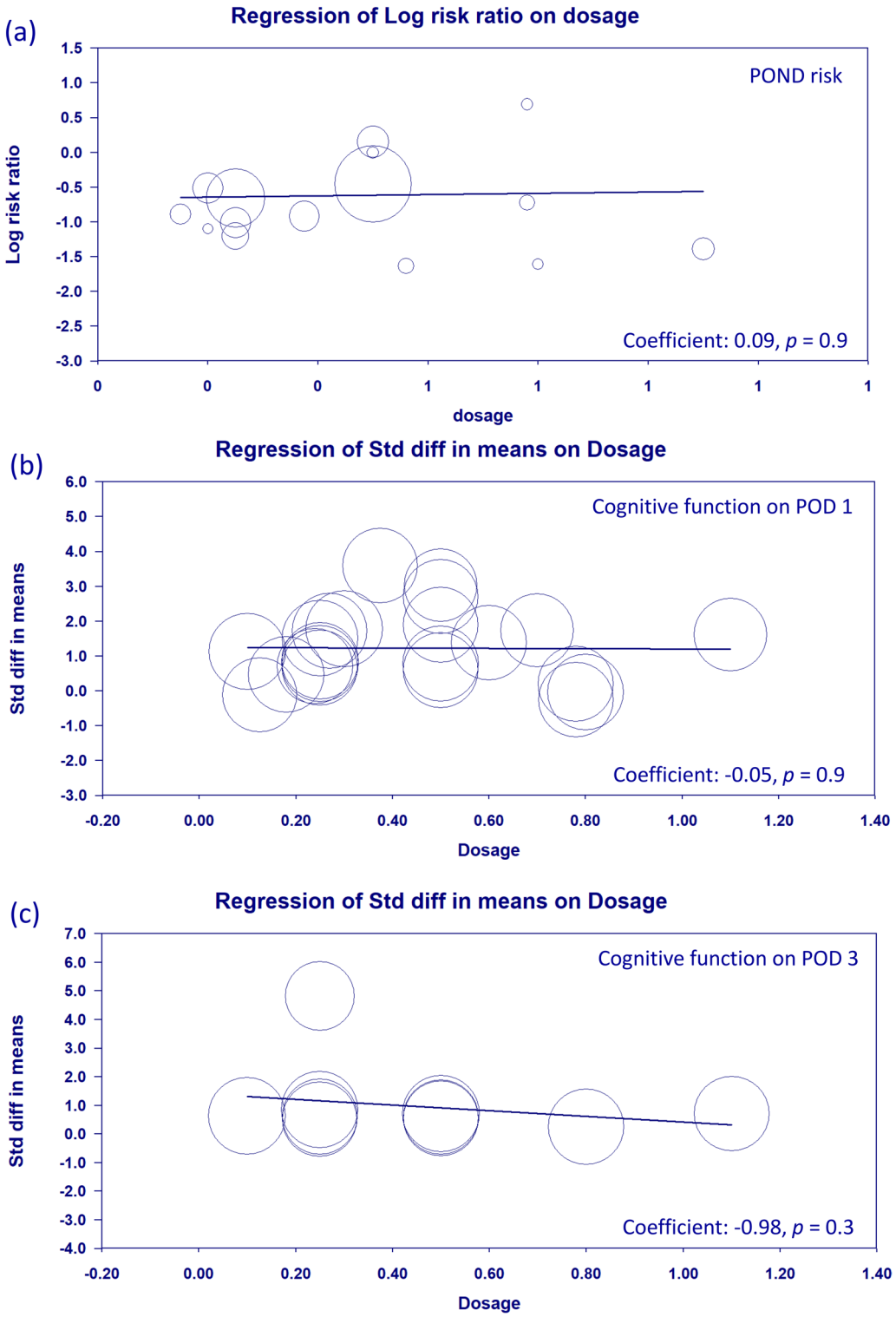

Fig. 12 Meta-regression analyses showing the correlation between the dosage of esketamine and the risk of postoperative neurocognitive disorders (POND) (**a**), as well as its association with cognitive function on the first (**b**) and third (**c**) days following surgery

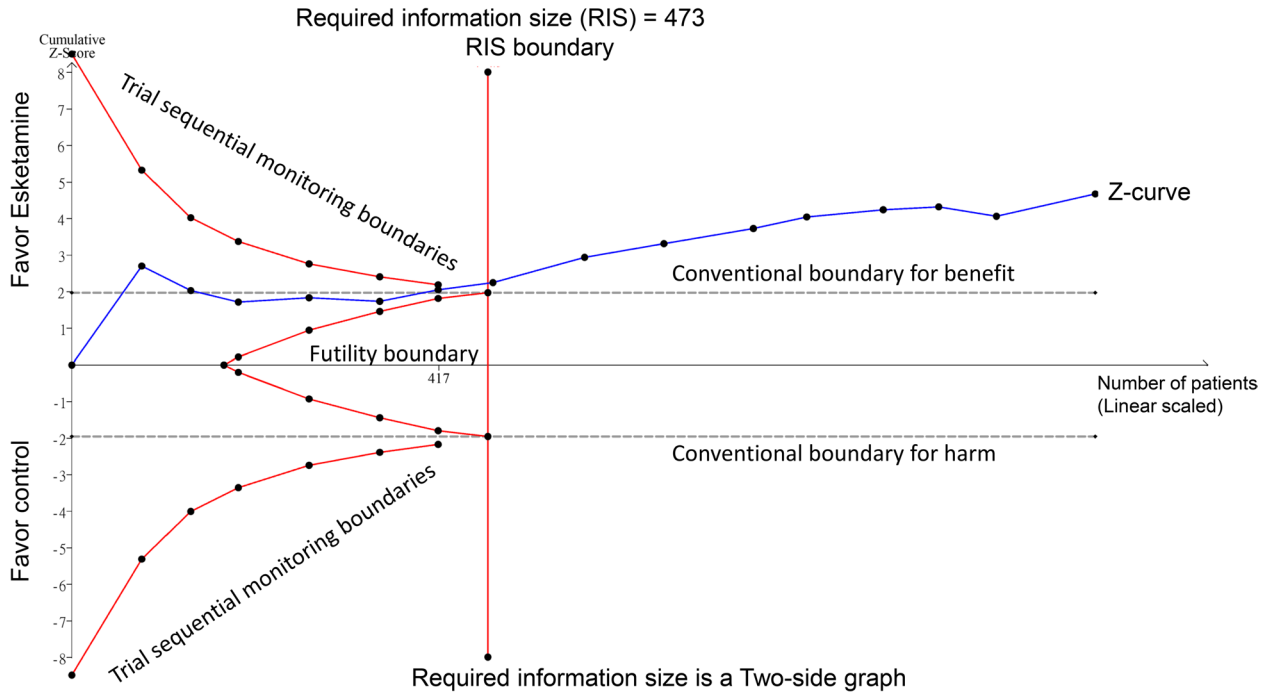

Fig. 13 Trial sequential analysis for risk of perioperative neurocognitive disorders (POND) with esketamine treatment. The trial sequential monitoring boundaries (red lines) demonstrate the adjusted threshold for statistical significance to account for repetitive testing, while the conventional boundaries for benefit and harm (grey dashed lines) provide a traditional significance reference. The surpassing of the required information size (RIS) by the Z-curve emphasizes the robustness of the evidence in favor of esketamine's effect on reducing POND risk

conditions such as severe pain and heightened inflammatory status [48–53]. As there are various risk factors for POND, and some of these factors cannot be immediately addressed before surgery, investigation of the effectiveness and safety of various pharmacological strategies could assist clinicians in selecting the most suitable medication for POND prophylaxis. For instance, patients with a history of depression may clinically benefit from the intraoperative use of medications that possess antidepressant properties.

This meta-analysis revealed that perioperative esketamine may be effective in reducing the incidence of POND and improving postoperative cognitive function in adult patients, regardless of patient age or esketamine administration type. This finding aligns with preclinical studies suggesting that esketamine may have a neuroprotective role in brain trauma and sepsis-induced encephalopathy [51, 54]. Its cognitive benefits likely involve multiple mechanisms, including inhibition of interferon gene stimulators and TANK-binding kinase 1 signaling [55], modulation of glutamatergic signaling [56], and anti-inflammatory properties [57, 58]. We found that esketamine was associated with significantly lower levels of inflammatory markers (IL-6 and TNF-α), indicating that its anti-inflammatory effects may play a role in mitigating cognitive risks. In addition, S100β is associated with the pathophysiology of neuronal injury and plays a role in postoperative cognitive dysfunction [13]. Consistently, our results indicated a significant decrease in S100β levels postoperatively in patients receiving esketamine.

Our subgroup analyses suggest that the use of esketamine is a valuable pharmacological approach for preventing cognitive decline, regardless of the patient's age and type of esketamine administration. This meta-regression analysis further revealed no significant association between esketamine dosage and cognitive outcomes, suggesting that the observed benefits are achievable across a range of doses. These findings have implications for protocol development and risk–benefit assessment, as lower dosages of esketamine may be effective in preventing POND while minimizing the risk of dose-related adverse effects. However, the optimal dosing regimen and administration protocol for maximizing cognitive benefits while ensuring patient safety remains unclear and warrants further investigation.

Two recent meta-analyses reported that ketamine use did not reduce the risk of POND, regardless of the dose, mode of administration, or surgical setting [16, 59]. One study by Fellous et al. (14 studies, 1,618 patients) focused exclusively on ketamine [16], whereas another study

Table 2 Certainty of evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach

Outcomes	n†	Participants	Certainty assessment (Domains)					Effect size [95% CI]	Certainty
			A	B	C	D	E‖		
POND	18	1340	−	+	+	+	+	RR 0.53 [0.43, 0.67]	⊕⊕⊕◯ Moderate
Cognitive function on POD 1	23	1651	−	−	+	+	+	SMD 1.22 [0.85, 1.59]	⊕⊕◯◯ Low
Cognitive function on POD 3	10	786	−	−	+	+	−	SMD 0.94 [0.46, 1.43]	⊕◯◯◯ Very Low
Extubation time	9	669	−	−	+	−	-	SMD -0.51 [-1.14, 0.12]	⊕◯◯◯ Very Low
Pain score§	12	845	−	−	+	+	−	SMD -0.81 [-1.17, -0.45]	⊕◯◯◯ Very Low
Agitation	4	314	−	+	+	−	-	RR 0.76 [0.37, 1.55]	⊕⊕◯◯ Low
Hallucination	7	497	−	+	+	−	-	RR 1.86 [0.53, 6.52]	⊕⊕◯◯ Low
PONV§	17	1265	−	+	+	−	+	RR 0.67 [0.47, 0.94]	⊕⊕◯◯ Low
Respiratory depression§	6	413	−	+	+	−	-	RR 0.35 [0.09, 1.46]	⊕⊕◯◯ Low
Nightmare	7	489	−	+	+	−	-	RR 2.93 [0.61, 13.92]	⊕⊕◯◯ Low
IL-6	18	1340	−	−	+	+	−	SMD -1.64 [-2.34, -0.93]	⊕◯◯◯ Very Low
TNF-a	23	1651	−	−	+	+	-	SMD -1.68 [-2.45, -0.91]	⊕⊕◯◯Low
S100β	10	786	−	−	+	+	−	SMD -1.59 [-2.13, -1.04]	⊕⊕◯◯Low

A: Risk of bias

B: Inconsistency

C: Indirectness

D: Imprecision

E: Publication bias

Green circular icon: not serious, Red circular icon: serious, POND Perioperative neurocognitive disorders, POD Postoperative Day, RR Risk Ratio, SMD Standardized Mean Difference, CI Confidence Interval, PONV Postoperative Nausea and Vomiting, IL-6 Interleukin 6, TNF-a Tumor Necrosis Factor-alpha, s100B A protein used as a biomarker for brain damage

†number of studies or datasets

‖Publication bias was evaluated when at least 10 studies/datasets were available for an outcome

§studies that used opioids in the control group were excluded during analysis

by Zhou et al. (9 studies, 573 patients) included studies on both ketamine ($n=7$) and esketamine ($n=2$) [59]. The meta-analysis by Fellous et al. did not evaluate the effect of ketamine on postoperative inflammation (e.g., IL-6) and found similar pain scores in patients with and without ketamine use [16]. The second meta-analysis by Zhou et al. did not evaluate postoperative inflammatory status or pain scores [59]. Our study specifically focused on esketamine and included a large number of RCTs (24 studies, 2,130 patients), providing updated evidence to support the potential role of esketamine in preventing POND. These contrasting findings between ketamine and esketamine studies may be attributed to two possible explanations. First, esketamine's higher affinity for NMDA receptors could provide more effective modulation of glutamatergic signaling, which is crucial for cognitive function. Second, our meta-analysis demonstrated significant reductions in inflammatory markers (IL-6, TNF-α) with esketamine use, an outcome not comprehensively evaluated in previous ketamine studies [16, 59]. This anti-inflammatory effect could be a key mechanism distinguishing esketamine's efficacy from ketamine in POND prevention.

In the current meta-analysis, esketamine reduced the risk of POND by 47%. In addition to esketamine, various pharmacological approaches have been found to be effective in decreasing the incidence of POND. For example, dexmedetomidine has been reported to reduce the incidence of POND by 53% compared with standard care [60], although concerns regarding extended extubation time and the risk of bradycardia have been raised. Melatonin receptor agonists, which induce a 30% risk reduction, and haloperidol, which induces a 38% risk reduction, are also effective for POND prophylaxis [61, 62]. Compared with these two agents, esketamine offers additional benefits, such as improved postoperative sleep quality, enhanced quality of recovery, as well as reduced pain score, inflammatory marker levels, and depressive symptoms [57, 60, 63].

The asymmetry observed in funnel plots for certain outcomes, particularly cognitive function on POD 3, IL-6 levels, and pain scores (Egger's test $p<0.05$), warrants careful interpretation. Several factors may contribute to this asymmetry. First, the predominance of positive results among smaller studies suggests potential small-study effects, where smaller trials tend to

show larger treatment effects. This could reflect publication bias, with smaller negative studies being less likely to be published. Second, the exclusive inclusion of studies from China may have introduced regional publication patterns that affect study dissemination. Third, methodological heterogeneity across studies, including variations in cognitive assessment timing, could contribute to the observed asymmetry. These factors collectively lowered our certainty in the evidence for these outcomes, as reflected in the GRADE assessment.

This meta-analysis revealed that the esketamine group had significantly lower pain scores than the control group, which could be attributed to the ability of esketamine to modulate glutamatergic signaling and its interaction with opioid receptors [19]. This finding is consistent with previous studies that have reported the analgesic properties of esketamine [19, 20]. Adequate pain control is crucial in the postoperative period, as severe pain has been identified as a risk factor for the development of POND [53]. In addition, esketamine is associated with a lower risk of PONV, which is a common complication after surgery. Since PONV can cause patient discomfort, delayed recovery, and increased healthcare costs [64], the reduced risk of PONV with the use of esketamine is noteworthy.

No significant differences were observed in other recovery outcomes, such as extubation time and the risks of respiratory depression, agitation, hallucinations, and nightmares. While the absence of increased psychotomimetic effects or respiratory depression with esketamine appears favorable, this finding must be interpreted cautiously given the low certainty of evidence. Individual patient factors such as age, comorbidities, and concurrent medications may influence susceptibility to adverse effects, necessitating careful patient selection. The optimal dosing strategies likely vary across different surgical populations and patient characteristics, highlighting the need for more targeted research. Future studies should focus on identifying patient-specific risk factors and developing tailored protocols to maximize safety while maintaining efficacy.

While esketamine's initial costs exceed conventional anesthetics, its potential economic benefits warrant consideration. Our finding of 47% POND risk reduction could translate to significant healthcare savings, as POND increases one-year healthcare costs through extended hospitalizations and additional interventions [6]. The observed improvements in pain control and PONV reduction may further decrease resource utilization. Formal cost-effectiveness analyses across different healthcare systems are needed to quantify these potential savings and guide implementation decisions. Nevertheless, implementation of esketamine protocols requires careful attention to secure storage and dispensing given its potential for diversion and misuse outside medical settings. Healthcare systems must balance these challenges against the potential benefits of reduced POND-related complications and costs when developing institutional policies for esketamine use.

This meta-analysis has several limitations that should be considered when interpreting the results. First, all included studies were conducted in China, which may introduce biases related to healthcare practices, clinical protocols, and patient characteristics specific to the Chinese healthcare system—for instance, differences in perioperative care pathways, anesthetic techniques, and postoperative monitoring standards could affect the generalizability of our findings. Additionally, potential cultural differences in cognitive assessment tools suggest that the efficacy of esketamine observed in this meta-analysis should be validated in diverse populations before broad implementation in other healthcare settings. Second, significant heterogeneity was observed among the included studies in terms of patient characteristics, surgical procedures, esketamine dosage, follow-up time, and cognitive assessment tools. Although the meta-regression analysis did not reveal a significant association between esketamine dosage and cognitive outcomes, the heterogeneity in dosing regimens and follow-up timing across the included studies may have influenced the interpretation of the overall effect of esketamine. Third, the certainty of evidence was low to very low for several outcomes (e.g., cognitive function on POD 3), highlighting the need for well-designed high-quality RCTs to obtain more robust evidence on the efficacy and safety of esketamine in preventing POND. In addition, the presence of potential bias in some outcomes (i.e., cognitive function on POD 3 and inflammatory marker levels) raises concerns about the influence of unpublished negative studies on the overall findings. Fourth, the diagnostic criteria for POND varied across studies, which may have affected the accuracy and comparability of the pooled results.

In conclusion, this meta-analysis revealed that patients treated with esketamine had a lower risk of POND, improved cognitive function on PODs 1 and 3, reduced pain, reduced incidence of PONV, and decreased inflammatory marker levels. Moreover, esketamine did not adversely affect other recovery indicators, such as extubation time and risks of respiratory depression, agitation, hallucinations, or nightmares. Our findings support the use of perioperative esketamine to prevent POND and improve postoperative cognitive function in adult patients undergoing surgery under general anesthesia. However, further research is warranted to confirm these findings, establish optimal dosing and administration protocols, and assess the safety and efficacy of esketamine in diverse patient populations and surgical settings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02807-1.

Supplementary Material 1.

Supplementary Material 2.

Authors' contributions
Kuo-Chuan Hung and Chia-Li Kao: Conceptualization, Methodology, Software; Chun-Ning Ho and Jheng-Yan Wu: Data curation; Kuo-Chuan Hung and I-Wen Chen: Writing- Original draft preparation; Chun-Ning Ho and Chien-Ming Lin: Visualization, Investigation; Chun-Ning Ho: Supervision; Ying-Jen Chang and I-Wen Chen: Software, Validation; Kuo-Chuan Hung and I-Wen Chen: Writing-Reviewing and Editing.

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Data availability
The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Declarations

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Not applicable.

Consent for publication
Not applicable.

Competing interests
None declared.

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