Systematic Review and Meta-Analysis

Effect of perioperative intravenous ketamine on postoperative sleep disturbance in patients undergoing non-cardiac surgery: A systematic review and meta-analysis

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Submitted: 15-Jan-2025
Revised: 09-Mar-2025
Accepted: 15-Mar-2025
Published: 16-Apr-2025

Access this article online
Website: https://journals.lww.com/ijaweb
DOI: 10.4103/ija.ija_75_25
Quick response code

ABSTRACT

Background and Aims: Postoperative sleep disturbance (PSD) is a common condition that may lead to pain, cognitive impairment, depression, and delayed recovery. This review evaluates the efficacy of perioperative intravenous ketamine in alleviating PSD and offers evidence-based recommendations for clinical practice. **Methods:** A systematic search was performed in PubMed, Embase, Cochrane Library, Wanfang Data, VIP Information Resource System, China National Knowledge Infrastructure and China Biology Medicine disc (SinoMed) up to 6th November 2024. This article included a meta-analysis of randomised controlled trials (RCTs) along with a Grading of Recommendations Assessment, Development and Evaluation analysis. **Results:** A total of 2355 patients from 21 RCTs were analysed. The pooled results indicated that ketamine improved sleep quality compared to placebo on the first postoperative day, as evidenced by a reduction in Pittsburgh Sleep Quality Index scores [mean difference (MD): −2.69; 95% confidence interval (CI): −3.95, −1.42; $P < 0.0001$, $I^2 = 96\%$]. Ketamine also improved sleep quality on the second postoperative day (MD: −2.45; 95% CI: −3.99, −0.91; $P = 0.002$, $I^2 = 96\%$) and during the first three postoperative days (MD: −2.90; 95% CI: −4.79, −1.00; $P = 0.003$, $I^2 = 97\%$). In addition, ketamine reduced Visual Analogue Scale scores for pain (MD: −0.38; 95% CI: −0.55, −0.21; $P < 0.00001$, $I^2 = 84\%$). These results suggest that ketamine reduces PSDs and pain without significantly increasing adverse reactions. However, given the high heterogeneity and limited quality of evidence in this review, the results should be interpreted with caution. **Conclusion:** This meta-analysis indicates that administering ketamine during the perioperative period can enhance postoperative sleep quality. However, the optimal dose, timing and method of administration remain undetermined, emphasising the need for further research to establish standardised guidelines.

Keywords: Anaesthesia, GRADE, ketamine, level of evidence, meta-analysis, Pittsburgh Sleep Quality Index, postoperative pain, postoperative sleep disturbance, surgery

INTRODUCTION

Postoperative sleep disturbances (PSDs) are defined as alterations in sleep structure and quality experienced by patients during the early postoperative phase. The main manifestations are sleep deprivation, disruption of circadian rhythm and structural abnormalities, which occur in 15%–72% of patients after surgery.[1] Multiple factors can influence PSD, including postoperative pain, anxiety and preoperative comorbidities.[2] Numerous studies have shown that PSD negatively

How to cite this article: Yang N, Peng L, Kuang R, Xu R, Zhou L, Wang Y. Effect of perioperative intravenous ketamine on postoperative sleep disturbance in patients undergoing non-cardiac surgery: A systematic review and meta-analysis. Indian J Anaesth 2025;69:434-49.

affects patient rehabilitation, potentially delaying recovery, increasing complications, reducing quality of life and adversely affecting long-term outcomes.[3]

Evidence suggests ketamine can improve sleep quality in patients with severe depression and sleep disorders, highlighting its potential for treating sleep disturbances. While studies indicate its effectiveness for PSD, further clinical research is needed to explore its potential fully.[4] Given that postoperative depression and sleep disorders often coexist, the antidepressant effects of ketamine may play a beneficial role in alleviating PSD.[5] Studies have shown that administering intravenous ketamine at various dosages (e.g. 0.5 and 1 mg/kg) can effectively improve sleep disorders in postoperative patients.[6] The mechanism by which ketamine enhances sleep quality is likely multifactorial, involving its antidepressant effects, anti-inflammatory properties, analgesic actions and regulation of the circadian rhythm system.[7] In addition, ketamine's neuroprotective, cognitive enhancement and anxiolytic effects may also be key mechanisms in its ability to improve sleep disorders.[8] These effects may offer a novel, comprehensive therapeutic strategy for improving sleep disorders and promoting postoperative recovery.[9] As the number of surgical cases increases and the demand for effective rehabilitation rises, developing interventions to improve sleep quality becomes increasingly important.[10] Existing studies offer inconsistent conclusions regarding PSDs, and there is still insufficient exploration of ketamine dosage and intervention timing. This meta-analysis aims to evaluate the effects of perioperative intravenous ketamine on PSDs, providing stronger clinical evidence while exploring administration protocols to establish standardised intervention strategies. Specifically, this study addresses the following questions based on the PICOS framework: Participants (P): adult patients undergoing non-cardiac surgery; Interventions (I): perioperative intravenous administration of ketamine; Comparisons (C): control group receiving placebo or standard perioperative management without ketamine; Outcomes (O): primary outcomes include the incidence and severity of PSDs, assessed through the Pittsburgh Sleep Quality Index (PSQI) and other relevant measures and Study design (S): systematic review and meta-analysis of randomised controlled trials (RCTs).

METHODS

This review followed the Cochrane Collaboration guidelines[11] and was registered in the PROSPERO collaboration network (ID: CRD42023494834).

Search and study selection

A comprehensive literature search was conducted in CENTRAL, PubMed, Embase, Wanfang Data, VIP Information Resource System, China National Knowledge Infrastructure and the China Biology Medicine Disc (SinoMed). The search strategy incorporated both medical subject headings and free-text terms,[12] using a combination of keywords such as 'ketamine' AND 'sleep disturbances', which were adapted to suit the specific requirements of each database [Supplementary Table 1]. There were no restrictions on language, publication type or publication year to ensure the inclusion of all potentially relevant studies. To minimise language bias from Chinese studies, this research used a clear search strategy with tailored queries for various databases, ensuring inclusion of multilingual literature. Sensitivity analysis was used to assess the impact of language bias, and non-Chinese literature was translated and quality controlled to ensure the study's comprehensiveness and reliability.

Criteria for inclusion

The study included articles that met the following criteria: RCTs involving adult patients (≥18 years) undergoing non-cardiac surgery under general anaesthesia, with the experimental group receiving intravenous ketamine or esketamine intervention and a control group receiving a placebo or other anaesthetic and analgesic agents.

This study excluded trials involving patients who (1) were allergic to ketamine or had contraindications to its use; (2) had severe cardiac, renal or liver disease, psychiatric disorders or a history of drug abuse and (3) underwent cardiac surgery. Furthermore, we excluded non-RCTs, non-journal articles, outpatient procedures and studies that lacked specific trial outcomes.

Outcome measures

Primary outcome: The incidence of PSDs was assessed using PSQI (where higher scores indicate worse sleep quality, with a score of ≥6 suggesting the presence of PSD).[13]

Secondary outcomes: Numeric Rating Scale (NRS) for subjective sleep quality, Visual Analogue Scale (VAS) scores, Athens Insomnia Scale scores, Insomnia Severity Index, Epworth Sleepiness Scale, General Sleep Disturbance Scale, Hospital Anxiety and Depression Scale scores and rate of analgesic remedies were assessed. The NRS score effectively assesses

postoperative sleep improvement following ketamine administration. Since sleep and pain often influence each other, monitoring pain can indirectly reflect sleep quality. In addition, psychological factors like anxiety and depression also impact sleep. Therefore, assessing the psychological status can further aid in evaluating postoperative sleep.

For the same outcome measures at different time points, we prioritised the first postoperative day. When the first day after surgery was not available as a time point, we used the earliest postoperative time point as the time point of the outcome measure. For studies that included multiple ketamine doses, we selected the commonly used dose of 0.5 mg/kg for analysis. Research indicates that intravenous ketamine at 0.5 mg/kg efficiently alleviates depressive manifestations and improves sleep quality in individuals suffering from depression.[6]

Data collection and analysis

Two researchers independently assessed the titles and abstracts to select relevant articles. After using EndNote to automatically remove duplicate references, they manually checked and excluded duplicates and irrelevant studies. Full-text articles were then retrieved to confirm studies meeting the inclusion criteria. The entire search and selection process was carefully documented to facilitate the creation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart [Figure 1].

Data were independently extracted by two researchers using a standardised template and entered into Review Manager 5.3 software (The Cochrane Collaboration, Oxford, UK) for statistical analysis. The main contents of data extraction included study design, age, American Society of Anesthesiologists classification, number of participants, number of dropouts, gender, inclusion/exclusion criteria, type of intervention (dose, concentration, duration, route), timing of intervention, outcome measures, the reported time points for these outcomes and information needed for assessing the risk of bias.

Risk of bias assessment

Two researchers independently assessed study quality using the Cochrane Risk of Bias tool,[11] covering domains such as random sequence generation, allocation concealment, blinding, data integrity and selective reporting. All studies included in this research were evaluated and classified as having a 'low risk of bias', 'unclear risk of bias' or 'high risk of bias'. To assess inter-rater agreement, Cohen's kappa statistic was applied. The interpretation of κ values is as follows: $\kappa \leq 0$ indicates no agreement, 0.01–0.20 represents minimal agreement, 0.21–0.40 indicates fair agreement, 0.41–0.60 represents moderate agreement, 0.61–0.80 indicates substantial agreement and 0.81–1.00 denotes almost perfect agreement.[14] The assessment results display a κ value of 0.84, indicating a good level of agreement between the assessors. Any discrepancies were addressed through discussion, and when necessary, a third reviewer was consulted to achieve consensus. A risk of bias graph [Figure 2] was created to show the results for each quality domain.

Subgroup analysis

Heterogeneity was evaluated using the I^2 statistic, where $I^2 > 50\%$ indicated substantial heterogeneity. If significant heterogeneity was present ($P < 0.05$ or $I^2 > 50\%$), a random-effects model was employed; otherwise, a fixed-effects model was applied. In the presence of significant heterogeneity, we sequentially omitted one study at a time to identify potential sources. Subgroup analyses of the primary sleep disturbance outcomes were performed to further explore the stability of ketamine's effects and identify potential sources of heterogeneity, analysing ketamine administration timing (intraoperative vs. postoperative), dosage levels (≥0.5 vs. <0.5 mg/kg)[6] and administration methods (single injection vs. continuous infusion: intraoperative vs. postoperative analgesia).

Statistical analysis

In this study, dichotomous data were analysed using the risk ratio (RR) with a 95% confidence interval (CI), while continuous data (sleep quality scores) were analysed using the mean difference (MD) with a 95% CI. For secondary outcomes with different metrics (e.g. VAS, NRS), we standardised them to a 0–10 scale. If continuous data were not reported as mean [standard deviation (SD)], we followed Cochrane Handbook guidelines for conversions. When results were reported as medians and interquartile ranges (IQRs) instead of mean (SD), we adopted a commonly used method to estimate the mean and SD for inclusion in the meta-analysis. This method assumes a symmetric data distribution, allowing the median to approximate the mean and enabling the estimation of SD from IQR using established formulas. Previous studies have shown that this method is reliable when the data are symmetric; but for clearly

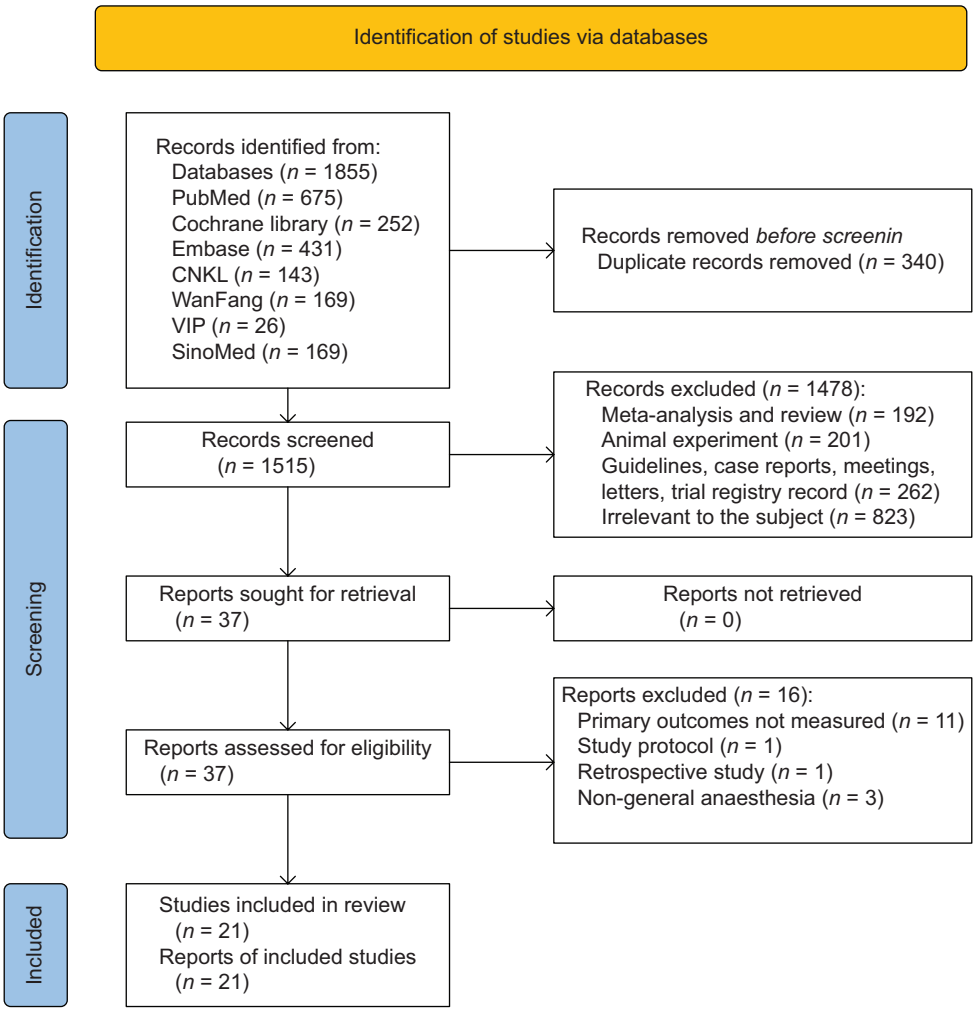

Figure 1: PRISMA flowchart. CNKL = China National Knowledge Infrastructure, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

asymmetric data, we excluded it to avoid bias.[15] To evaluate the potential influence of this assumption on the study results, sensitivity analyses were performed.

Certainty of evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was employed to evaluate the quality of evidence for primary outcomes. Randomised trials start as high-quality evidence, but can be downgraded due to five limitations: risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias. Each category can lead to a downgrade of 1–2 levels. Conversely, if a substantial treatment effect is observed, the rating can be upgraded accordingly. For example, an I^2 value >50% indicates moderate heterogeneity and >75% indicates high heterogeneity, leading to a downgrade of one or two levels, respectively.[16] These factors determine the certainty of evidence and classify it as high, moderate, low or very low. GRADEpro version 3.6 software was used to grade the certainty levels.

RESULTS

Study selection and characteristics

The initial online search identified 1855 potentially relevant articles. After removing duplicates, 1515 articles remained for screening. Of these, 1478 articles were excluded based on title and abstract screening. The remaining 37 studies were subjected to full-text review by two independent researchers, resulting in 16 articles being excluded. Twelve studies were excluded for not having sleep-related outcome measures, three studies were excluded for not involving general anaesthesia procedures and one study was excluded for lacking specific outcomes in the protocol. Finally, 21 articles were included in the meta-analysis [Figure 1].[1,17–36] A total of 2355 adult patients undergoing non-cardiac surgery were included in the 21 articles. Of these,

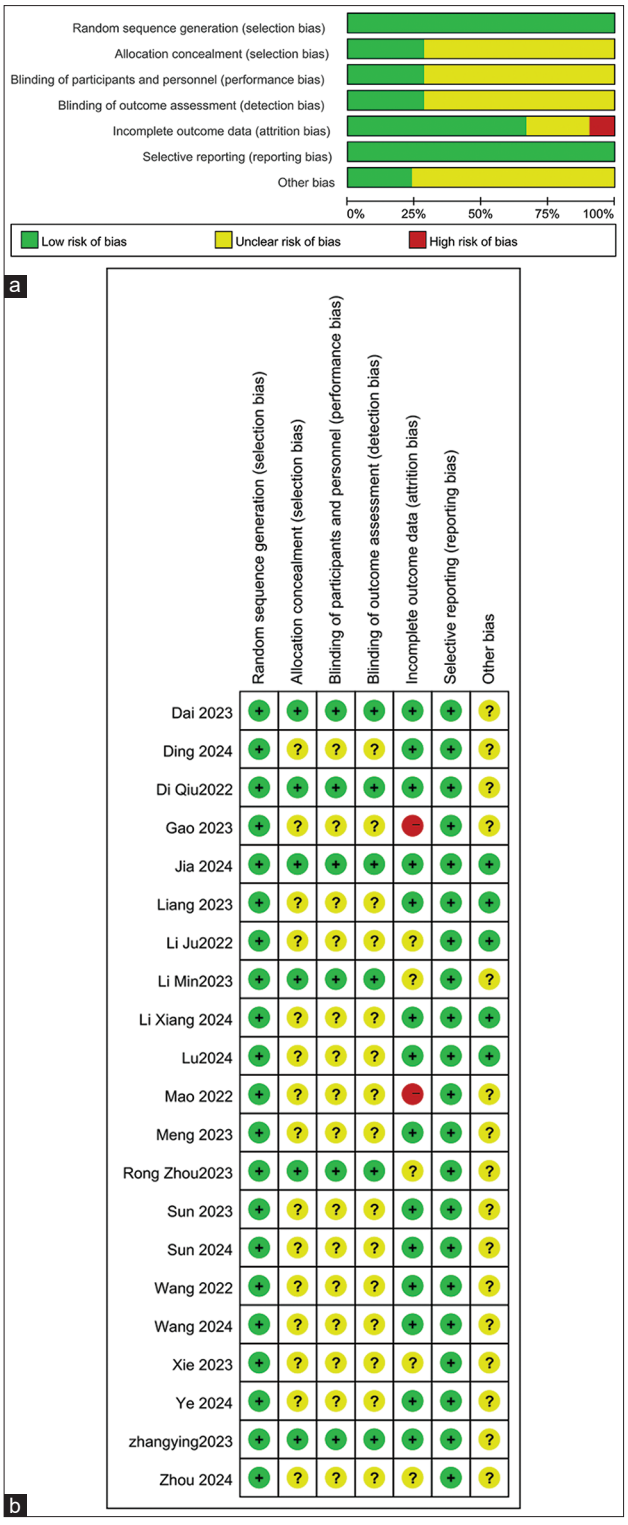

Figure 2: Literature quality was assessed using tools recommended by the Cochrane Collaboration (green: low risk of bias, yellow: uncertain risk of bias, red: high risk of bias). (a) Risk of bias summary. (b) Risk of bias for individual studies

three studies were international[1,17,18] and published in English, while 18 studies were from China and published in Chinese.[19–36] Among the interventions of the 21 studies, two studies involved a combination of esketamine and dexmedetomidine,[17,20] 18 articles used only esketamine[1,18,19,21–35] and one study used esketamine for anaesthesia induction, maintenance and postoperative patient-controlled analgesia.[36] The control group included only one comparison with sufentanil; all other comparisons were with a placebo (i.e. saline). Furthermore, six articles involved the continuous infusion of esketamine during surgery,[1,20–22,26,30]10 articles used esketamine for postoperative analgesia[17,23–25,28,29,32,34–36] and five articles involved intravenous bolus of esketamine.[18,19,27,31,33] The detailed characteristics of the included studies are presented in Table 1.

Quality assessment

The risk of bias for each primary outcome was assessed [Figure 2]. Generally, no studies were found to have an overall low risk of bias. All included RCTs mentioned the use of randomisation techniques, but the authors of 15 articles did not provide specific information regarding the randomisation process (allocation sequence or concealment). Fifteen articles included in the analysis did not describe the blinding of participants and assessors, and two articles failed to mention the methods used for handling missing data.

Primary outcome

The preliminary segment of the study assessed the potential therapeutic effects of ketamine on PSDs, measured using PSQI. In this study, the PSQI scores in some articles were asymmetrically distributed and presented as medians and IQRs. As a result, these data were not converted to means and SDs. Sleep quality was assessed during the first 3 days post-surgery, and the findings revealed that intravenous ketamine infusion on the first postoperative day significantly improved sleep disturbances compared to placebo (MD: −2.69; 95% CI: −3.95, −1.42; $P < 0.0001$, $I^2 = 96\%$). In addition, esketamine significantly improved sleep disturbances on the second (MD: −2.45; 95% CI: −3.99, −0.91; $P = 0.002$, $I^2 = 96\%$) and third (MD: −2.90; 95% CI: −4.79, −1.00; $P = 0.003$, $I^2 = 97\%$) postoperative days. The corresponding forest plot is shown in Figure 3.1.

Variations in assessment time points and ketamine dosages across studies may have contributed to the variability in the results. Furthermore, the study results showed considerable heterogeneity, which may be attributed to differences in surgical types, the timing of ketamine administration, dosage, administration methods, the timing of postoperative sleep quality

Table 1: Study characteristics

Reference	Year	Type of operation	Groups (number of patients)	Ketamine administration time and duration	Postoperative analgesia	Adverse events
Ying Zhang *et al*.[17]	2023	Scoliosis correction surgery	(1) Esketamine: PCIA with esketamine 50 mg, dexmedetomidine 200 mg and sufentanil 4 mg/kg/h (up to 250 mg) for 72 h (*n*=99); (2) control: PCIA with sufentanil 4 mg/kg/h (up to 250 mg) for 72 h (*n*=100)	(1) After extubation or while intubating after leaving the operating room for ICU and (2) last 72 h	PCIA	Nausea, vomiting, dizziness, constipation, itching, psychiatric symptoms and other symptoms
Di Qiu *et al*.[1]	2022	Gynaecological laparoscopic surgery	(1) Esketamine: esketamine infusion 0.3 mg/kg/h (n=92); (2) control: normal saline equivalent infusion (*n*=91)	Intraoperative continuous infusion	(1) PCIA includes hydromorphone (0.2 mg/kg) for 48 h; (2) rescue analgesia: flurbiprofen axidate 50 mg	Vomiting and nausea, dizziness, itching, nightmares
Rong Zhou *et al*.[18]	2023	Elective two-port VATS for unilateral pulmonary lesions (including lung wedge resection, segmentectomy, lobectomy and radical lung cancer resection)	(1) Esketamine: intravenous injection of *S*-ketamine 0.5 mg/kg (*n*=195); (2) control : intravenous injection of normal saline (*n*=192)	Intravenous injection of 0.5 mg/kg before anaesthesia induction	(1) PCIA includes sufentanil 0.15 mg/kg, used before leaving PACU; (2) rescue analgesia: intravenous flurbiprofen 50 mg	Nausea, vomiting and dizziness
Liang *et al*.[19]	2023	Laparoscopic total hysterectomy	(1) Esketamine: intravenous injection of 0.3 mg/kg esketamine (*n*=53); (2) control: equal amount of normal saline (*n*=53)	Intravenous injection before incision was 0.3 mg/kg	PCIA includes sufentanil 100 μg and ondansetron 12 mg	Laryngeal spasm, postoperative nausea, vomiting, headache, delirium
Dai *et al*.[22]	2023	Laparoscopic colorectal cancer surgery	(1) Esketamine: continued infusion of esketamine 0.2 mg/kg/h until the end of surgery (*n*=39); (2) control: infusion of equal volume of 0.9% sodium chloride solution (*n*=38)	(1) Continuous infusion of esketamine 0.2 mg/kg/h after endotracheal intubation (2) continued until the end of surgery	Postoperative PCIA with sufentanil at 2 μg/kg	Respiratory depression, nausea, vomiting, headache
Mao *et al*.[24]	2022	Traumatic amputation	(1) Esketamine: PCIA with fentanyl 8 μg/kg + esketamine 50 mg+0.9% 100 ml saline for 50 h (*n*=42); (2) control: PCIA with fentanyl 8 μg/kg + 0.9% 100 ml saline for 50 h (*n*=42)	Last 50 h	PCIA	/
Li Ju *et al*.[25]	2022	Radical mastectomy	(1) Esketamine: PCIA with sufentanil 2 μg/kg + esketamine 0.5 mg/kg + azasketone 20 mg, continued infusion for 48 h (*n*=45); (2) control: PCIA with sufentanil 2 μg/kg + azasetron 20 mg for 48 h (*n*=45)	Last 48 h	PCIA	Restlessness, nausea, vomiting, dizziness, respiratory suppression, remedial analgesia, blurred vision
Zhou *et al*.[26]	2024	Radical mastectomy	(1) Esketamine: continued infusion of 0.3 mg/(kg·h) esketamine (*n*=40); (2) control: continued infusion of the same amount of normal saline during the operation (*n*=40)	(1) Continued infusion of esketamine 0.3 mg/(kg·h) during the operation; (2) continued until the end of the operation	PCIA	Nausea, vomiting, dizziness
Li Min *et al*.[27]	2023	Modified radical mastectomy	(1) Esketamine: intravenous injection of esketamine 0.2 mg/kg for 1 min (*n*=40) and (2) control: intravenous injection of the same amount of normal saline for 1 min (*n*=40)	(1) Esketamine 0.2 mg/kg was injected intravenously 30 min before the end of the operation and (2) last 1 min	PCIA	Nausea, vomiting, nightmares, hallucinations

Contd...

Table 1: Contd...

Reference	Year	Type of operation	Groups (number of patients)	Ketamine administration time and duration	Postoperative analgesia	Adverse events
Meng *et al*.[28]	2023	Laparoscopic myomectomy	(1) Ketamine: PCIA with 10 mg butorphanol + 20 mg domperidone + 1 mg/kg ketamine.(*n*=55) and (2) control: PCIA with 10 mg butorphanol+20 mg domperidone (*n*=55)	(1) After extubation at the end of surgery and (2) last 24–48 h	PCIA	Nausea and vomiting, somnolence, dizziness and headache, hallucinations
Sun *et al*.[20]	2024	Modified radical mastectomy	(1) Esketamine: infusion of propofol 3–5 mg/(kg·h), esketamine 0.2 mg/(kg·h), dexmedetomidine 0.5 μg/(kg·h) (n=44) and (2) control: infusion of propofol 4–6 mg/kg/h, remifentanil 0.1–0.3 μg/(kg·min) (*n*=43)	Intraoperative continuous infusion	PCIA: sufentanil 0.02 μg/(kg·h) + ondansetron 10 mg	Postoperative agitation, dizziness, nausea and vomiting, hypotension, pruritus, nightmares
Gao *et al*.[21]	2023	VATS lobectomy	(1) Esketamine: intravenous infusion of esketamine hydrochloride injection 0.5 mg/kg (n=40) and (2) control: intravenous infusion of an equivalent volume of normal saline (*n*=40)	(1) After the catheter is inserted into the chest and (2) continuous infusion until 30 min before surgery	PCIA: sufentanil citrate 100 μg+dezocine 10 mg+tropisetron 10 mg	Respiratory depression, pruritus or itching, nausea and vomiting, blood pressure fluctuations, palpitations, somnolence or drowsiness
Xie *et al*.[23]	2023	Laparoscopic radical colectomy	(1) Esketamine: PCIA with esketamine 1 mg/kg + sufentanil 1.5 μg/kg (*n*=52) and (2) control: PCIA with sufentanil 2 μg/kg (*n*=52)	Last 36 h	PCIA	Hypotension, nausea and vomiting, bradycardia, vertigo
Lu *et al*.[29]	2024	Laparoscopic total hysterectomy	(1) Ketamine: PCIA with esketamine 0.5 mg/kg + oxycodone 40 mg+dexmedetomidine 100 μg + tropisetron 5 mg+0.9% sodium chloride injection up to 100 ml (*n*=39) and (2) control: PCIA: with oxycodone 40 mg+dexmedetomidine 100 μg+tropisetron 5 mg+0.9% sodium chloride injection up to 100 ml (*n*=39)	Immediately after surgery	PCIA	Nausea and vomiting, dizziness, hallucinations, blurred vision
Li *et al*.[30]	2024	Open reduction and internal fixation of traumatic long bone fractures of the extremities	(1) *S*-ketamine: intravenous infusion of 0.5 mg/kg/h *S*-ketamine until the end of the surgery (*n*=42) and (2) control: intravenous infusion of an equal volume of normal saline during the surgery (*n*=42)	Intraoperative continuous infusion	PCIA	Nausea, vomiting, hallucinations, nightmares
Sun *et al*.[31]	2023	Laparoscopic radical nephrectomy for renal cancer	(1) Ketamine: intravenous injection of 0.3 mg/kg esketamine before surgery (*n*=48) and (2) control: intravenous injection of an equal volume of normal saline before surgery (*n*=48)	Intravenous injection before surgery	PCIA	Postoperative agitation, nausea and vomiting
Ye *et al*.[32]	2024	Thoracoscopic radical lung cancer surgery	(1) Esketamine: PCIA with sufentanil 1.5 μg/kg, esketamine 1.0 mg/kg, azasetron 10 mg, diluted to 100 ml with 0.9% sodium chloride solution (*n*=43)	(1) Connect the analgesia pump for PCIA 10 min before the end of the surgery; (2) last 48 h	Rescue analgesia: intravenous injection of tramadol 100 mg	Nausea and vomiting, respiratory depression, dizziness, skin itching, delirium

Contd...

Table 1: Contd...

Reference	Year	Type of operation	Groups (number of patients)	Ketamine administration time and duration	Postoperative analgesia	Adverse events
			and (2) control: azasetron 10 mg and sufentanil 2.5 μg/kg, diluted to 100 ml with 0.9% sodium chloride solution (*n*=43)			
Ding *et al*.[33]	2024	Laparoscopic total hysterectomy	(1) Ketamine: administer intravenous esketamine 0.3 mg/kg before skin incision (*n*=55); (2) control: administer an equivalent dose of normal saline before skin incision (*n*=55)	Intravenous injection before skin incision	(1) PCIA (2) Rescue analgesia: intravenous injection of tramadol 50 mg	Nausea, vomiting, headache, dizziness
Wang *et al*.[36]	2024	Radical mastectomy	(1) Ketamine: induction: 0.1 mg/kg esketamine; maintenance: 0.1 mg/kg/h esketamine; PCIA: 1 mg/kg esketamine (*n*=33) and (2) control: equivalent volume of normal saline (*n*=33)	Induction: 0.1 mg/kg esketamine; maintenance: 0.1 mg/kg/h esketamine; PCIA: 1 mg/kg esketamine	PCIA	/
Jia *et al*.[34]	2024	Thoracoscopic lung resection surgery	(1) Ketamine: PCIA with sufentanil 1.5 μg/kg+esketamine 1 mg/kg+ondansetron 4 mg (*n*=48) and (2) control: PCIA with sufentanil 2 μg/kg + ondansetron 4 mg (*n*=48)	PCIA	(1) PCIA (2) Rescue analgesia: intravenous injection of flurbiprofen axetil 50 mg	Hypotension, bradycardia, dizziness, nausea, vomiting, drowsiness, skin itching, respiratory depression
Wang *et al*.[35]	2022	Abdominal surgery	(1) Ketamine: PCIA with 0.6 mg/kg esketamine combined with 0.3 mg/kg dezocine (*n*=38); (2) control: PCIA with sufentanil 2 μg/mg combined with 0.3 mg/kg dezocine (*n*=38)	PCIA	PCIA	Nausea and vomiting, drowsiness, fatigue, dizziness and arrhythmia

ICU=intensive care unit, PACU=post-anaesthesia care unit, PCIA=patient-controlled intravenous analgesia, VATS=video-assisted thoracoscopic surgery

assessments and the baseline characteristics of patients, such as age and gender.

Secondary outcome

Furthermore, we also compared the differences in VAS scores between patients who received ketamine and saline interventions on the first day after surgery. The results demonstrated that ketamine caused a statistically significant improvement in VAS scores on the first postoperative day, compared to placebo (MD: −0.38; 95% CI: −0.55, −0.21; $P < 0.00001$, $I^2 = 84\%$), indicating that ketamine effectively reduces postoperative pain on the first day after surgery. The corresponding forest plot is shown in Figure 3.2. Overall, ketamine shows limited effectiveness in postoperative pain relief and does not support its routine use for postoperative analgesia. Therefore, its widespread use as a standard analgesic is not currently recommended.

Lastly, the analysis of analgesic rescue rates between the two groups showed that the ketamine group experienced a significantly lower rate of rescue compared to the placebo group (RR: 0.48; 95% CI: 0.33, 0.70; $P = 0.0001$, $I^2 = 53\%$), further confirming the effectiveness of ketamine in postoperative pain management [Figure 3.3]. However, due to the small overall effect size indicated in the forest plot, the study shows that ketamine has limited efficacy in alleviating postoperative pain. While ketamine possesses some analgesic properties, its effect on postoperative pain may be insufficient to support its widespread use in clinical practice.

Adverse effects

In analysing postoperative adverse effects, we synthesised the reported reactions, including nausea, vomiting, dizziness, headache, constipation, itching and psychiatric symptoms such as delirium and nightmares. Our evaluation found no statistically significant differences in postoperative adverse reactions when comparing the ketamine group with the control group. This result suggests that the risk of postoperative adverse reactions does not

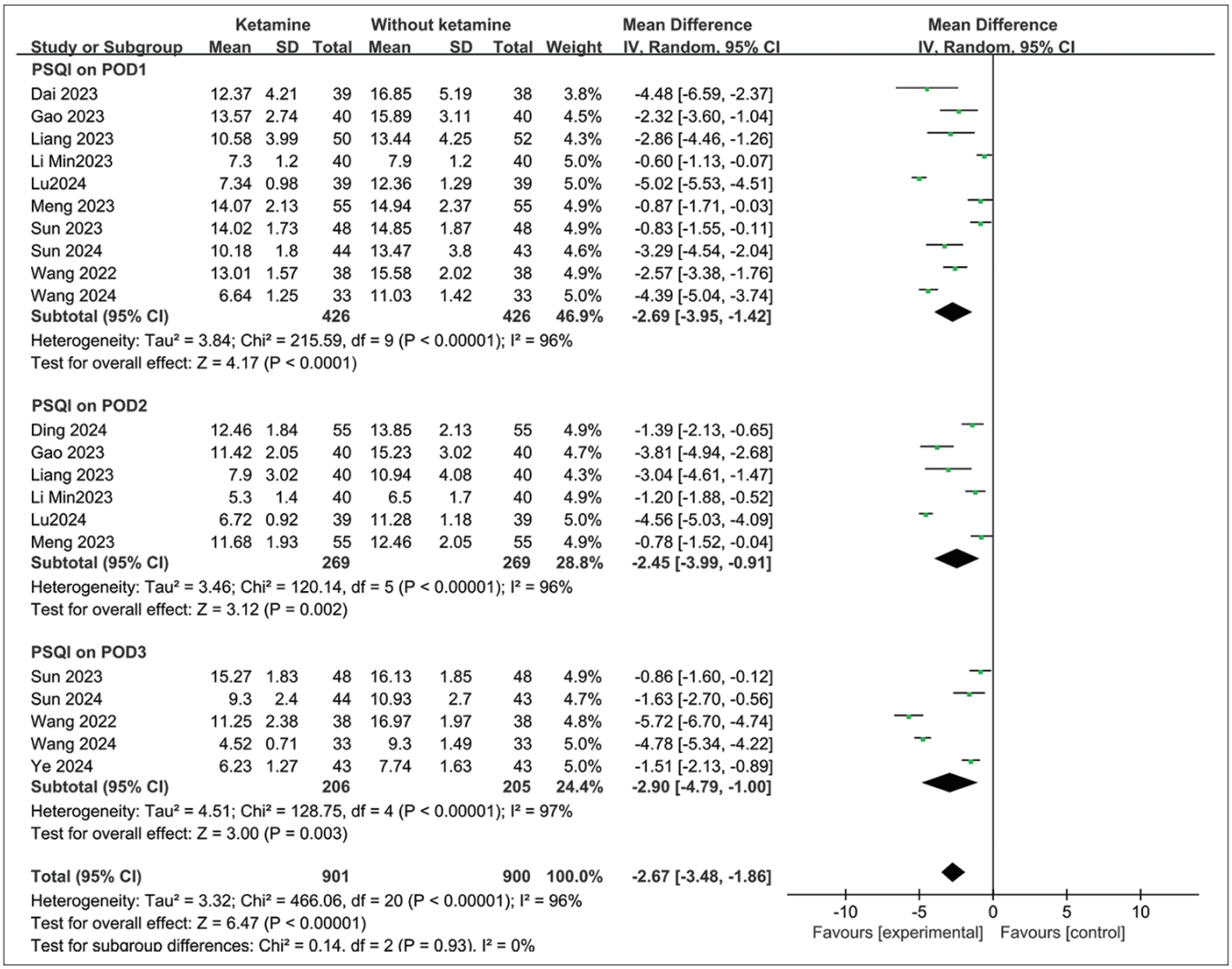

Figure 3.1: Forest plots of the incidence of postoperative sleep disturbance measured by PSQI on POD1, POD2 and POD3 (I^2 = heterogeneity). CI = confidence interval, df = degrees of freedom, IV = inverse variance, POD = postoperative day, PSQI = Pittsburgh Sleep Quality Index, SD = standard deviation

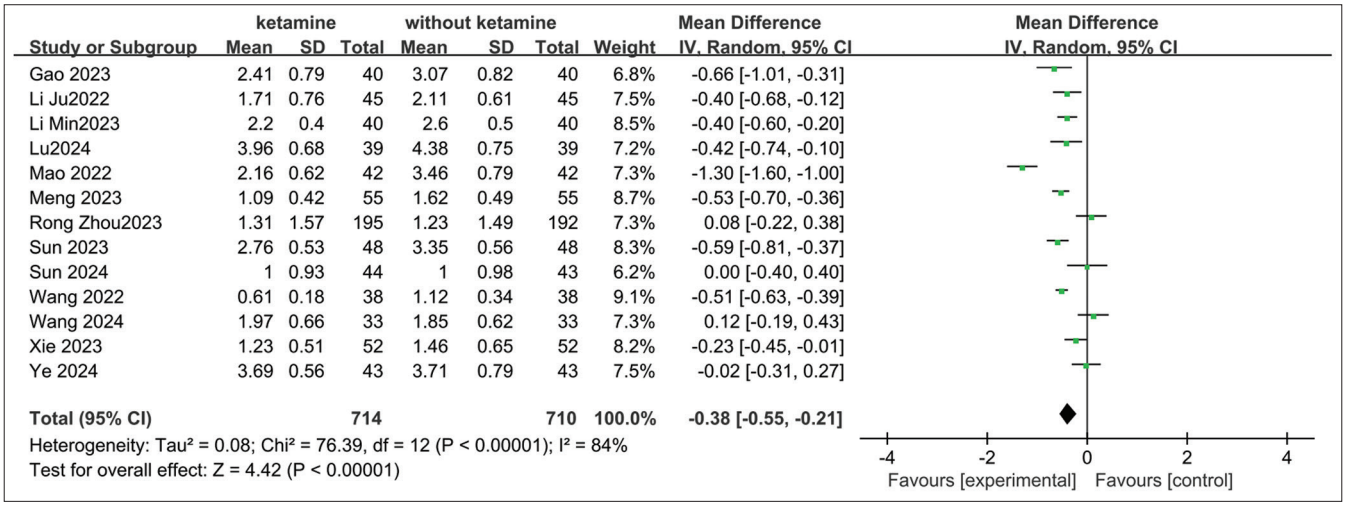

Figure 3.2: Forest plots of postoperative pain intensity (measured by VAS) on POD1 (I^2 = heterogeneity)). CI = confidence interval, df = degrees of freedom, IV = inverse variance, POD = postoperative day, SD = standard deviation, VAS = Visual Analogue Scale

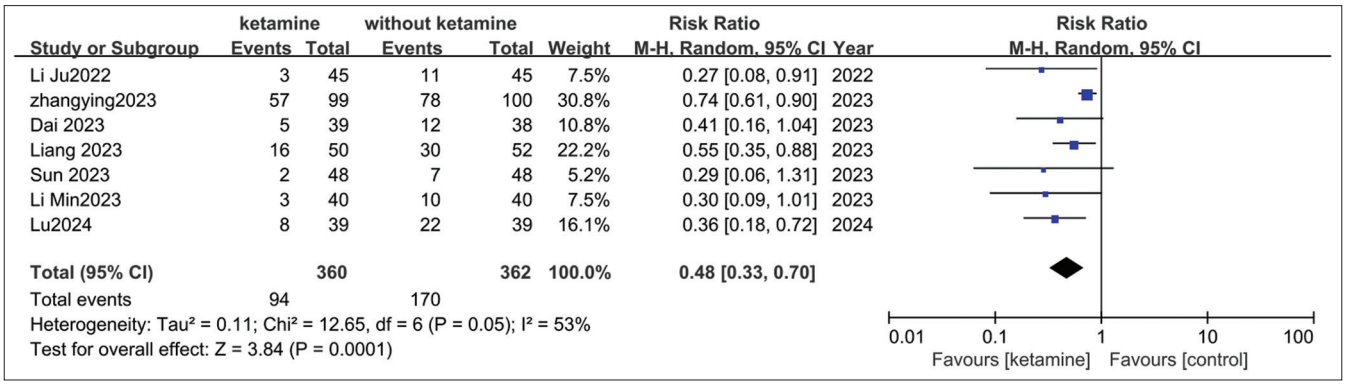

Figure 3.3: Forest plots of analgesic rescue rate within 1 week postoperatively (I^2 = heterogeneity). CI = confidence interval, df = degrees of freedom, MH = Mantel–Haenszel

increase significantly with perioperative intravenous administration of ketamine [Supplementary Figure 1]. However, the follow-up periods related to ketamine's adverse reactions are generally short, and there is a lack of comprehensive data from extended follow-up studies. This makes the prolonged safety profile of ketamine uncertain, especially in the context of its use in sustained or high-dose applications, where potential risks and side effects have not been fully evaluated.

Sensitivity analysis

Given the high heterogeneity of the results, sensitivity analysis was employed to evaluate the stability of the primary outcome. This approach involved progressively removing each study to assess its effect on the overall effect size, thus assessing the robustness of the results.[37] The current analysis indicates that the MDs in each study are negative, and the 95% CIs do not include zero, suggesting a statistically significant difference between the ketamine group and the control group, regardless of which study was excluded. Although heterogeneity values are high, they remain relatively stable after excluding any individual study, suggesting that the variability in effect size estimates across studies exists but is not influenced by any single study. This confirms the stability and reliability of our main result – the efficacy of ketamine in improving postoperative sleep quality – suggesting that the overall assessment of PSD remains stable [Table 2].

Subgroup analysis

Due to the high heterogeneity and variability in surgical types within the study, subgroup analyses were performed on the timing, dosage and administration methods of ketamine to explore the factors contributing to the heterogeneity. This article subdivided the timing of ketamine administration into two subgroups, intraoperative and postoperative, to evaluate its impact on postoperative sleep quality. The results showed that, regardless of whether ketamine was administered intraoperatively or postoperatively, there was a significant reduction in PSQI scores assessing postoperative sleep quality (intraoperative: MD: −2.17; 95% CI: −3.27, −1.08; $P < 0.0001$, $I^2 = 85\%$; postoperative: MD: −2.84; 95% CI: −5.38, −0.30; $P = 0.03$, $I^2 = 97\%$) [Figure 4]. Regarding the dosage of ketamine, the study divided it into dose ≥0.5 mg/kg and dose <0.5 mg/kg groups.[6] The study results demonstrated that intravenous injection of ketamine at both dosages positively improved PSDs (≥0.5 mg/kg group: MD: −2.72; 95% CI: −4.78, −0.65; $P = 0.01$, $I^2 = 96\%$; <0.5 mg/kg group: MD: −2.16; 95% CI: −3.41, −0.92; $P = 0.0007$, $I^2 = 87\%$) [Figure 5]. In addition, this study analysed the methods of ketamine administration, including single intravenous injection and continuous infusion. The results indicated that both continuous intravenous infusion and single intravenous injection of ketamine significantly improved the therapeutic effect compared to the control group (intravenous injection: MD: −1.12; 95% CI: −2.02, −0.23; $P = 0.01$, $I^2 = 71\%$; continuous infusion: MD: −3.06; 95% CI: −4.61, −1.50; $P = 0.0001$, $I^2 = 94\%$) [Figure 6].

Grading the certainty of evidence

Table 3 presents the results of the evidence quality evaluation based on the GRADE system. For studies evaluating sleep quality on postoperative day 1 (POD1) using PSQI, evidence quality was rated low due to substantial heterogeneity, despite no major concerns about bias, indirectness or imprecision. These findings indicate that, although ketamine could have some potential to improve the sleep quality on POD1, the evidence is insufficient and should be interpreted with caution. Similar findings were observed for PSQI scores on postoperative days 2 (POD2) and 3 (POD3),

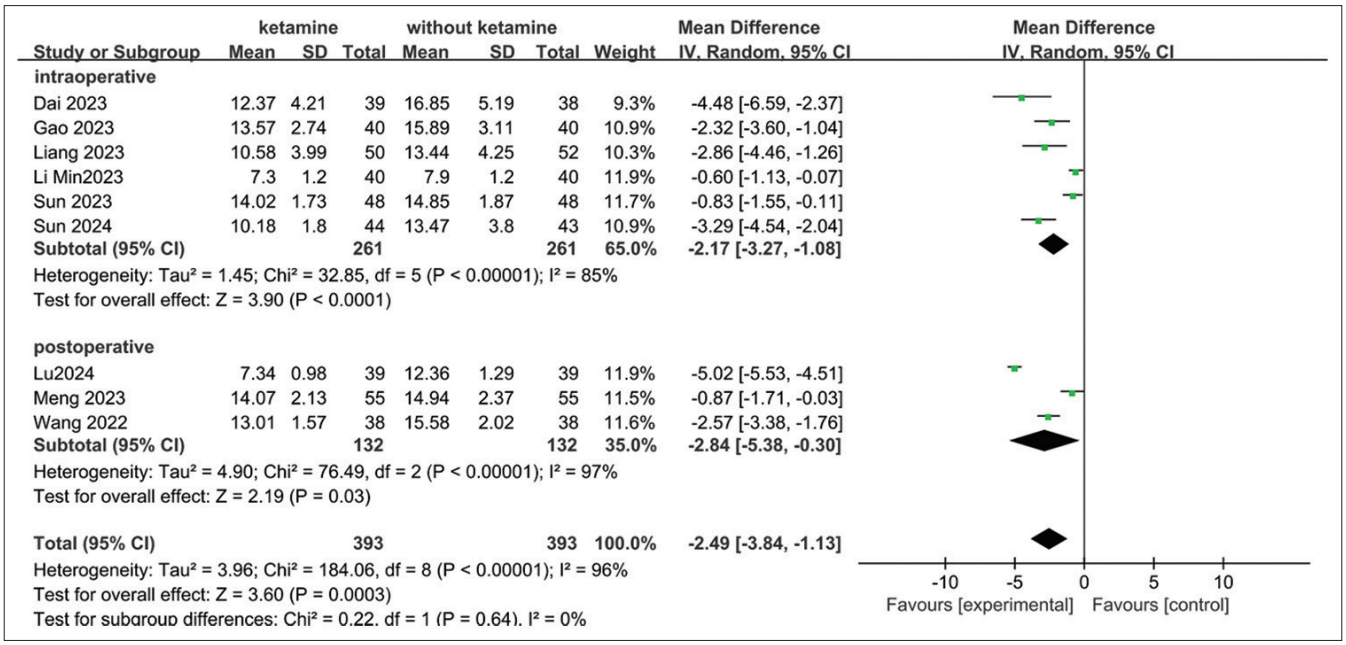

Figure 4: Forest plot of PSQI score on POD1 by subgroup – timing of ketamine administration (intraoperative and postoperative) (I^2 = heterogeneity). CI = confidence interval, df = degrees of freedom, IV = inverse variance, POD = postoperative day, PSQI = Pittsburgh Sleep Quality Index, SD = standard deviation

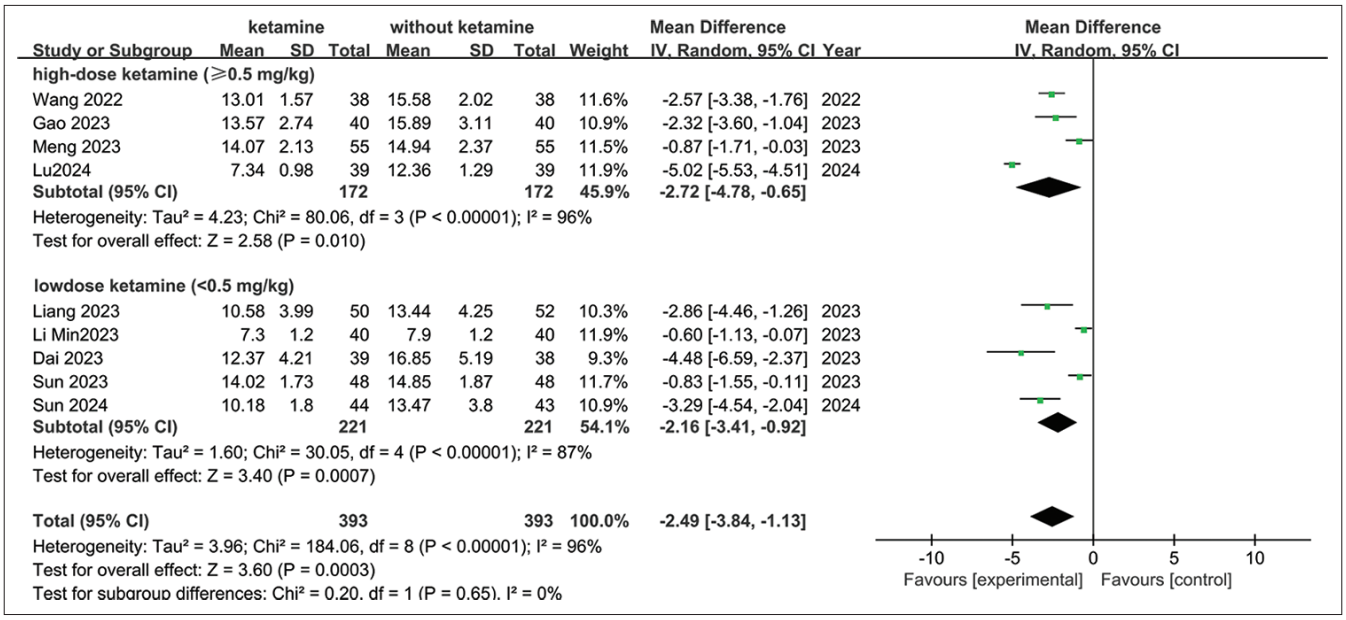

Figure 5: Dose of ketamine administration (dose ≥0.5 mg/kg, dose < 0.5 mg/kg) (I^2 = heterogeneity). CI = confidence interval, df = degrees of freedom, IV = inverse variance, SD = standard deviation

where high heterogeneity led to a low-quality rating. Although there are indications that ketamine may improve postoperative sleep quality, the evidence remains of low quality and requires careful consideration.

The evidence quality for postoperative pain, evaluated using the VAS score, was found to be very low. This was mainly due to severe imprecision, as the 95% CIs covered both increases and decreases in pain scores, combined with high heterogeneity. This suggests that, while some evidence points to ketamine potentially providing postoperative pain relief, the estimates of effect are highly uncertain.

Overall, this study demonstrates that ketamine has some effect in improving postoperative sleep quality and alleviating pain. However, the existing evidence is

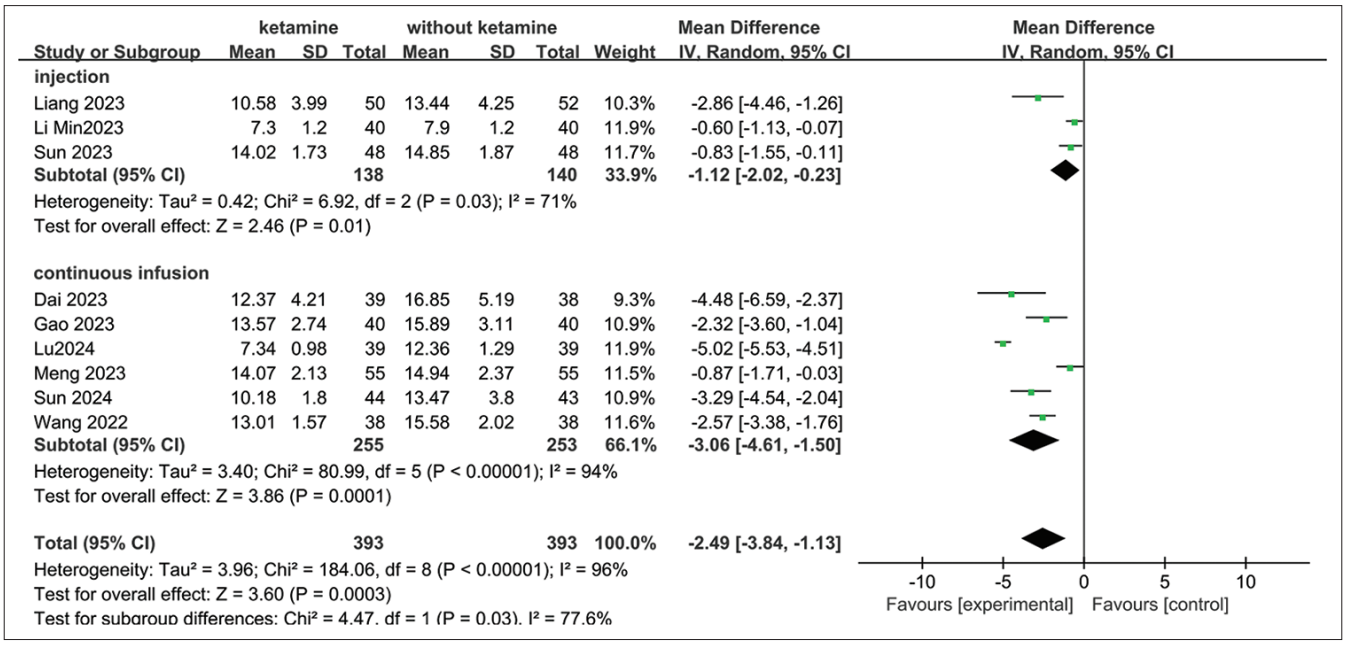

Figure 6: Mode of ketamine administration (single injection, continuous infusion) (I^2 = heterogeneity). CI = confidence interval, df = degrees of freedom, IV = inverse variance, SD = standard deviation

Table 2: Sensitivity analysis of sleep quality (measured by PSQI) on POD1

Outcome	Exclusion of one by one	MD	95% CI	I^2
PSQI on POD1	Dai 2023	−2.52	(−3.85, −1.20)	96%
	Gao 2023	−2.73	(−4.09, −1.36)	96%
	Liang 2023	−2.67	(−4.02, −1.32)	96%
	Lin Min 2023	−2.93	(−4.16, −1.70)	94%
	Meng 2023	−2.9	(−4.24, −1.55)	96%
	Sun 2024	−2.62	(−3.99, −1.26)	96%
	Lu 2024	−2.39	(−3.49, −1.28)	93%
	Sun 2023	−2.9	(−4.25, −1.56)	96%
	Wang 2022	−2.7	(−4.12, −1.29)	96%
	Wang 2024	−2.49	(−3.84, −1.13)	96%

CI=confidence interval, MD=mean difference, POD1=postoperative day 1, PSQI=Pittsburgh Sleep Quality Index. I^2=heterogeneity

generally of low quality, with limited sample sizes and numerous limitations in study design. Therefore, more high-quality, large-scale studies are urgently needed to confirm the actual role of ketamine in managing postoperative pain and sleep.

Publication bias

We used R software (version 4.3.3 'Angel Food Cake', R Core Team, 2024) to conduct Begg's rank correlation test and Egger's linear regression test, with the aim of evaluating the publication bias of PSQI on the first day after surgery. Begg's test ($P = 0.751$) and Egger's test ($P = 0.129$) indicated no significant publication bias. In addition, we created funnel plots for visual inspection. Observation of the funnel plot revealed that the data points were symmetric, suggesting no publication bias. However, due to the limited number of studies included, this finding should be interpreted cautiously, as the observed symmetry may be a random result arising from the small sample size [Figure 7].

DISCUSSION

The meta-analysis included 21 eligible studies and found that ketamine improved PSDs, providing evidence to support its clinical use in managing postoperative sleep. Furthermore, ketamine also reduced the occurrence of postoperative pain and decreased the rate of rescue analgesia, indicating its benefits in improving pain management. Considering the high heterogeneity and the limited quality of evidence in this study, caution is needed when interpreting the results.

PSDs are widespread in clinical practice,[38] and are influenced by factors including age, the severity of surgery, postoperative pain and environmental stressors.[3] Despite its significant impact, PSD is often overlooked in clinical care and research. Most strategies focus on physiological recovery rather than sleep quality. Given PSD's multifactorial nature, integrated multimodal approaches are recommended.[39] These approaches include reducing preoperative anxiety, minimally invasive surgery, effective non-opioid pain management, pharmacological treatments (e.g. dexmedetomidine, zolpidem, melatonin) and non-pharmacological

Table 3: The GRADE level of certainty for primary outcome

No. of studies	Study design	Certainty assessment					No. of patients		Effect	Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ketamine	Saline	Relative (95% CI)	Absolute (95% CI)		
PQSI on POD1 (assessed with: PQSI; scale from 0 to 21)												
10	Randomised trials	Not serious	Very serious[a]	Not serious	Not serious	None	426	426	-	MD 0 (3.95 lower to 1.42 lower)	⊕⊕◯◯ Low[a]	CRITICAL
PSQI on POD2 (assessed with: PSQI; scale from 0 to 21)												
6	Randomised trials	Not serious	Very serious[a]	Not serious	Not serious	None	269	269	-	MD 0 SD (3.99 lower to 0.91 lower)	⊕⊕◯◯ Low[a]	CRITICAL
PSQI on POD3 (assessed with: PSQI)												
5	Randomised trials	Not serious	Very serious[a]	Not serious	Not serious	None	206	205	-	0 (4.79 lower to 1 lower)	⊕⊕◯◯ Low[a]	CRITICAL
VAS (assessed with: VAS; scale from 0 to 10)												
13	Randomised trials	Not serious	Very serious[a]	Not serious	Serious[b]	None	714	710	-	MD 0 (0.55 lower to 0.21 lower)	⊕◯◯◯ Very low[a,b]	IMPORTANT

CI=confidence interval, MD=mean difference, POD=postoperative day, PSQI=Pittsburgh Sleep Quality Index, VAS=Visual Analogue Scale. [a]Quality was rated down for inconsistency because I^2 >75%. bThe 95% CI includes both a reduction and an increase in pain scores

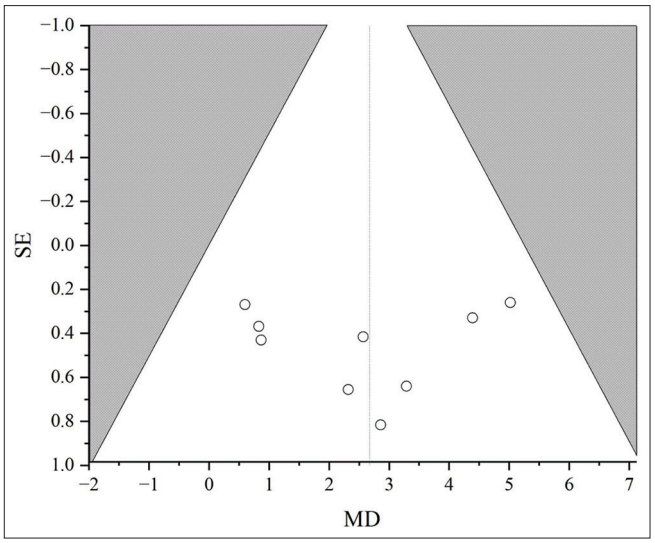

Figure 7: A funnel plot of PSQI scores on POD1 (O indicates the included studies). MD = mean difference, POD = postoperative day, PSQI = Pittsburgh Sleep Quality Index, SE = standard error

methods like Enhanced Recovery After Surgery protocols. Currently, pharmacological interventions remain the most commonly used approach to improve postoperative sleep.[40]

Ketamine, as an N-methyl-d-aspartate (NMDA) receptor antagonist, is widely used in clinical practice.[41] It may regulate sleep cycles, alleviate pain and reduce postoperative stress responses by affecting multiple pathways in the central nervous system.[9,42,43] Early studies suggest that the perioperative use of ketamine can improve patients' sleep quality. The improvement in sleep quality is thought to result from ketamine's antidepressant effects, anti-inflammatory properties, analgesic action, interactions with the circadian system and neurocognitive and anxiolytic impacts.[44] Furthermore, current research is focused on determining the optimal ketamine dosage, the timing of its administration and its combination with other anaesthetic drugs. While existing studies support the idea that perioperative ketamine use can improve postoperative sleep quality, the evidence remains insufficient, and further research is needed to validate these findings.

This meta-analysis demonstrates that intravenous ketamine alleviates PSDs. The statistical analysis further supports its positive effect, emphasising ketamine's potential value in postoperative management, particularly in controlling pain and mitigating sleep disorders. However, the mechanisms underlying these effects require further exploration. In addition, the results exhibit considerable heterogeneity,

likely due to variations in surgical types, timing, dosage and administration methods of ketamine, as well as patient baseline characteristics such as age and gender. The inclusion of diverse surgeries, such as breast, thoracoscopic, laparoscopic and limb fracture surgeries, limited the ability to assess the impact of surgical type on sleep improvement. Variations in ketamine administration timing, dosage and methods, along with differences in gender and age among participants, contributed to this heterogeneity. The small number of studies also restricted the ability to perform subgroup analyses considering these factors, which, in turn, heightened the heterogeneity. Future research should focus on specific patient populations tailored to different surgical types, while standardising the administration method, dosage and timing of ketamine. This would help reduce heterogeneity and improve result reliability.

Furthermore, this article primarily compared ketamine with saline and found it effective in improving PSDs. However, it did not compare ketamine with other common interventions, such as dexmedetomidine or sufentanil, limiting a comprehensive assessment of ketamine's relative advantages and safety. In addition, we extensively explored the impact of ketamine administration timing, method and dosage on PSDs. Based on the subgroup analysis conducted, the results indicate that continuous infusion of ketamine demonstrates more significant and stable clinical effects compared to a single intravenous injection regimen. This finding suggests that continuous infusion may be a more effective strategy for postoperative recovery than single-dose administration. Continuous infusion maintains stable ketamine plasma levels, prolongs therapeutic effects and reduces fluctuations that could affect sleep quality. In contrast, single-dose administration may have limited efficacy due to rapid metabolism. Further large-scale trials are needed to determine the optimal dosing, infusion duration and safety across different surgeries to refine clinical practice and guidelines. Ketamine doses ≥0.5 mg/kg were more effective than lower doses, and administration during surgery was superior to postoperative pain management. Given these findings, continuous ketamine infusion at ≥0.5 mg/kg during surgery is recommended to alleviate PSDs. Although caution is required in interpreting the results because of the high heterogeneity and low quality of evidence, this study offers valuable insights into ketamine's role in enhancing postoperative sleep. Nevertheless, further research is needed to determine optimal ketamine dosages for effectively mitigating PSDs. Many studies in this field come from China, and their specific design, sample size and population characteristics could affect the broader applicability of the findings. Although funnel plot showed no clear bias, the overrepresentation of regional studies could influence the applicability and reliability in interpreting the results. Future research should involve diverse regions and patient populations to strengthen the evidence.

Although this analysis provides some supportive evidence for the positive effects of ketamine in improving PSDs, several key limitations should be acknowledged. First, only 10 of the 21 studies used PSQI to assess sleep, and many had small sample sizes, limiting generalisability. Second, significant variability existed across the included studies, particularly regarding ketamine administration methods, dosages and timing, potentially influencing stability and credibility in analysis results. Third, most studies focused on the short-term improvement effects of ketamine on PSDs, with inadequate discussion of its long-term impacts and potential long-term side effects. Fourth, the results of this study exhibited high heterogeneity and low quality of evidence; therefore, caution is needed when interpreting the findings. Given the aforementioned limitations, future research should involve high-quality, large-scale trials to address variations in surgery types, administration protocols and the effects of ketamine in different patient populations. In addition, studies should explore ketamine's potential synergistic effects with other drugs, such as dexmedetomidine, and extend follow-up periods to assess long-term sleep improvements and safety.

CONCLUSION

The results suggest that ketamine improves postoperative sleep quality, supporting its use in perioperative management. This finding underscores the clinical importance of PSDs and encourages further exploration of improvement strategies. Nevertheless, given high heterogeneity and limited evidence quality, the results require further validation. Future research should focus on reducing heterogeneity and bias through larger, more rigorous trials, as well as long-term follow-up studies on ketamine's efficacy and safety. In addition, exploring its mechanisms, efficacy and safety across different surgeries and patient groups will help optimise sleep management and recovery.

Data availability

The data for this systematic review and/or meta-analysis may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared upon request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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REFERENCES

1. Qiu D, Wang XM, Yang JJ, Chen S, Yue CB, Hashimoto K, *et al*. Effect of intraoperative esketamine infusion on postoperative sleep disturbance after gynecological laparoscopy: A randomized clinical trial. JAMA Netw Open 2022;5:e2244514. doi: 10.1001/jamanetworkopen.2022.44514.
2. Butris N, Tang E, Pivetta B, He D, Saripella A, Yan E, *et al*. The prevalence and risk factors of sleep disturbances in surgical patients: A systematic review and meta-analysis. Sleep Med Rev 2023;69:101786. doi: 10.1016/j.smrv.2023.101786.
3. Su X, Wang DX. Improve postoperative sleep: What can we do? Curr Opin Anaesthesiol 2018;31:83-8.
4. Han C, Ji H, Guo Y, Fei Y, Wang C, Yuan Y, *et al*. Effect of subanesthetic dose of esketamine on perioperative neurocognitive disorders in elderly undergoing gastrointestinal surgery: A randomized controlled trial. Drug Des Devel Ther 2023;17:863-73.
5. Duncan WC Jr, Zarate CA Jr. Ketamine, sleep, and depression: Current status and new questions. Curr Psychiatry Rep 2013;15:394.
6. Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, *et al*. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry 2020;25:1592-603.
7. Song B, Zhu J. A Novel application of ketamine for improving perioperative sleep disturbances. Nat Sci Sleep 2021;13:2251-66.
8. Chen Z, Wang S, Meng Z, Ye Y, Shan G, Wang X, *et al*. Tau protein plays a role in the mechanism of cognitive disorders induced by anesthetic drugs. Front Neurosci 2023;17:1145318. doi: 10.3389/fnins.2023.1145318.
9. Song B, Zhu JC. Mechanisms of the rapid effects of ketamine on depression and sleep disturbances: A narrative review. Front Pharmacol 2021;12:782457. doi: 10.3389/fphar.2021.782457.
10. Yang D, Yang L, Li Q, Zuo Y. Pharmacotherapy for improving postoperative sleep quality: A protocol for a systematic review and network meta-analysis. BMJ Open 2023;13:e069724. doi: 10.1136/bmjopen-2022-069724.
11. Higgins J, Thomas J. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaborative Group. doi: 10.1002/9780470712184.
12. Schiavenato M, Chu F. PICO: What it is and what it is not. Nurse Educ Pract 2021;56:103194. doi: 10.1016/j.nepr.2021.103194.
13. Pilz LK, Keller LK, Lenssen D, Roenneberg T. Time to rethink sleep quality: PSQI scores reflect sleep quality on workdays. Sleep 2018;41. doi: 10.1093/sleep/zsy029.
14. McHugh ML. Interrater reliability: The kappa statistic. Biochem Med (Zagreb) 2012;22:276-82.
15. McGrath S, Zhao X, Steele R, Thombs BD, Benedetti A; DEPRESsion Screening Data (DEPRESSD) Collaboration. Estimating the sample mean and standard deviation from commonly reported quantiles in meta-analysis. Stat Methods Med Res 2020;29:2520-37.
16. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64:383-94.
17. Zhang Y, Cui F, Ma JH, Wang DX. Mini-dose esketamine-dexmedetomidine combination to supplement analgesia for patients after scoliosis correction surgery: A double-blind randomised trial. Br J Anaesth 2023;131:385-96.
18. Zhou R, Zhang Y, Tang S, Zhang X, Wang Y, Liu Y, *et al*. A single preoperative dose of S-ketamine has no beneficial effect on chronic postsurgical pain in patients undergoing video-assisted thoracoscopic surgical lung lesion resection: A prospective randomized controlled study. J Cardiothorac Vasc Anesth 2023;37:1433-41.
19. Liang SR, Wang JG, Tian SY, Guo ZJ, Zhu J, Feng YS, *et al*. The effect of subanesthetic dose of esketamine on postoperative sleep quality in patients undergoing total hysterectomy. Pract Pharm Clin Remedies 2023;26:122-6.
20. Sun YM, Xia XQ, Gao X, Tao ZG. The effect of low-dose esketamine combined with dexmedetomidine on sleep and recovery in patients after radical mastectomy. Heilongjiang MedPharm 2024;37:11-6.
21. Gao JJ, Qian XD, Zhou HO. The effect of low-dose esketamine on postoperative analgesia and inflammatory factors in patients undergoing thoracoscopic surgery. China Pharm 2023;34:719-23.
22. Dai L, Deng HW, Guo HJ, Huang FR. The effect of intraoperative continuous infusion of esketamine on postoperative sleep quality in patients undergoing laparoscopic colorectal cancer surgery. Chin J Gen Surg Literature (Electronic Ed) 2023;17:408-12.
23. Xie F, Du JN, Xu X. The effect of esketamine combined with sufentanil on postoperative analgesia and hemodynamics in laparoscopic radical surgery for colon cancer. Chin J Mod Med 2023;33:19-24.
24. Mao HF, Mei KB, Wang QM, Liu FL. The effect of esketamine combined with fentanyl in patients with phantom limb pain after traumatic amputation. China Contemp Med 2022;29:119-21.
25. Li J, Liu MH, Shi J, Sun J. The effect of esketamine on postoperative analgesia, inflammatory factors, and early emotional state in breast cancer patients. J Bengbu Med Coll 2022;47:1188-91.
26. Zhou YH, Tan QL, Zhang Y, Tao T. The effect of esketamine on postoperative sleep and recovery in patients undergoing radical mastectomy under general anesthesia. Pract Pharm Clin Remedies 2024;27:26-30.
27. Li M, Feng T, Yu XT, Mei M, Dai WT, Liang QS. The effect of esketamine pretreatment on postoperative sleep quality and psychological state in patients undergoing breast tumor surgery. J Qiqihar Med Coll 2023;44:794-7.
28. Meng W, Gao L, Yang M, Huang ZB, Guo SS. The effect of low-dose ketamine combined with butorphanol on postoperative analgesia and recovery in patients undergoing myomectomy. Chin J Fam Plann 2023;31:1057-62.
29. Lu W, Jiang XF, Cai LB, Tang F, Peng WY. The effect of low-dose esketamine combined with oxycodone on postoperative

analgesia and sleep quality in patients undergoing total laparoscopic hysterectomy. Chin J Clin Pharm 2024;33:514-9.
30. Li X, Zhou QM, Xu B. The effect of intraoperative infusion of S-ketamine on improving postoperative sleep disorders in patients undergoing open reduction and internal fixation for traumatic long bone fractures. Chin J Traumatol 2024;40:628-34.
31. Sun XJ, Wang YM, Meng CX, Liu YM, Zhao LC. The effect of ultrasound-guided quadratus lumborum block combined with esketamine in elderly patients undergoing laparoscopic radical nephrectomy. Chin J Clin Doctors 2023;51:1222-5.
32. Ye S, Chen YH, Zhang B, Ji HX, Xia Q. Clinical study on the application of esketamine in patient-controlled intravenous analgesia after thoracoscopic radical lung cancer surgery. Shaanxi Med J 2024;53:391-4.
33. Ding MP, Li J, Liu Y, Wu D. The effect of pre-incisional esketamine administration on postoperative depressive symptoms and sleep quality in patients undergoing laparoscopic total hysterectomy. Chin J Fam Plann 2024;32:1791-5.
34. Jia WY, Lei SQ. The effect of esketamine combined with sufentanil in patient-controlled intravenous analgesia on postoperative sleep quality in thoracoscopic surgery patients. J Wuhan Univ (Med Ed) 2024;45:862-7.
35. Wang F, Zhao W, Lü YL, Liu MY. Study on the effect of dezocine combined with low-dose esketamine for postoperative analgesia in elderly patients undergoing abdominal surgery. China Health Care Food 2022;4:73-5.
36. Wang JP, Zhang QM, Xia XQ, Xiong M. Intervention effect of esketamine combined with serratus anterior and pectoral nerve plane block on postoperative depression in breast cancer patients. Med Inform 2024;37:102-6.
37. Parpia S, Morris TP, Phillips MR, Wykoff CC, Steel DH, Thabane L, *et al*. Sensitivity analysis in clinical trials: Three criteria for a valid sensitivity analysis. Eye (Lond) 2022;36:2073-4.
38. Scarpa M, Pinto E, Saraceni E, Cavallin F, Parotto M, Alfieri R, *et al*. Randomized clinical trial of psychological support and sleep adjuvant measures for postoperative sleep disturbance in patients undergoing oesophagectomy. Br J Surg 2017;104:1307-14.
39. Liu XY, Guo LZ, Wang E. Research progress on the impact of sleep disorders on postoperative recovery in elderly patients. Chin J Anesthesiol 2021;41:888-92.
40. Rampes S, Ma K, Divecha YA, Alam A, Ma D. Postoperative sleep disorders and their potential impacts on surgical outcomes. J Biomed Res 2019;34:271-80.
41. Mion G, Himmelseher S. Esketamine: Less drowsiness, more analgesia. Anesth Analg 2024;139:78-91.
42. Brinck EC, Tiippana E, Heesen M, Bell RF, Straube S, Moore RA, *et al*. Perioperative intravenous ketamine for acute postoperative pain in adults. Cochrane Database Syst Rev 2018;12:CD012033. doi: 10.1002/14651858.CD012033.pub4.
43. Guo J, Qiu D, Gu HW, Wang XM, Hashimoto K, Zhang GF, *et al*. Efficacy and safety of perioperative application of ketamine on postoperative depression: A meta-analysis of randomized controlled studies. Mol Psychiatry 2023;28:2266-76.
44. Adegbola A, Gritsenko K, Medrano EM. Perioperative use of ketamine. Curr Pain Headache Rep 2023;27:445-8.

SUPPLEMENTARY TABLE 1: SEARCH STRATEGY

1. Various database search methods:

Cochrane library

#1 ketamine

#2 Ketamine OR CI-581 OR CI 581 OR CI581 OR Ketalar OR Ketaset OR Ketanest OR Calipsol OR Kalipsol OR Calypsol OR Ketamine Hydrochloride

#3 #1 OR #2

#4 Sleep Wake Disorders

#5 Sleep Wake Disorders OR Disorder, Sleep Wake OR Disorders, Sleep Wake OR Sleep Wake Disorder OR Wake Disorder, Sleep OR Wake Disorders, Sleep OR Subwakefullness Syndrome OR Subwakefullness Syndromes OR Syndrome, Subwakefullness OR Syndromes, Subwakefullness OR Sleep Disorders OR Disorder, Sleep OR Disorders, Sleep OR Sleep Disorder OR Sleep-Related Neurogenic Tachypnea OR Neurogenic Tachypnea, Sleep-Related OR Neurogenic Tachypneas, Sleep-Related OR Sleep Related Neurogenic Tachypnea OR Sleep-Related Neurogenic Tachypneas OR Tachypnea, Sleep-Related Neurogenic OR Tachypneas, Sleep-Related Neurogenic OR Long Sleeper Syndrome OR Long Sleeper Syndromes OR Sleeper Syndrome, Long OR Sleeper Syndromes, Long OR Syndrome, Long Sleeper OR Syndromes, Long Sleeper OR Short Sleeper Syndrome OR Short Sleeper Syndromes OR Sleeper Syndrome, Short OR Sleeper Syndromes, Short OR Syndrome, Short Sleeper OR Syndromes, Short Sleeper OR Short Sleep Phenotype OR Phenotype, Short Sleep OR Phenotypes, Short Sleep OR Short Sleep Phenotypes OR Sleep Phenotypes, Short OR sleep disturbance

#6 #4 OR #5

#7 #3 AND #6

Embase

#1. 'ketamine'/exp OR ketamine (using both Mesh and free-text terms in title/abstract)

#2. '2-(2-chlorophenyl)-2-(methylamino) cyclohexanone':ab, ti OR 'ci-581':ab, ti OR 'ci 581':ab, ti OR 'ci581':ab, ti OR 'ketalar':ab, ti OR 'ketaset':ab, ti OR 'ketanest':ab, ti OR 'calipsol':ab, ti OR 'kalipsol':ab, ti OR 'calypsol':ab, ti OR 'ketamine hydrochloride':ab, ti OR 'ketamine':ab, ti

#3. #1 OR #2

#4. ('sleep'/exp OR sleep) AND wake AND ('disorders'/exp OR disorders)

#5. 'disorder, sleep wake':ab, ti OR 'disorders, sleep wake':ab, ti OR 'sleep wake disorder':ab, ti OR 'wake disorder, sleep':ab, ti OR 'wake disorders, sleep':ab, ti OR 'subwakefullness syndrome':ab, ti OR 'subwakefullness syndromes':ab, ti OR 'syndrome, subwakefullness':ab, ti OR 'syndromes, subwakefullness':ab, ti OR 'sleep disorders':ab, ti OR 'disorder, sleep':ab, ti OR 'disorders, sleep':ab, ti OR 'sleep disorder':ab, ti OR 'sleep-related neurogenic tachypnea':ab, ti OR 'neurogenic tachypnea, sleep-related':ab, ti OR 'neurogenic tachypneas, sleep-related':ab, ti OR 'sleep related neurogenic tachypnea':ab, ti OR 'sleep-related neurogenic tachypneas':ab, ti OR 'tachypnea, sleep-related neurogenic':ab, ti OR 'tachypneas, sleep-related neurogenic':ab, ti OR 'long sleeper syndrome':ab, ti OR 'long sleeper syndromes':ab, ti OR 'sleeper syndrome, long':ab, ti OR 'sleeper syndromes, long':ab, ti OR 'syndrome, long sleeper':ab, ti OR 'syndromes, long sleeper':ab, ti OR 'short sleeper syndrome':ab, ti OR 'short sleeper syndromes':ab, ti OR 'sleeper syndrome, short':ab, ti OR 'sleeper syndromes, short':ab, ti OR 'syndrome, short sleeper':ab, ti OR 'syndromes, short sleeper':ab, ti OR 'short sleep phenotype':ab, ti OR 'phenotype, short sleep':ab, ti OR 'phenotypes, short sleep':ab, ti OR 'short sleep phenotypes':ab, ti OR 'sleep phenotypes, short':ab, ti OR 'sleep disturbance':ab, ti

#6. #4 OR #5

#7. #3 AND #6

PubMed

#1 "Ketamine"[Mesh]

#2 ((((((((((ketamine[Title/Abstract]) OR (2-(2-Chlorophenyl)-2-(methylamino) cyclohexanone[Title/Abstract])) OR (CI-581[Title/Abstract])) OR (CI 581[Title/Abstract])) OR (CI581[Title/Abstract])) OR (Ketalar[Title/Abstract])) OR (Ketaset[Title/Abstract])) OR (Ketanest[Title/Abstract])) OR (Calipsol[Title/Abstract])) OR (Kalipsol[Title/Abstract])) OR (Calypsol[Title/Abstract])) OR (Ketamine Hydrochloride[Title/Abstract])

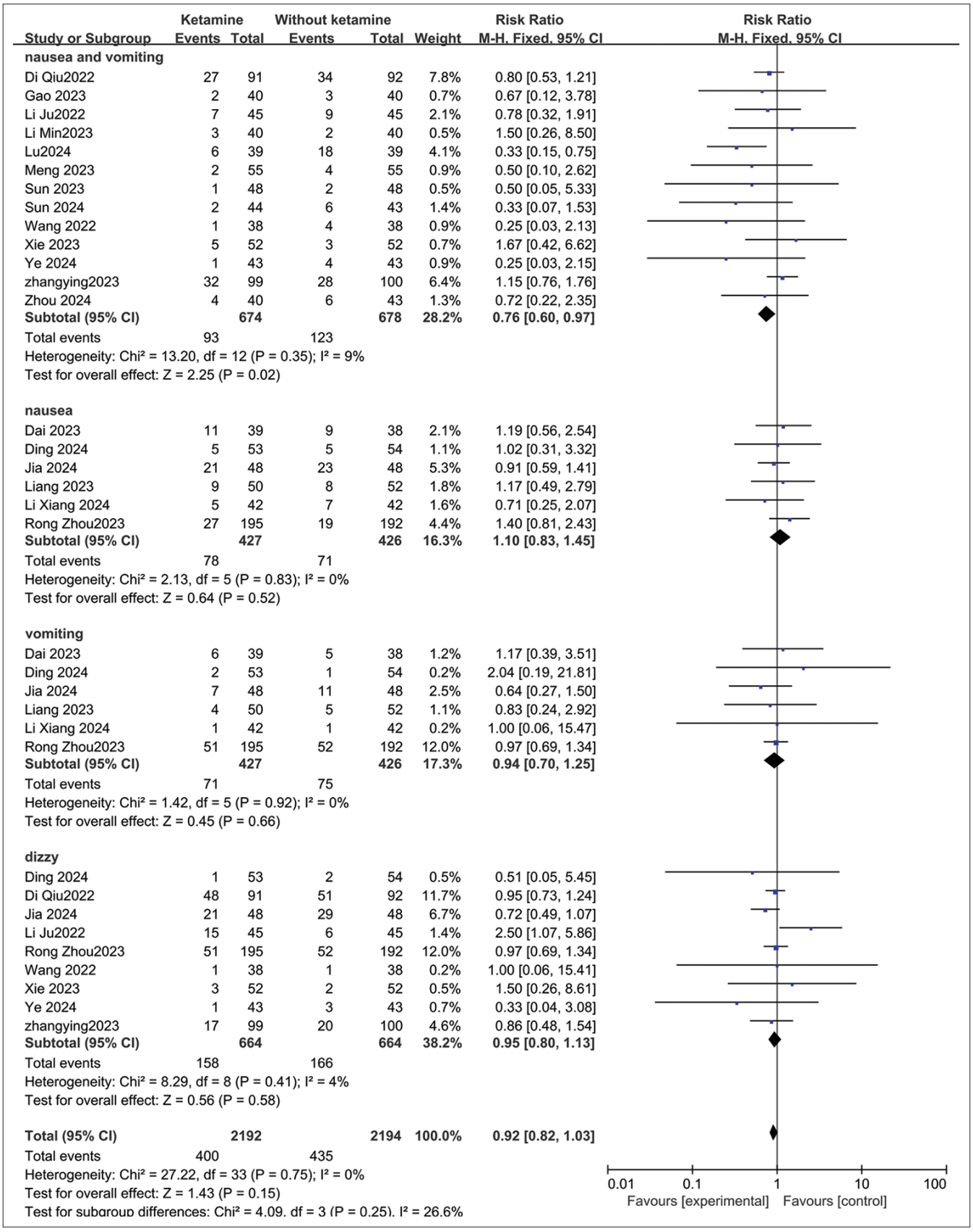
#3 #1 OR #2

#4 "Sleep Wake Disorders"[Mesh]

#5 ((((((((((((((((((((((((((((((((((((Sleep Wake Disorders[Title/Abstract]) OR (Sleep Wake Disorders[Title/Abstract])) OR (Sleep Wake Disorder[Title/Abstract])) OR (Wake Disorder, Sleep[Title/Abstract])) OR (Wake Disorders, Sleep[Title/Abstract])) OR (Subwakefullness Syndrome[Title/Abstract])) OR (Subwakefullness Syndromes[Title/Abstract])) OR (Syndrome, Subwakefullness[Title/Abstract])) OR (Syndromes, Subwakefullness[Title/Abstract])) OR (Sleep Disorders[Title/Abstract])) OR (Disorder, Sleep[Title/Abstract])) OR (Disorders, Sleep[Title/Abstract])) OR (Sleep Disorder[Title/Abstract])) OR (Sleep Disturbance[Title/Abstract])) OR (Sleep-Related Neurogenic Tachypnea[Title/Abstract])) OR (Neurogenic Tachypnea, Sleep-Related[Title/Abstract])) OR (Neurogenic Tachypneas, Sleep-Related[Title/Abstract])) OR (Sleep Related Neurogenic Tachypnea[Title/Abstract])) OR (Sleep-Related Neurogenic Tachypneas[Title/Abstract])) OR (Tachypnea, Sleep-Related Neurogenic[Title/Abstract])) OR (Tachypneas, Sleep-Related Neurogenic[Title/Abstract])) OR (Long Sleeper Syndrome[Title/Abstract])) OR (Long Sleeper Syndromes[Title/Abstract])) OR (Sleeper Syndrome, Long[Title/Abstract])) OR (Sleeper Syndromes, Long[Title/Abstract])) OR (Syndrome, Long Sleeper[Title/Abstract])) OR (Syndromes, Long Sleeper[Title/Abstract])) OR (Short Sleeper Syndrome[Title/Abstract])) OR (Short Sleeper Syndromes[Title/Abstract])) OR (Sleeper Syndrome, Short[Title/Abstract])) OR (Sleeper Syndromes, Short[Title/Abstract])) OR (Syndrome, Short Sleeper[Title/Abstract])) OR (Syndromes, Short Sleeper[Title/Abstract])) OR (Short Sleep Phenotype[Title/Abstract])) OR (Phenotype, Short Sleep[Title/Abstract])) OR (Phenotypes, Short Sleep[Title/Abstract])) OR (Short Sleep Phenotypes[Title/Abstract])) OR (Sleep Phenotypes, Short[Title/Abstract])

#6 #4 OR #5

#7 #3 AND #6



Supplementary Figure 1: Adverse events within 1 week postoperatively (adverse events include nausea, vomiting, dizziness, constipation, itching, psychiatric symptoms and other symptoms) (I^2 = heterogeneity). CI = confidence interval, df = degrees of freedom, MH = Mantel–Haenszel