Systematic Review and Meta-Analysis

Safety and efficacy of remimazolam in general anaesthesia during laparoscopic cholecystectomy: A systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Background and Aims: Laparoscopic cholecystectomy (LC) presents anaesthetic challenges such as haemodynamic instability and postoperative complications. Remimazolam (RMZ), a novel ultra-short acting benzodiazepine, has emerged as a promising alternative to the standard propofol, with a potentially superior safety profile. This study aimed to compare the efficacy and safety of RMZ with propofol for anaesthesia during LC. **Methods:** A systematic review and meta-analysis were conducted to synthesise evidence from randomised controlled trials (RCTs). A search of PubMed, Web of Science, Scopus, and Google Scholar through May 2025 was conducted. We pooled dichotomous outcomes using risk ratios (RRs) and continuous outcomes using mean differences (MDs), and 95% confidence intervals (CIs). **Results:** Six RCTs involving 452 patients were included in the analysis. Compared to the control group, RMZ was associated with a significantly longer anaesthesia onset time (MD: 13.26, 95% CI: 0.47, 26.05, $P = 0.04$), recovery time (MD: 2.72, 95% CI: 0.44, 5.01, $P = 0.02$), and postanaesthesia care unit (PACU) stay (MD: 5.54, 95% CI: 0.86, 10.22, $P = 0.02$). However, RMZ significantly reduced the incidence of injection pain (RR: 0.03, 95% CI: 0.01, 0.15, $P < 0.001$), and no significant differences were observed in surgery duration ($P = 0.30$), extubation time ($P = 0.14$), or the incidence of hypotension ($P = 0.15$), bradycardia ($P = 0.13$), or postoperative nausea and vomiting ($P = 0.67$). **Conclusion:** With uncertain evidence, RMZ significantly prolonged anaesthesia onset time, recovery time, and time to PACU discharge compared to control in patients undergoing LC. Still, RMZ improved patient comfort through significantly decreased incidence of injection pain and is associated with a comparable haemodynamic safety profile to propofol.

Keywords: Cholecystectomy, haemodynamic, laparoscopy, meta-analysis, nausea, pain, propofol, recovery, remimazolam, safety, sedation, surgery

INTRODUCTION

Laparoscopic cholecystectomy (LC) is now considered the gold standard surgical approach for gallbladder diseases due to its minimally invasive nature, reduced blood loss, and faster patient recovery.[1] Nevertheless, the procedure presents certain challenges to the anaesthesiologists. Pneumoperitoneum induction

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may cause notable haemodynamic instability, while the procedure itself elevates the risk of postoperative nausea and vomiting (PONV).[2] Accordingly, total intravenous anaesthesia (TIVA) in laparoscopic surgery is frequently preferred to inhalational sedation, given its demonstrated advantages in maintaining haemodynamic stability.[3] Propofol has been the cornerstone in TIVA for several decades, given its rapid onset and quick recovery.[4] Although extensively utilised, the use of propofol is associated with various documented adverse effects, such as hypotension, bradycardia, respiratory depression, injection site pain, and, in rare instances, the potentially fatal propofol infusion syndrome.[5,6] These limitations have motivated the investigation of alternative anaesthetic agents offering comparable efficacy and enhanced safety.[2]

Remimazolam (RMZ) has recently emerged as a promising sedative agent that can substitute propofol in TIVA. This novel benzodiazepine derivative exhibits ultrashort action, mediating its sedative and hypnotic effects via the GABA-A receptor.[7] The distinctive metabolic profile of RMZ is characterised by rapid hydrolysis, mediated by nonspecific tissue esterases, resulting in an inactive metabolite that is independent of organ function.[8] This yields a predictable and rapid onset and offset of action.[9] Also, a key benefit of RMZ is its superior haemodynamic profile compared to propofol.[10] RMZ has been shown in multiple studies to significantly reduce the incidence of hypotension during both induction and maintenance of anaesthesia.[10–12] In addition, RMZ produces minimal to no pain during injection and displays the antiemetic properties intrinsic to benzodiazepines.[2] Finally, the availability of flumazenil, a specific antagonist capable of rapidly reversing effects, provides a distinct safety advantage.

Although RMZ shows promise, its clinical profile is still debatable. Studies indicate that RMZ's emergence and recovery from anaesthesia might be slower than propofol's, especially in the absence of a reversal agent.[13,14] Additionally, studies indicate that patients receiving RMZ have longer extubation and postanaesthesia care unit (PACU) discharge times.[1,6] Despite the increasing use, more research is needed to understand the efficacy of RMZ in various clinical settings and patient groups, especially among elderly patients and those undergoing laparoscopic procedures. While many randomised controlled trials (RCTs) have compared RMZ to propofol and other anaesthetics, their results have been inconsistent.[11] Recently, several RCTs have investigated RMZ during LC, with promising results.[1,2,4,6,14,15] Therefore, this systematic review and meta-analysis aims to synthesise the current evidence from RCTs to comprehensively evaluate the efficacy and safety of RMZ versus propofol for TIVA during LC. The primary objective was to investigate the effect of RMZ on anaesthesia onset time and anaesthesia recovery duration, while the secondary objectives were operation duration, bispectral index (BIS) during maintenance, extubating time, PACU length of stay, and adverse events.

METHODS

Protocol registration

This systematic review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD420251086238). The systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16] and the Cochrane Handbook for Systematic Reviews of Interventions.[17]

Data sources and search strategy

On 25 May 2025, an electronic search was conducted by MA using the databases: Web of Science (WOS), PubMed, Google Scholar, and Scopus. The search strategy included the search entries: "(remimazolam OR RMZ OR "CNS 7056" OR "ONO 2745" OR ONO-2745 OR ONO2745) AND (cholecystectomy OR gallbladder)". The search was comprehensive across most databases; however, in Scopus, it was limited to titles, abstracts, and keywords. [Supplementary Table 1]. Finally, the reference lists of all the identified trials were screened for any relevant studies.

Eligibility criteria

RCTs conducted using the following PICO criteria were included: population (P), patients undergoing laparoscopic cholecystectomy, regardless of its indication; intervention (I), RMZ, irrespective of the dosing protocol; control (C), propofol, regardless of the dosing protocol; and outcomes (O): the primary outcomes included anaesthesia onset time and anaesthesia recovery duration. Secondary procedural outcomes included operation duration, BIS during maintenance, extubating time, and PACU length of stay. The safety outcomes included the incidence of injection pain, bradycardia, hypotension, and postoperative nausea and vomiting (PONV). Furthermore, our

analysis excluded quasi randomised trials, conference presentations and proceedings, observational studies, *in vitro* research, and review articles.

Study selection

A comprehensive screening process was conducted by at least two independent reviewers (AbA, ShA, SaA, AlA, MaA, MoA, RA, FA) utilising Covidence. Duplicate records were removed, and then each unique record was assessed in two phases. First, titles and abstracts were screened; second, a full-text review was conducted on records meeting the initial screening criteria. Discrepancies among reviewers were addressed via discussion and consensus.

Data extraction

To develop an Excel extraction form, we initially collected the full texts of all relevant publications to conduct a pilot extraction. The form was structured into three parts: (1) summary characteristics of the included trials (e.g., study ID, country, study design, total number of patients, treatment protocols, adjuvant drugs, recovery duration definition, primary outcome, and main inclusion criteria); (2) baseline characteristics of the included participants (e.g., age, gender, body mass index (BMI), and American Society of Anesthesiologists (ASA) physical status classification); and (3) outcomes, as previously described.

Independent data extraction was performed by at least two reviewers (AbA, ShA, SaA, AlA, MaA, MoA, RA, FA), with the first author mediating any discrepancies through discussion. Dichotomous outcomes were recorded in an event/total format, while continuous outcomes were described using means and standard deviations. To estimate mean and standard deviation (SD) from median and interquartile range (IQR) (or range), we used the formulas in Wan *et al*.[18]

Risk of bias and certainty of evidence

The risk of bias (RoB) for the included RCTs was evaluated by at least two independent reviewers (AbA, ShA, SaA, AlA, MaA, MoA, RA, and FA) using the revised Cochrane Collaboration tool (RoB 2).[19] This assessment covered key domains, including selection, performance, attrition, and reporting biases, as well as other potential sources of bias. Any discrepancies in the risk of bias assessment were resolved through consensus. Subsequently, the certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework.[20,21] This framework was used to evaluate the body of evidence for inconsistencies, imprecision, indirectness, publication bias, and the overall risk of bias. Disagreements that arose during the GRADE evaluation were resolved through collaborative discussions, with all final judgments being explicitly justified and documented.

Statistical analysis

Statistical analysis of the extracted data was conducted utilising StataCorp. 2024. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC. Effect measures for dichotomous outcomes were determined by calculating the risk ratio (RR), whereas continuous outcomes were assessed using the mean difference (MD). All results are presented with their corresponding 95% confidence intervals (CIs). The primary analysis employed a fixed-effect model. The presence of statistical heterogeneity was evaluated using the Chi-squared test and the I^2 statistic. If significant heterogeneity was detected ($P < 0.10$ for the Chi-squared test or $I^2 \geq 50\%$), a random-effects model was adopted for the analysis. Also, in case of significant heterogeneity, a leave-one-out sensitivity analysis was conducted to evaluate the source of heterogeneity, along with Galbraith plots to identify the outliers. Following Cochrane guidelines, formal testing for publication bias was omitted as each outcome included fewer than 10 RCTs.[22] Finally, trial sequential analysis (TSA) was performed to assess the robustness and conclusiveness of the meta-analytic results. TSA was conducted using the Trial Sequential Analysis software.[23] The TSA evaluates the size of the information and the cumulative z-curve to assess the adequacy and strength of the existing evidence. Boundary controls were established to manage the risks associated with Type I and Type II errors.

RESULTS

Search results and study selection

After searching the literature, 151 records were identified from databases and registers, and 33 duplicates were removed. Following the screening of titles and abstracts, 109 studies that did not meet the inclusion criteria were excluded, resulting in nine full-text articles being assessed for eligibility. Of these, three studies were excluded for having the wrong comparator ($n = 2$) or wrong patient population (n = 1), leaving six studies eligible for inclusion in both qualitative and quantitative syntheses [Figure 1].

Characteristics of included studies

Six RCTs and 452 patients were included in our analysis.[1,2,4,6,14,15] RMZ and comparator (propofol in

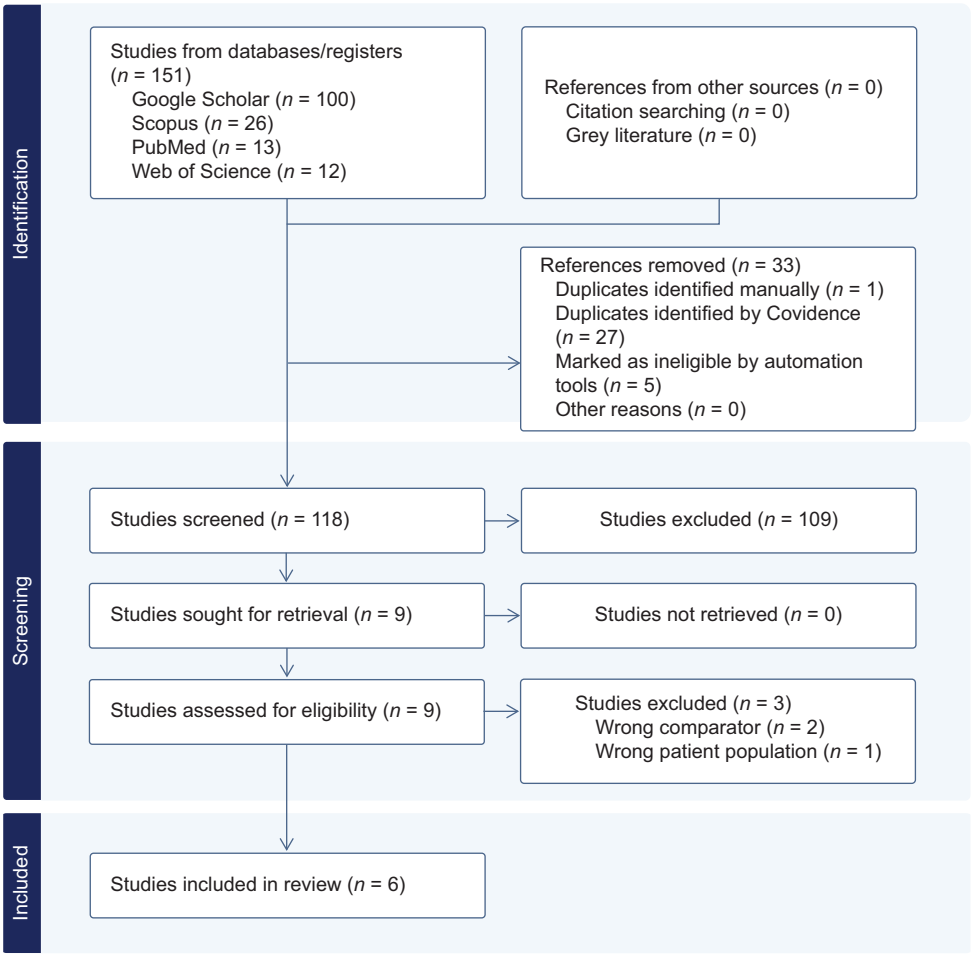

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the screening process

five RCTs or sevoflurane in one trial) dosing protocols were different throughout the included trials [Table 1]. All six RCTs infused an adjuvant opioid, such as remifentanil or sufentanil, for analgesia. The number of patients in each arm of the included studies, along with baseline ASA status and BMI [Table 2].

Risk of bias and certainty of evidence

Four RCTs showed an overall low risk of bias.,[1,2,14,15] one trial showed some concerns,[4] and another trial showed a high risk of bias[6] [Figure 2]. Lee *et al*. 2023 and So *et al*. showed some concerns of detection bias due to the potentially open-lapel assessment of outcomes.[4,6] Also, So *et al*. showed a high risk of attrition bias as the study excluded three patients from the RMZ group after they had received propofol for a low anaesthetic depth score.[6] Additionally, we illustrated the certainty of evidence assessment in a GRADE evidence profile [Table 3].

Primary outcomes

RMZ was associated with a significantly longer anaesthesia onset time (MD: 13.26, 95% CI: 0.47, 26.05, $P = 0.04$, $I^2 = 95.25\%$) [Figure 3a] and anaesthesia recovery time (MD: 2.72, 95% CI: 0.44, 5.01, $P = 0.02$, $I^2 = 62.58\%$) [Figure 3b].

For anaesthesia onset time, the leave-one-out sensitivity analysis showed that the results were not robust as the overall effect became non-significant after excluding any of the individual studies [Supplementary Figure 1]. Also, the Galbraith plot identified So *et al*. as an outlier contributing to significant heterogeneity [Supplementary Figure 2]. For recovery duration, the sensitivity analysis showed that the prolonged recovery time with remimazolam became non-significant after excluding either Lee *et al*. 2023 ($P = 0.075$) or So *et al*. ($P = 0.053$) [Supplementary Figure 3], while the Galbraith plot identified Lee *et al*. 2025 as an outlier [Supplementary Figure 4].

Secondary procedural outcomes

There was no significant difference between the

Table 1: Summary characteristics of the included RCTs

Study ID	Study Design	Country	Total Participants	Remimazolam	Control (Propofol)	Adjuvant Drugs	Recovery Time Definition	Primary Outcome	Main inclusion criteria
Lee *et al*. 2023[4]	Single-centre, single-blinded, RCT	Republic of Korea	101	Induction: 0.2 mg/kg slow bolus over 1 min. Maintenance: Started at 1.5 mg/kg/h, adjusted within 1-2 mg/kg/h.	Induction: 2.0 mg/kg bolus. Maintenance: Started at 8 mg/kg/h, adjusted within 4-12 mg/kg/h.	Remifentanil, Rocuronium, Sugammadex. Flumazenil was not administered.	Complete recovery, defined as the time until an Aldrete score of 9 as the primary surrogate marker of complete recovery.	Time to achieve an Aldrete score of 9 as the primary surrogate marker of complete recovery.	Ages 20–80 years, ASA physical status I-III, scheduled for elective laparoscopic cholecystectomy.
Lee *et al*. 2025[14]	Double-blinded RCT	Republic of Korea	48	Induction: 6 mg/kg/h flow rate. Maintenance: Adjusted to maintain Patient State Index (PSI) target of 40.	Induction: Target-controlled infusion (TCI) at effect-site concentration of 4 µg/mL. Maintenance: Adjusted to maintain the PSI target of 40.	Remifentanil, Glycopyrrolate.	Time to Aldrete 9.	To explore patterns of brain electrical activity (EEG) in delayed emergence. (The main clinical recovery outcome was time to Aldrete 9).	Ages 19 to 65 years, ASA physical status I to III, undergoing laparoscopic cholecystectomy.
Luo *et al*. 2024[1]	Single-centre, single-blinded, RCT	China	112	Induction: 0.3 mg/kg slow bolus over 1 min. Maintenance: 1.0-2.0 mg/kg/h.	Induction: 2.0 mg/kg bolus. Maintenance: 4-10 mg/kg/h.	Sufentanil, Cisatracurium, Remifentanil.	Time to extubation, and time to discharge from PACU.	Time to bispectral index (BIS) ≤ 60.	Ages 18 to 60 years, ASA physical status I to II, BMI of 18 to 28 kg/m².
Mao *et al*. 2025[2]	Double-blinded RCT	China	70	Premedication: IV injection of remimazolam 0.1 mg/kg, 15 min before induction. Intraoperative anaesthesia was with propofol.	Premedication: IV injection of normal saline. Intraoperative anaesthesia was with propofol.	Propofol, Sufentanil, Cisatracurium, Remifentanil.	Time to first postoperative exhaust and defecation.	Time to first postoperative flatus.	Ages 18-64, ASA physical status I or II, scheduled for elective laparoscopic cholecystectomy.
So *et al*. 2023[6]	Single-centre, single-blinded, RCT	Republic of Korea	81	Induction: 6 mg/kg/h until loss of consciousness (LOC). Maintenance: 1 mg/kg/h, adjusted up to 2 mg/kg/h.	Induction: 1.0-1.5 mg/kg over 1 min. Maintenance: 100 µg/kg/min, adjusted.	Remifentanil, Rocuronium, Sugammadex. Flumazenil, if needed (used in 3 patients).	Time to eye-opening, extubation time, time to discharge from the operating room.	Time to lose consciousness (LOC).	Ages >65 years, ASA physical status I-III, scheduled for elective laparoscopic cholecystectomy.
Yoo *et al*. 2024[15]	Single-centre, single-blinded, RCT	Republic of Korea	40	Induction: 6 mg/kg/h IV infusion. Maintenance: 1-2 mg/kg/h IV injection.	Control was Sevoflurane. Induction: Sevoflurane 5%. Maintenance: Sevoflurane 1.6-2%.	Remifentanil, Rocuronium, Fentanyl, Ketorolac, Ramosetron, Sugammadex, and Flumazenil (0.2 mg given to all in the RMZ group).	Quality of Recovery-15 (QoR-15) score at 24 h postoperatively.	Incidence of PONV for 24 h after surgery.	Ages 20–80 years undergoing elective laparoscopic cholecystectomy or hemicolectomy.

RCT=Randomised controlled trial, RMZ=remimazolam, IV=intravenous, RCT=randomised controlled trial, ASA=American Society of Anesthesiologists, BMI=body mass index, PONV=postoperative nausea and vomiting

groups regarding operation duration (MD: -1.47, 95% CI: -4.26, 1.32, $P = 0.30$, $I^2 = 27.36\%$) [Figure 3c], extubation time (MD: 3.32, 95% CI: -1.07, 7.70, $P = 0.14$, $I^2 = 96.35\%$) [Figure 3d], total remifentanil dose (SMD: 0.14, 95% CI: -0.07, 0.35, $P = 0.20$, $I^2 = 8.04\%$) [Figure 4a]. However, the PACU length of stay was significantly longer for the RMZ group (MD: 5.54, 95% CI: 0.86, 10.22, $P = 0.02$, $I^2 = 57.99\%$) [Figure 4b]. BIS during maintenance was also significantly higher with RMZ (MD: 5.46, with 95% CI: 3.54, 7.39, $P < 0.001$, $I^2 = 0\%$) [Figure 4c]. Regarding extubation time, the leave-one-out analysis revealed that the non-significant overall result became significant ($P = 0.048$) after excluding Lee *et al*. 2023 [Supplementary Figure 5],

Table 2: Baseline characteristics of the included participants

Study ID	Number of participants in each group		Age (Years), Mean (SD)		ASA status (I/II)		BMI, Mean (SD)	
	Remimazolam	Propofol	Remimazolam	Propofol	Remimazolam	Propofol	Remimazolam	Propofol
Lee *et al*. 2023[4]	51	50	51.6 (14.2)	55.8 (15.8)	18/25	15/24	24.2 (3.6)	24.9 (3.2)
Lee *et al*. 2025[14]	24	24	47.7 (9.5)	47.9 (9.1)	14/8	13/9	24.0 (2.9)	23.6 (3.3)
Luo *et al*. 2024[1]	56	56	42.8 (10.4)	43.0 (9.1)	45/11	48/8	23.9 (2.1)	23.9 (2.3)
Mao *et al*. 2025[2]	35	35	44.1 (11.1)	45.3 (10.5)	18/17	17/18	24.5 (2.6)	24.2 (2.5)
So *et al*. 2023[6]	42	39	74.5 [70-78.3]	76 [70-81]	4/35	6/27	24.9 [23.7-26.7]	24 [20.7-27.5]
Yoo *et al*. 2024[15]	20	20	55.1 (11.9)	50.9 (10.0)	NA	NA	24.9 (3.9)	27.1 (3.8)

Data presented as mean (standard deviation) or median [interquartile range]; SD=standard deviation; NA =not available; N=number of patients, ASA=American Society of Anesthesiologists; BMI=body mass index

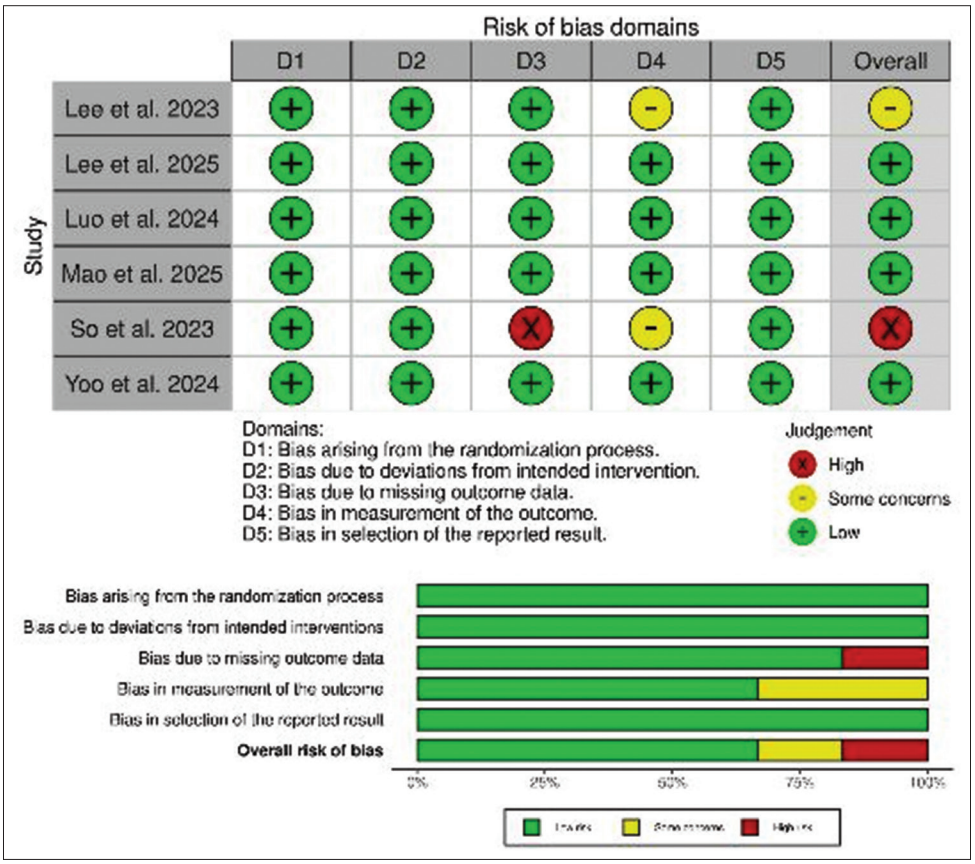

Figure 2: Quality assessment of risk of bias in the included trials. The upper panel presents a schematic representation of risks (low = green, unclear = yellow, and high = red) for specific types of biases of the studies in the review. The lower panel presents risks (low = red, unclear = yellow, and high = red) for the subtypes of biases of the combination of studies included in this review

and the corresponding Galbraith plot identified Luo *et al*. as an outlier [Supplementary Figure 6].

Secondary safety outcomes

RMZ was associated with a significantly lower risk of injection pain (RR: 0.03, 95% CI: 0.01, 0.15, $P < 0.001$, $I^2 = 0\%$) [Figure 5a]. However, there was no significant difference in the risk of PONV (RR: 0.72, 95% CI: 0.16, 3.32, $P = 0.67$, $I^2 = 59.79\%$) [Figure 5b], bradycardia (RR: 0.40, 95% CI: 0.12, 1.29, $P = 0.13$, $I^2 = 0\%$) [Figure 5c], or hypotension (RR: 0.62, 95% CI: 0.33, 1.20, $P = 0.15$, $I^2 = 0\%$) [Figure 5d]. Finally, for PONV, the leave-one-out sensitivity analysis showed consistent results, with the outcome remaining non-significant regardless of which study was excluded [Supplementary Figure 7], and the Galbraith plot identified Luo *et al*. as an outlier [Supplementary Figure 8].

Trial sequential analysis

For the anaesthesia onset time, the cumulative Z-curve did not cross any of the monitoring boundaries for significance or futility, indicating that the current evidence is inconclusive [Supplementary Figure 9]. Therefore, further research is needed to draw a

Table 3: Grading of Recommendations Assessment, Development, and Evaluation (GRADE) evidence profile

Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Summary of Findings (95% CI)
Anaesthesia and Recovery							
Anaesthesia Onset Time	Serious[a]	Very Serious[b]	Not serious	Serious[c]	Not assessed	⊕◯◯◯ Very Low	MD 13.26 [0.47, 26.05]
Anaesthesia Recovery Time	Serious[a]	Serious[d]	Not serious	Serious[c]	Not assessed	⊕◯◯◯ Very Low	MD 2.72 [0.44, 5.01]
Extubation Time	Serious[a]	Very Serious[b]	Not serious	Serious[c]	Not assessed	⊕◯◯◯ Very Low	MD 3.32 [-1.07, 7.70]
Length of PACU Stay	Not serious	Serious[d]	Not serious	Serious[c]	Not assessed	⊕⊕◯◯ Low	MD 5.54 [0.86, 10.22]
Intraoperative Parameters							
Operation Duration	Not serious	Not serious	Not serious	Serious[c]	Not assessed	⊕⊕⊕◯ Moderate	MD -1.47 [-4.26, 1.32]
Total Remifentanil Dose	Serious[a]	Not serious	Not serious	Not serious	Not assessed	⊕⊕⊕◯ Moderate	SMD 0.14 [-0.07, 0.35]
BIS during Maintenance	Not serious	Not serious	Not serious	Very serious[e]	Not assessed	⊕⊕◯◯ Low	MD 5.46 [3.54, 7.39]
Adverse Events							
Injection Pain	Not serious	Not serious	Not serious	Very serious[f]	Not assessed	⊕⊕◯◯ Low	RR 0.03 [0.01, 0.15]
PONV	Not serious	Serious[c]	Not serious	Very Serious[c,f]	Not assessed	⊕◯◯◯ Very Low	RR 0.72 [0.16, 3.32]
Bradycardia	Not serious	Not serious	Not serious	Very Serious[c,f]	Not assessed	⊕⊕◯◯ Low	RR 0.40 [0.12, 1.29]
Hypotension	Not serious	Not serious	Not serious	Very Serious[c,f]	Not assessed	⊕⊕◯◯ Low	RR 0.62 [0.33, 1.20]

CI=confidence interval; RR=risk ratio; MD=mean difference; SMD=standardised mean difference; PACU=postanaesthesia care unit; BIS=bispectral Index. PONV=postoperative nausea and vomiting. Explanations: [a]Downgraded for risk of bias: a significant portion of the evidence came from a study with a high risk of bias. [b]Downgraded twice for inconsistency: significant heterogeneity with I^2 >75%. [c]Downgraded for imprecision: the confidence interval is wide and does not exclude the appreciable risk of harm or benefit. [d]Downgraded for inconsistency: significant heterogeneity with I^2 >50%. [e]Downgraded for imprecision: low number of participants. [f]Downgraded for imprecision: low number of events

definitive conclusion regarding this outcome. In contrast, for the anaesthesia recovery duration, the cumulative Z-curve crossed the lower trial sequential monitoring boundary, indicating that this finding is robust [Supplementary Figure 10].

DISCUSSION

This systematic review and meta-analysis synthesising data from six RCTs involving 452 patients revealed that RMZ was associated with a significantly longer anaesthesia onset time, a prolonged anaesthesia recovery period, and an extended stay in PACU, with intraoperative monitoring with BIS showing higher values in the RMZ group. Still, RMZ showed a significantly lower incidence of injection pain.

Our results show that RMZ is associated with slower recovery, with patients experiencing longer anaesthesia recovery (2.72 min longer) and PACU stays (5.54 min longer), which aligns with the pharmacological effects of un-antagonised benzodiazepines versus propofol.[24] Although RMZ is rapidly metabolised by tissue esterases, resulting in a short context-sensitive half-life, its clinical effects can outlast those of propofol without an active reversal agent.[25] The absence of flumazenil, a significant modulating factor, is noteworthy in our trials. To clarify, inconsistent flumazenil application throughout the literature presents a major confounding variable as routine administration may markedly shorten emergence time, potentially accelerating recovery from RMZ compared to propofol.[26–28] This practice, however, is not risk-free; specifically, it carries the potential for re-sedation if the antagonist's action is of shorter duration than the residual anaesthetic, a significant concern after prolonged infusions.[29]

Moreover, intraoperative BIS values were significantly higher in patients receiving RMZ than in those receiving propofol, although the total remifentanil dose did not significantly differ. This necessitates a critical evaluation of the efficacy of standard BIS monitoring (target range 40–60) within the context of RMZ based anaesthesia.[30] Elevated BIS values may not signify shallower anaesthesia, but instead, the unique neurophysiological effects of benzodiazepines, which the BIS algorithm—primarily developed and tested using agents such as propofol—may not reliably measure.[31,32] The absence of intra-operative awareness in the included studies, despite elevated BIS readings, supports this interpretation.[4,14] This clinical discrepancy poses a challenge; anaesthesiologists may increase RMZ dosage to normalise BIS values,

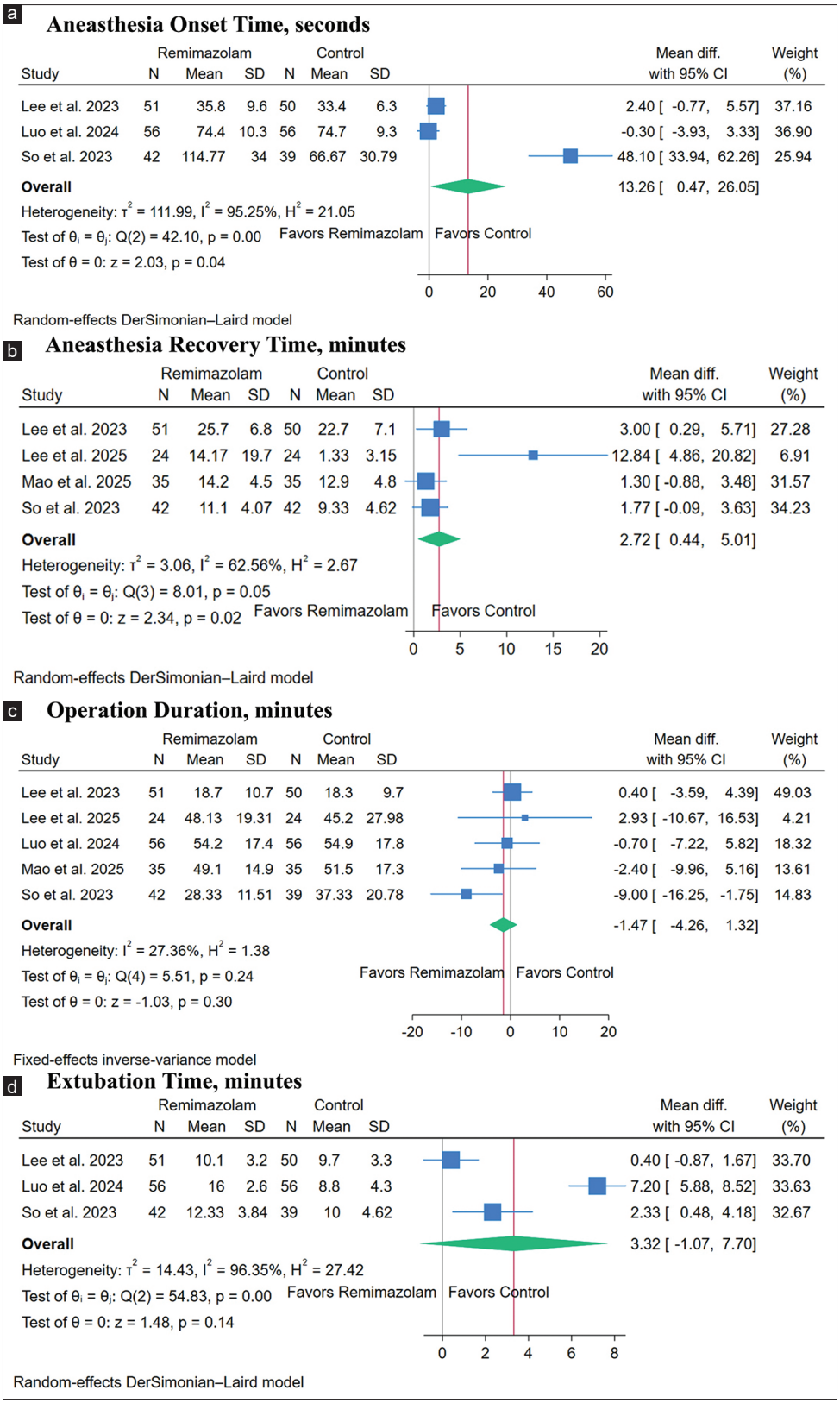

Figure 3: Forest plots of the procedural outcomes. (a) Aneasthesia Onset Time, seconds, (b) Aneasthesia Recovery Time, minutes, (c) Operation Duration, minutes, (d) Extubation Time, minutes), CI = confidence interval; SD = standard deviation; N = number of patients

potentially deepening anaesthesia and prolonging recovery as observed in our analysis. This highlights the urgent necessity of investigating the recalibration of the BIS or validating alternative depth-of-anaesthesia

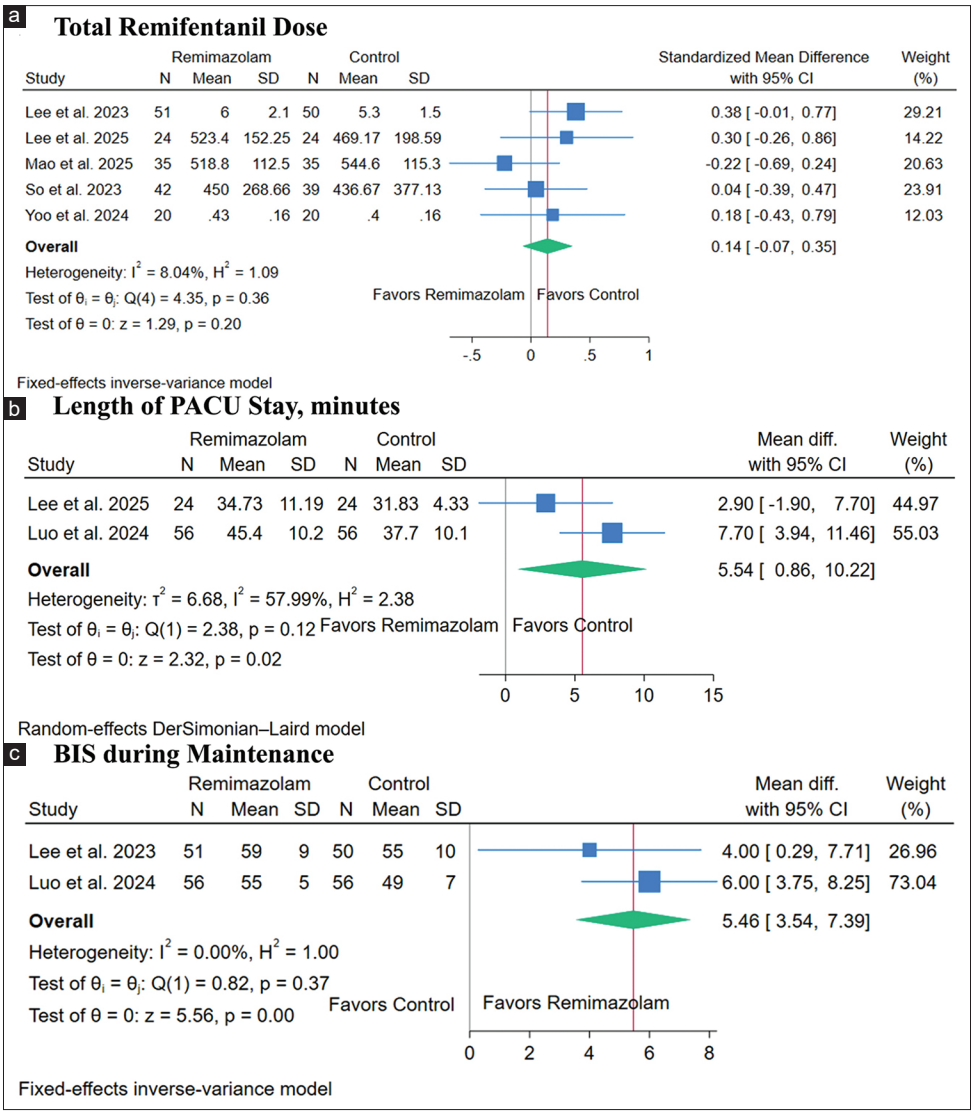

Figure 4: Forest plots of the procedural outcomes. (a) Total Remifentanil Dose, (b) Length of Post-Anaesthesia Care Unit (PACU) Stay, minutes, (c) Bispectral Index (BIS) during Maintenance), CI = confidence interval; SD = standard deviation; N = number of patients

monitoring systems, including the Patient State Index or raw electroencephalographic analysis, to ensure more dependable guidance for RMZ target-controlled infusion.[14]

Furthermore, RMZ's safety profile for TIVA in LC is favourable, yet certain aspects warrant consideration. The primary advantage of RMZ, supported by substantial evidence, is its haemodynamic stability, rendering it a more suitable choice than propofol, especially in patients with limited cardiovascular reserve or among the elderly.[24] Additionally, the lack of injection pain, noted in our analysis, significantly improves patient safety and satisfaction. Nevertheless, the primary safety concerns regarding the RMZ centre on its recovery time. The observed delayed emergence and prolonged PACU stays in our analysis significantly impact operating room efficiency and the effective utilisation of healthcare resources.

Our meta-analysis revealed no statistically significant difference in the occurrence of hypotension or bradycardia. This result contrasts sharply with the substantial evidence from multiple meta-analyses, which consistently demonstrate RMZ's superior haemodynamic stability and significantly lower risk of hypotension compared to propofol.[11,33,34] This discrepancy can be attributed to several factors identified during our review. First, our study focused primarily on low-risk patients (ASA I-II) undergoing LC, a group with a low baseline rate of severe haemodynamic events. Hence, RMZ's positive effects on the cardiovascular system may be more evident and measurable in higher-risk populations,

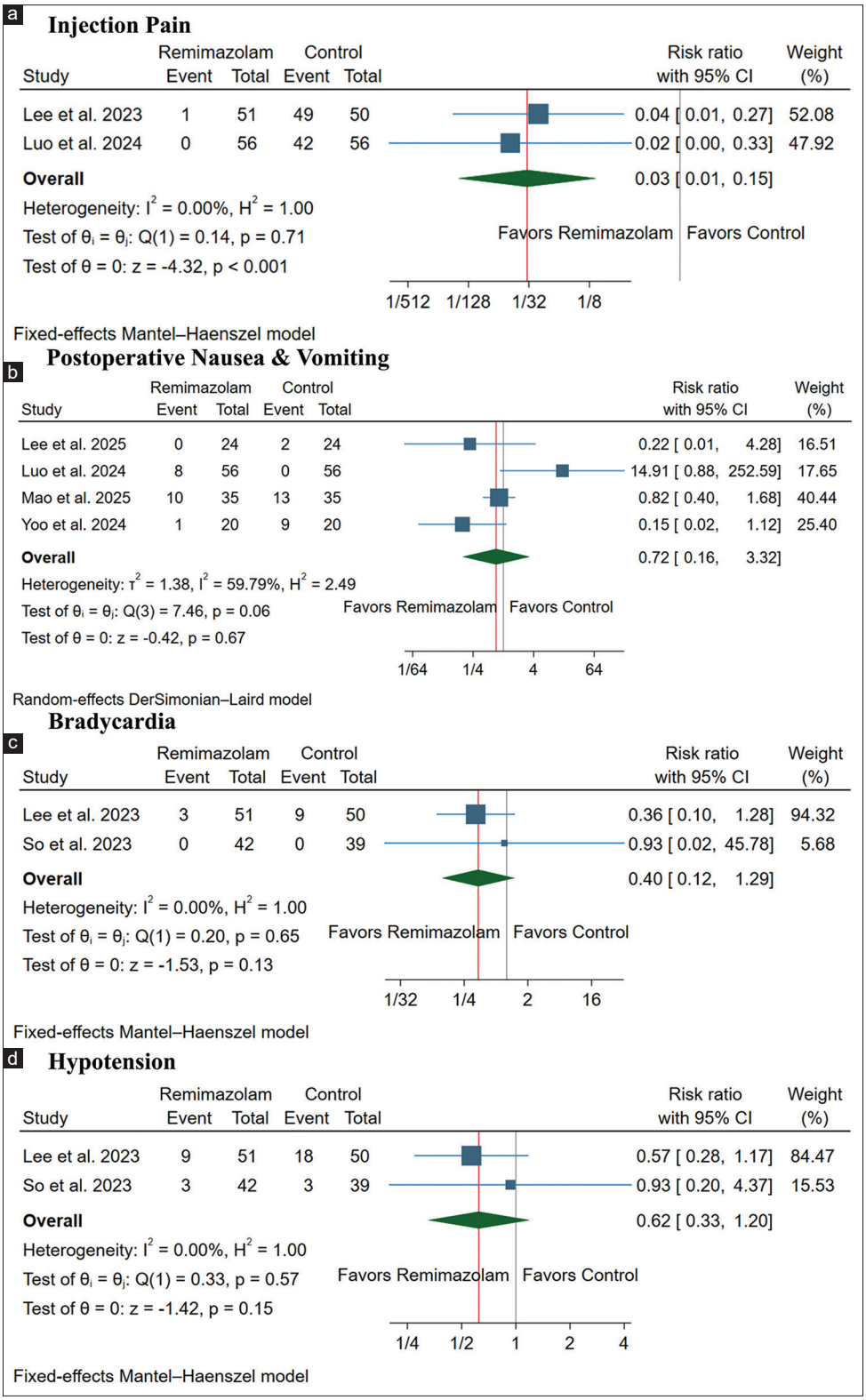

Figure 5: Forest plots of the safety outcomes. (a) Injection Pain, (b) Postoperative Nausea & Vomiting, (c) Bradycardia, (d) Hypotension, CI = confidence interval

including the elderly and those undergoing extensive cardiac procedures.[15,35] Second, only two trials were included in the pooled analysis of bradycardia and hypotension, so the pooled analysis may be underpowered to detect an effect. Thus, although our study was inconclusive, the strong evidence supporting RMZ's haemodynamic stability should not be ignored.

Strengths and limitations

The rigorous methodology employed ensures that this is a robust systematic review and meta-analysis. The study protocol was prospectively registered with PROSPERO, and the conduct and reporting adhered to the PRISMA statement, ensuring transparency and reproducibility. This review synthesises recent trials to give an updated overview of the evidence comparing RMZ and propofol for LC. The analysis thoroughly examined various efficacy and safety outcomes, providing valuable information for clinicians. Despite its strengths, this meta-analysis has a few notable limitations. A significant source of concern is the substantial statistical and clinical variability across the studies; thus, caution is advised when interpreting the pooled results. The observed heterogeneity was attributable to several factors: a study utilising sevoflurane as a control,[15] a trial where RMZ served only as premedication,[2] a study exclusively enroling elderly participants,[6] and significant discrepancies in dosing and flumazenil administration protocols. Additionally, the limited number of trials, with some outcomes based on only two studies, resulted in insufficient statistical power for our analysis. Consequently, a formal assessment of publication bias, as recommended by Cochrane guidelines, was not feasible. Finally and accordingly, the certainty of evidence was low to very low, warranting careful interpretation.

CONCLUSION

With uncertain evidence, remimazolam significantly prolonged anaesthesia onset time, recovery time, and time to postanaesthesia care unit discharge and had a higher bispectral index level during maintenance compared to control in patients undergoing laparoscopic cholecystectomy. Still, remimazolam improved patient comfort through significantly decreased incidence of injection pain and is associated with a comparable haemodynamic safety profile to propofol. Also, the significant heterogeneity in the current evidence highlights the need for additional high quality randomised controlled trials to determine remimazolam efficacy in this frequently performed surgical procedure.

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Presentation at conferences/CMEs and abstract publication

This manuscript was not presented at any conference.

Study data availability

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

Disclosure of use of artificial intelligence (AI)-assistive or generative tools

The AI tools or language models (LLM) have not been utilised in the manuscript, except that software has been used for grammar corrections and references.

Declaration of use of permitted tools

All figures and tables are freely available and not subject to copyright.

Authors contributions

MA conceived the idea, designed the research workflow, searched the databases, and performed the analysis. AA, SA, SA, AA, MA, MA, RA and F. screened the retrieved records, extracted relevant data, assessed the quality of evidence, and MA resolved the conflicts. MA AA, SA, SA, AA, MA, MA, RA, and FA wrote the final manuscript. MA and RM supervised the project. All authors have read and agreed to the final version of the manuscript.

Supplementary material

This article has supplementary material and can be accessed at this link. Supplementary Material at http://links.lww.com/IJOA/A67.

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Conflicts of interest

There are no conflicts of interest.

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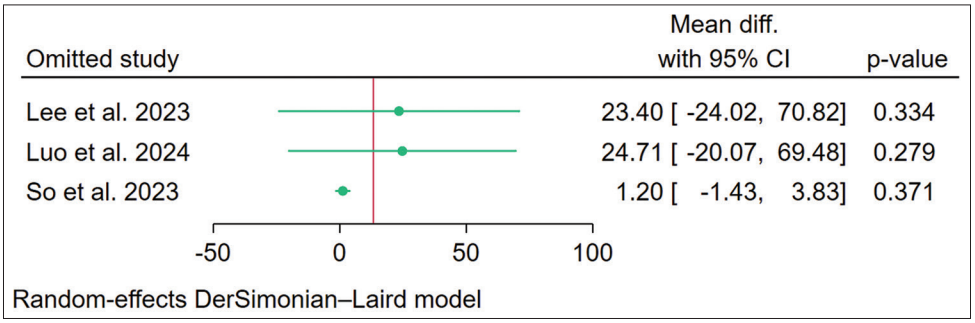
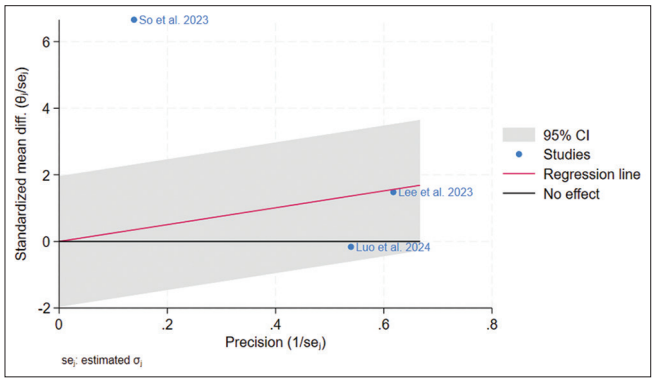
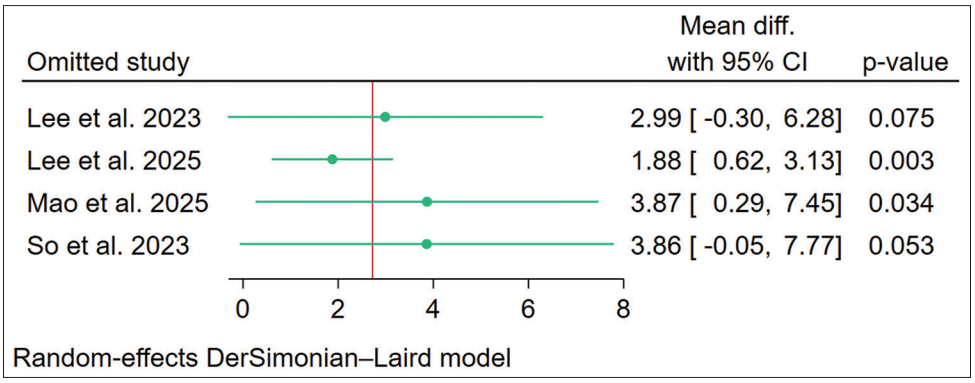
Supplementary Table 1: Search Strategy			
Database	**Search Terms**	**Search Field**	**Search Results**
PubMed	(remimazolam OR RMZ OR "CNS 7056" OR "ONO 2745" OR ONO-2745 OR ONO2745) AND (cholecystectomy OR gallbladder)	All Fields	13
Scopus	TITLE-ABS-KEY((remimazolam OR RMZ OR "CNS 7056" OR "ONO 2745" OR ONO-2745 OR ONO2745) AND (cholecystectomy OR gallbladder))	Title, Abstract, Keywords	26
WOS	(remimazolam OR RMZ OR "CNS 7056" OR "ONO 2745" OR ONO-2745 OR ONO2745) AND (cholecystectomy OR gallbladder)	All Fields	12
Google Scholar	(remimazolam OR RMZ OR "CNS 7056" OR "ONO 2745" OR ONO-2745 OR ONO2745) AND (cholecystectomy OR gallbladder)	All Fields	100



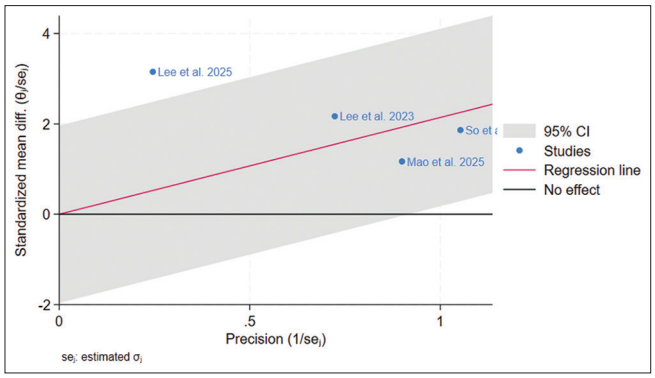
Supplementary Figure 1: Leave-one-out sensitivity analysis of anaesthesia onset time, CI = confidence interval



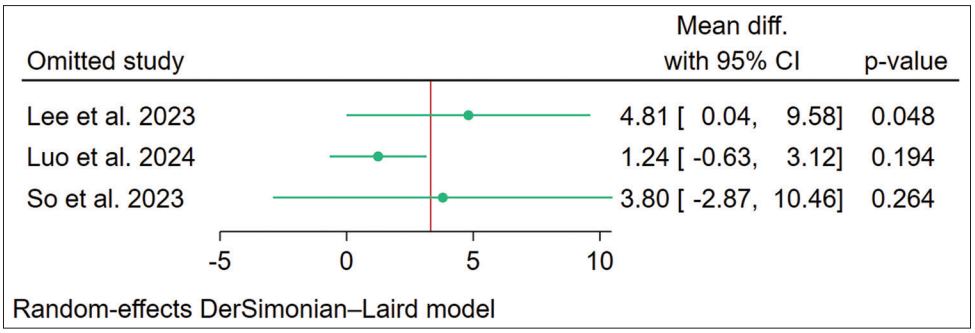
Supplementary Figure 2: Galbraith plot of anaesthesia onset time, CI = confidence interval



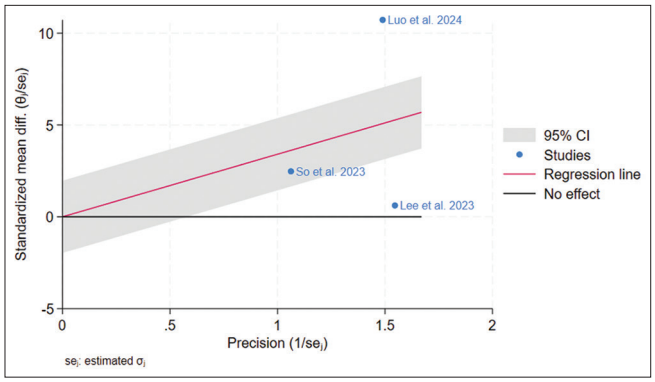
Supplementary Figure 3: Leave-one-out sensitivity analysis of recovery duration, CI = confidence interval



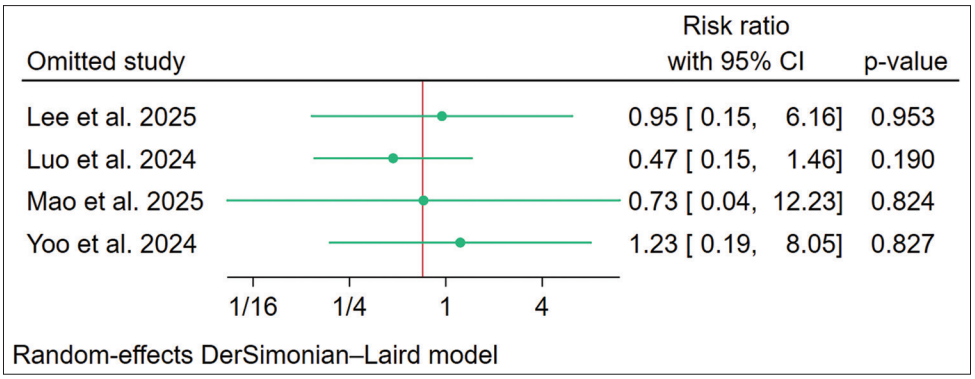
Supplementary Figure 4: Galbraith plot of recovery duration, CI = confidence interval



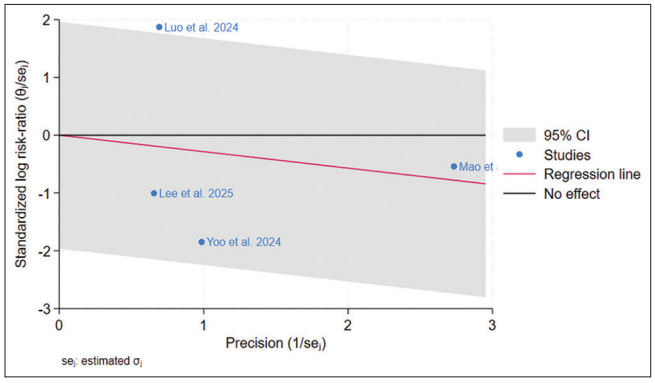
Supplementary Figure 5: Leave-one-out sensitivity analysis of extubation time, CI = confidence interval



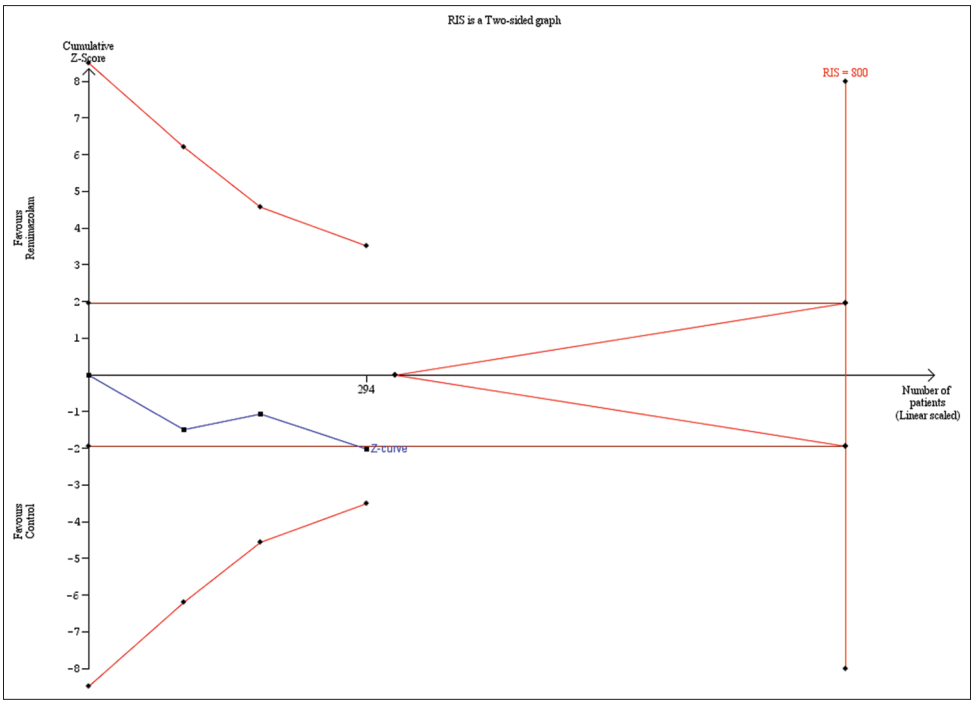
Supplementary Figure 6: Galbraith plot of extubation time, CI = confidence interval



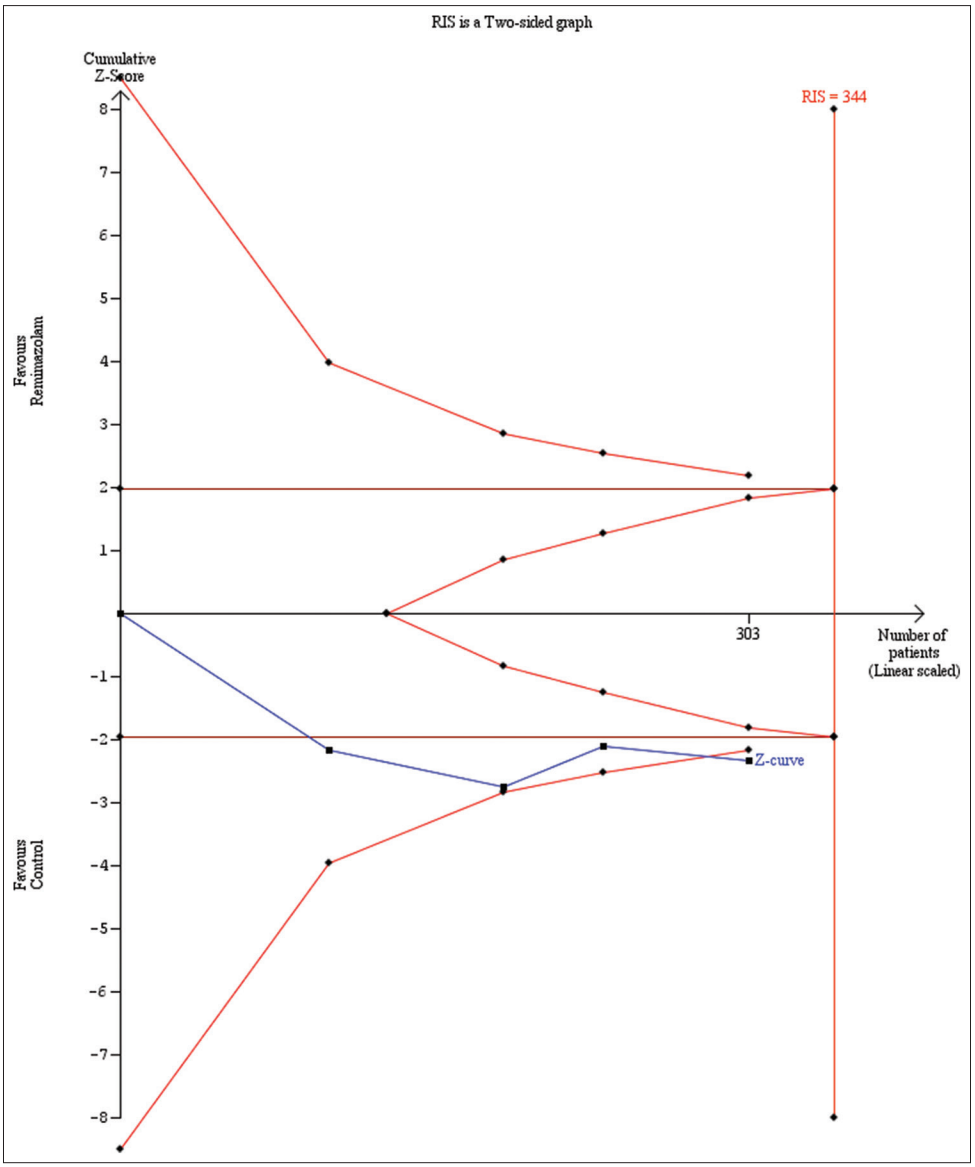
Supplementary Figure 7: Leave-one-out sensitivity analysis of PONV, CI = confidence interval



Supplementary Figure 8: Galbraith plot of PONV, CI = confidence interval



Supplementary Figure 9: Trial sequential analysis of anaesthesia onset time, RIS; required information size



Supplementary Figure 10: Trial sequential analysis of recovery duration; RIS; required information size