

ORIGINAL ARTICLE

Safety and efficacy of perioperative low-dose esketamine for pain management in laparoscopic cholecystectomy: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Laparoscopic cholecystectomy (LC) is frequently associated with early postoperative pain and opioid-related adverse effects. We evaluated the efficacy and safety of perioperative low-dose esketamine in adults undergoing LC.

Methods: Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance, PubMed, the Cochrane Library, Embase, and Web of Science were searched from inception to February 2026 for randomized controlled trials comparing esketamine with placebo or a standard anesthetic regimen. Random-effects meta-analyses generated mean differences, standardized mean differences, or risk ratios with 95% confidence intervals (CIs).

Results: Nine trials involving 699 participants were included. Esketamine reduced pain within 2 hours (MD -0.67; 95% CI -0.90 to -0.45) and reduced pain at rest and with movement through 72 hours, although several later estimates were highly heterogeneous. Intraoperative remifentanyl consumption (SMD -0.74; 95% CI -1.31 to -0.18) and propofol consumption (SMD -0.55; 95% CI -0.98 to -0.11) were lower. Awakening time, post-anesthesia care unit stay, and anesthesia duration did not differ significantly. No clear increase was observed in common adverse events, including nausea, vomiting, hallucinations, or agitation.

Conclusion: Perioperative low-dose esketamine modestly reduced postoperative pain and anesthetic requirements without a clear increase in common adverse events. However, the average early pain reduction was below a commonly used 1-point minimal clinically important difference, and substantial heterogeneity and imprecision limit confidence in the clinical importance and generalizability of these findings (PROSPERO: CRD420251251995).

Keywords: Esketamine, laparoscopic cholecystectomy, postoperative pain, opioid sparing, meta-analysis.

Introduction

Laparoscopic cholecystectomy (LC) is the standard surgical treatment for symptomatic gallstone disease and is widely performed because it shortens recovery and hospital stay compared with open surgery [1]. Nevertheless, many patients experience substantial early postoperative pain, including shoulder-tip pain related to pneumoperitoneum and diaphragmatic irritation, which

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can persist despite routine multimodal regimens [2,3]. Postoperative nausea and vomiting (PONV) also remains common after LC and can delay recovery and reduce patient satisfaction [4].

Opioids are frequently used to manage intraoperative and postoperative pain after LC, but dose-dependent adverse effects, including PONV, sedation, dizziness, pruritus, and respiratory depression, can undermine enhanced recovery goals [5]. These concerns have accelerated the adoption of multimodal analgesia, which combines nonopioid agents and technique-based strategies to reduce opioid requirements while maintaining adequate analgesia. Contemporary evidence in LC supports multimodal pathways that lower perioperative opioid exposure, motivating continued evaluation of adjuncts that provide reliable opioid sparing without compromising safety [6].

Ketamine and its enantiomers have gained renewed interest as opioid-sparing adjuvants because N-methyl-D-aspartate (NMDA) receptor antagonism can attenuate central sensitization and perioperative hyperalgesia [7]. Consensus guidance supports the use of subanesthetic ketamine-class agents as part of broader efforts to reduce reliance on opioids in the acute perioperative setting [8]. Esketamine (S-ketamine), the S-enantiomer of ketamine, has a more potent analgesic and anesthetic profile than R-ketamine and acts through NMDA blockade and additional receptor interactions that may influence analgesia, hemodynamics, and recovery [9]. Potential adverse effects, including psychomimetic symptoms, dizziness, and sedation, remain clinically important when findings are translated across procedures and dosing strategies.

In recent years, randomized trials and meta-analyses have evaluated perioperative esketamine in laparoscopic surgery, but results have varied across outcomes, doses, and administration schedules, limiting their direct applicability to LC-specific pathways [10]. Although broader laparoscopic-surgery syntheses are available, LC has distinct pain mechanisms, antiemetic practices, and anesthetic workflows that warrant a focused procedure-specific evaluation. We therefore performed a systematic review and meta-analysis of randomized controlled trials (RCTs) in adults undergoing LC to evaluate postoperative pain, opioid and anesthetic consumption, recovery parameters, adverse events, surgical outcomes, and perioperative hemodynamics.

Methods

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. The protocol was prospectively registered in PROSPERO (CRD420251251995).

Eligibility criteria

We included RCTs that compared perioperative esketamine with a control group receiving placebo or a standard anesthetic regimen without esketamine in adults (aged 18 years or older) undergoing LC.

Studies were eligible if they reported at least one predefined outcome: postoperative pain intensity measured with a validated scale; analgesic consumption, including intraoperative or postoperative opioid use and rescue analgesia; anesthetic consumption, such as propofol; recovery parameters, including awakening or extubation time, postanesthesia care unit (PACU) stay, and anesthesia duration; perioperative adverse events, including nausea, vomiting, dizziness, drowsiness, pruritus, respiratory distress, double vision, hallucinations, nightmares, delirium, or agitation; surgical duration or estimated blood loss; or hemodynamic parameters, including heart rate and mean arterial pressure (MAP).

Low-dose esketamine was operationally defined as a subanesthetic adjunct administered primarily for perioperative analgesia rather than as the principal anesthetic, consistent with acute-pain guidance on subanesthetic ketamine [8]. Because no universally accepted esketamine-specific cutoff exists, eligibility was based on the trial's stated analgesic intent and dosing context. Most boluses in eligible trials were 0.5 mg/kg or less, and most infusions were 0.5 mg/kg/hour or less; one older trial used 20 mcg/kg/minute (1.2 mg/kg/hour) but explicitly described the regimen as low-dose S(+)-ketamine. We imposed no additional restrictions on timing or route of administration. We excluded nonrandomized studies, case reports, reviews, and reports not published in English.

For hemodynamic synthesis, baseline was defined as the preinduction measurement; early intraoperative measurements were obtained after induction and before or shortly after pneumoperitoneum; mid-intraoperative measurements were obtained during established pneumoperitoneum; end-of-surgery measurements were obtained immediately before extubation; and awakening measurements were obtained immediately after extubation or in the PACU. These categories harmonized clinical phases because exact clock times differed across trials.

Information sources and search strategy

A comprehensive search of PubMed, the Cochrane Library, Embase, and Web of Science was conducted from database inception to February 2026. The strategy combined keywords and Medical Subject Headings related to esketamine and cholecystectomy. We also reviewed the reference lists of included articles to identify additional eligible studies. Detailed search strategies are presented in Table 1.

Study selection and data collection

Two reviewers independently screened all retrieved titles and abstracts. Full texts of potentially relevant reports were then assessed against the predefined eligibility criteria. Disagreements at either stage were resolved through discussion or, when necessary, consultation with a third reviewer. Two reviewers independently extracted study characteristics (first author, publication year, country, design, and sample size), participant characteristics (age, sex, American Society of Anesthesiologists [ASA] physical status, and body mass index [BMI]), intervention

Table 1. Search strategies used for each database.

Database	Search terms	Search field	Search results
PubMed	("Esketamine" OR "S-ketamine" OR "S ketamine" OR "Spravato" OR "JNJ-54135419") AND (cholecystectomy OR gallbladder)	All fields	15
Cochrane	("Esketamine" OR "S-ketamine" OR "S ketamine" OR "Spravato" OR "JNJ-54135419") AND (cholecystectomy OR gallbladder)	All text	43
Embase	("Esketamine" OR "S-ketamine" OR "S ketamine" OR "Spravato" OR "JNJ-54135419") AND (cholecystectomy OR gallbladder)	Broad search	34
WOS	("Esketamine" OR "S-ketamine" OR "S ketamine" OR "Spravato" OR "JNJ-54135419") AND (cholecystectomy OR gallbladder)	All fields	15

Abbreviations: WOS, Web of Science.

details (dose, timing, and route), comparator details, and predefined outcomes.

Risk-of-bias assessment

Two reviewers independently assessed the methodological quality and risk of bias of each included RCT using the revised Cochrane risk-of-bias tool for randomized trials [12]. The tool evaluates five domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of the reported result. Disagreements were resolved by discussion to reach a consensus judgment of low risk, some concerns, or high risk for each domain and overall.

Statistical analysis

All analyses used inverse-variance random-effects models to account for anticipated clinical and methodological heterogeneity. Statistical heterogeneity was quantified with the I^2 statistic derived from Cochran's Q . We interpreted I^2 as follows: 0%-40% might not be important; 30%-60% may represent moderate heterogeneity; 50%-90% may represent substantial heterogeneity; and 75%-100% represents considerable heterogeneity [13]. For continuous outcomes measured on the same scale, we calculated pooled mean differences with 95% confidence intervals (CIs); when scales or units differed, we calculated standardized mean differences. For dichotomous outcomes, we calculated pooled risk ratios (RRs) with 95% CIs. For studies with zero events in both groups, a continuity correction of 0.5 was added to all cells to permit inclusion in the RR calculation.

Prespecified subgroup analyses examined the timing and regimen of esketamine administration (intraoperative infusion, presurgical bolus, or combined regimen), and leave-one-out sensitivity analyses evaluated the influence of individual studies. Additional subgroup analyses by dose, background anesthetic regimen, co-interventions, or geographic region and meta-regression were not undertaken because most outcomes contained only two to five studies, making such estimates unstable. Outcomes with I^2 greater than 90% were retained in quantitative synthesis only when at least two trials were clinically comparable at the broad outcome level; these pooled estimates were treated as exploratory summaries, and narrative interpretation was prioritized because a random-effects model does not remove underlying inconsistency.

No outcome included 10 or more studies. Accordingly, funnel plots and formal tests of asymmetry, including Egger's regression and Begg's test, were not performed, consistent with Cochrane guidance that these methods have low power with fewer than 10 studies [13]. The possibility of unpublished negative trials was therefore addressed qualitatively in the Discussion. Analyses were performed in R (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria) using the meta package. All tests were two-sided, and $p < 0.05$ indicated statistical significance.

Results

Study selection

The search identified 107 records. After 53 duplicates were removed, 54 records underwent title and abstract screening, of which 40 were excluded. Fourteen full-text reports were assessed for eligibility, and 9 RCTs [14–22] met the inclusion criteria. The selection process is shown in the PRISMA flow diagram (Figure 1).

Study characteristics

This review included 9 RCTs (7 from China and 2 from Brazil) with 699 adults: 382 in esketamine groups and 317 in control groups. All trials used double-blind designs. Interventions comprised bolus regimens (generally 0.1–0.5 mg/kg), continuous intraoperative infusions (0.1–0.5 mg/kg/hour in most trials and 20 mcg/kg/minute [1.2 mg/kg/hour] in one older trial), and postoperative patient-controlled analgesia containing esketamine. One trial compared esketamine with the active comparator dezocine in patient-controlled analgesia. Follow-up ranged from immediate postextubation assessment to 72 hours. Study characteristics are summarized in Table 2, and baseline demographic and clinical characteristics are presented in Table 3.

Risk of bias assessment

Most studies had a low risk of bias; two studies [15,22] raised some concerns, primarily related to blinding and selective reporting (Figure 2).

Primary outcome: postoperative pain (VAS score)

Across four studies, esketamine reduced pain within 2 hours (2 studies; MD -0.67; 95% CI -0.90 to -0.45; p

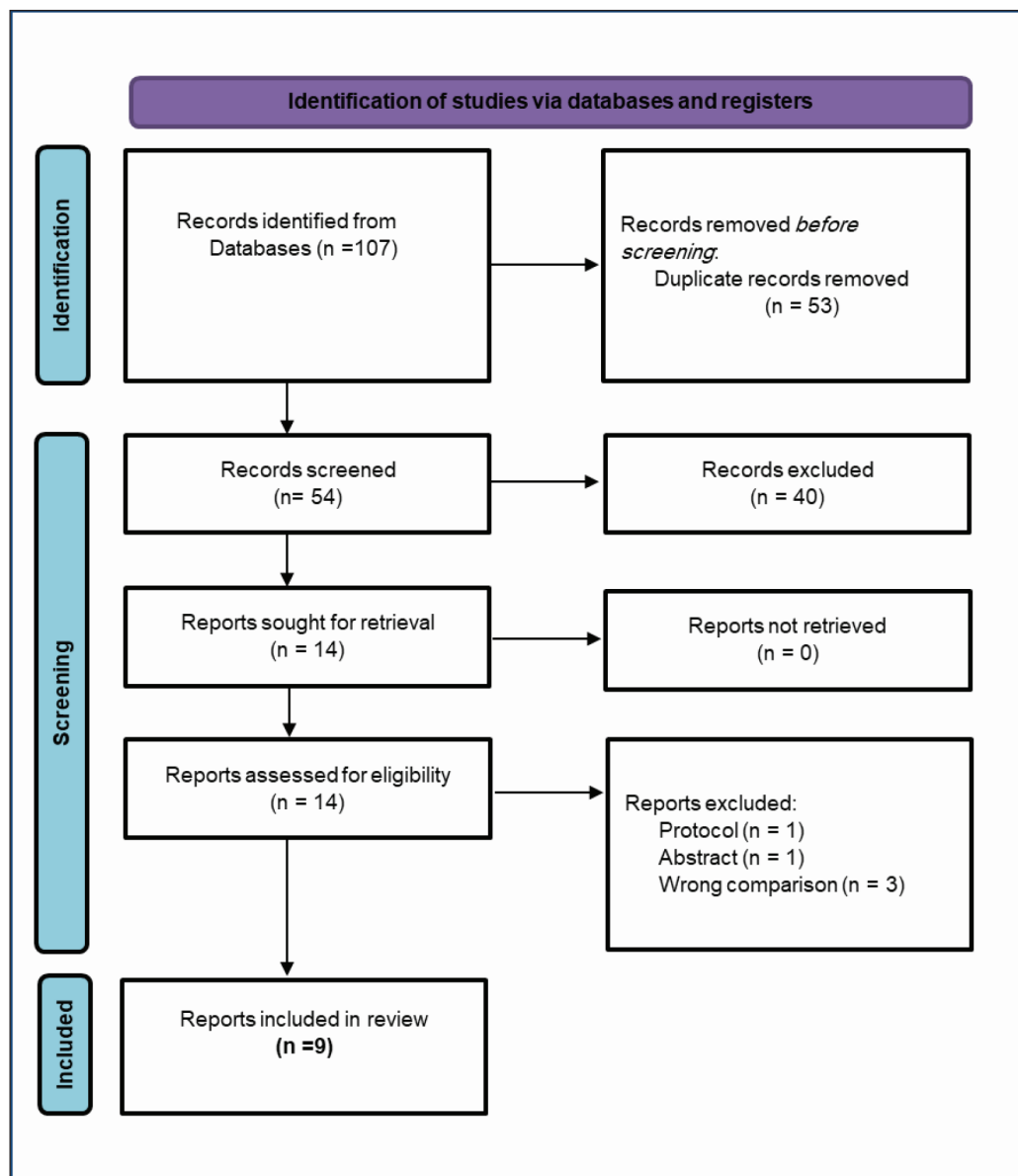


Figure 1. PRISMA flow diagram of study selection.

< 0.0001 ; $I^2 = 0\%$) and within 12 hours (2 studies; MD -2.00; 95% CI -3.90 to -0.10; $p = 0.04$; $I^2 = 77.4\%$), with no statistically significant subgroup difference ($p = 0.46$) (Figure 3). For movement-related pain, scores were lower at 24 hours (3 studies; MD -0.62; 95% CI -0.79 to -0.44; $p < 0.0001$; $I^2 = 0\%$), 48 hours (2 studies; MD -0.98; 95% CI -1.60 to -0.36; $p = 0.002$; $I^2 = 83.4\%$), and 72 hours (2 studies; MD -0.71; 95% CI -1.23 to -0.19; $p = 0.007$; $I^2 = 90.1\%$; subgroup-difference $p = 0.53$). Pain at rest was also lower at 24 hours (3 studies; MD -0.56; 95% CI -0.73 to -0.39; $p < 0.0001$; $I^2 = 28.8\%$), 48 hours (2 studies; MD -0.67; 95% CI -1.27 to -0.08; $p = 0.027$; $I^2 = 92.6\%$), and 72 hours (2 studies; MD -0.47; 95% CI -0.80 to -0.13; $p = 0.0069$; $I^2 = 80.8\%$; subgroup-difference $p = 0.81$). The 48- and 72-hour estimates were generally based on only two trials and had substantial or considerable heterogeneity; they should therefore be interpreted as exploratory summaries.

Secondary outcomes

Opioid- and anesthetic-sparing effects

Across five studies, esketamine was associated with lower intraoperative remifentanyl consumption (SMD -0.74; 95% CI -1.31 to -0.18; $p = 0.01$; $I^2 = 82.8\%$). The considerable overall heterogeneity limits interpretation of the average effect. Subgroup analysis showed an interaction by administration regimen, with the largest and most consistent reduction in the intraoperative-infusion subgroup (2 studies; SMD -1.23; 95% CI -1.61 to -0.85; $p < 0.0001$; $I^2 = 0\%$).

Esketamine was also associated with lower total propofol consumption (3 studies; SMD -0.55; 95% CI -0.98 to -0.11; $p = 0.014$; $I^2 = 50.5\%$; Figure 4a). Sufentanil consumption did not differ statistically between groups (2 studies; MD -7.52 mcg; 95% CI -24.75 to 9.70; $p = 0.40$; $I^2 = 99.3\%$). Because only two trials contributed and heterogeneity was extreme, the sufentanil estimate is

Table 2. Characteristics of included randomized controlled trials.

Study	Registry/country	Blinding	Randomization/ concealment	Recruitment	Esketamine	Control	Participants (E/C/Total)	Follow-up	Main inclusion criteria
Deng et al. [14]	ChiCTR2300072011 / China	Patients; anesthesiologists; surgeons; outcome assessors	Computer-generated random sequence (SPSS); allocation concealment not specified	Jun-Aug 2023	Postoperative PCA: sufentanil + esketamine 1.5 mg/kg in PCA solution + ondansetron	Sufentanil + dexmedetomidine 0.3 mg/kg + ondansetron	26 / 26 / 52	48 hours	Age 18-65 year; ASA I-II; BMI 18.5-24.0 kg/ m ² ; elective LC
Hu et al. [15]	- / China	Patients; anesthesiologists; outcome assessors	Random-number table; allocation concealment not specified	Apr 2019-Mar 2020	Dexmedetomidine 1 mcg/kg load then 0.5 mcg/kg/hour + esketamine 0.4 mg/kg load then 0.1 mg/kg/hour	Dexmedetomidine alone	55 / 55 / 110	24 hours	ASA I-II; no narcotic allergy; no severe organ dysfunction, cognitive impairment, or coagulopathy
Mendes et al. [16]	- / Brazil	Patients; anesthesiologists; surgeons; outcome assessors	Computer-generated random sequence; sequentially numbered sealed opaque envelopes	-	Group 1: S(+)-ketamine 100 mcg/kg bolus + 20 mcg/kg/ minute infusion; Group 2: 100 mcg/kg bolus + placebo infusion; Group 3: placebo bolus + S(+)-ketamine 20 mcg/kg/minute infusion	Pre-surgery saline placebo	57 / 21 / 78	24 hours	Age 18-65 year; BMI <35 kg/m ² ; ASA I-III; able to understand VAS
Miziara et al. [17]	NCT02421913 / Brazil	Patients; surgeons; outcome assessors	Computer-generated random sequence (randomizer); sealed envelopes	Jun 2012-Feb 2014	S(+)-ketamine 0.3 mg/kg/ hour intraoperative infusion	Saline placebo infusion	21 / 21 / 42	12 hours	Age 18-65 year; ASA I-II; scheduled for LC
Wu et al. [18]	ChiCTR2400083826 / China	Patients; anesthesiologists; surgeons; outcome assessors	Computer-generated random-number table (SPSS 26.0); concealment not specified	May-Aug 2024	Esketamine 0.5 mg/kg/hour intraoperative infusion	Normal saline placebo infusion	43 / 43 / 86	72 hours	Age ≥18 year; ASA I-II; BMI 18-30 kg/m ² ; elective LC
Xu et al. [19]	ChiCTR2200066663 / China	Patients; anesthesiologists	Computer-generated random sequence; sealed opaque envelopes	-	Pre-incision dose-finding bolus; dose varied by Dixon method, starting at 0.3 mg/kg	Normal saline placebo bolus	27 / 27 / 54	PACU assessment 15 minutes after extubation	Age ≥18 year; BMI 18-28 kg/m ² ; ASA I-II; elective LC
Zhang et al. [20]	ChiCTR2000040077 / China	Patients; anesthesiologists	Computer-generated random-number table (SPSS); concealment not specified	Dec 2020-Mar 2021	Esketamine 0.2 mg/kg induction bolus before propofol	Normal saline placebo bolus	23 / 24 / 47	PACU assessments 15 and 30 minutes after extubation	Age 18-65 year; ASA I-II; elective LC
Zhang et al. [21]	ChiCTR2400079362 / China	Patients; anesthesiologists; surgeons	Computer-generated random sequence; concealment not specified	Jan-Apr 2024	Esketamine 0.3 mg/kg pre- incision bolus	Normal saline placebo bolus	70 / 70 / 140	72 hours	Age 18-60 year; ASA I-II; elective LC
Zhao et al. [22]	ChiCTR2300067596 / China	Patients; anesthesiologists	Randomization schedule; sequentially numbered sealed opaque envelopes	Feb 2022-Jan 2023	LS: 0.5 mg/kg bolus + 2 mcg/ kg/minute infusion; HS: 0.5 mg/kg bolus + 4 mcg/kg/ minute infusion	Saline bolus + saline infusion	LS 30; HS 30 / 30 / 90	24 hours	Age 18-65 year; ASA I-II; elective LC; normal communication abilities

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; C, control; E, esketamine; HS, high-dose esketamine group; LC, laparoscopic cholecystectomy; LS, low-dose esketamine group; PACU, postanesthesia care unit; PCA, patient-controlled intravenous analgesia; VAS, visual analog scale.

Table 3. Baseline demographic and clinical characteristics of included participants (esketamine/control).

Study	Age, years	Male, n (%)	BMI, kg/m ²	ASA I, n (%)	ASA II, n (%)	ASA III, n (%)	Diabetes, n (%)	Hypertension, n (%)
Deng et al. [14]	44.15±10.36 / 43.19±10.44	11 (42.3%) / 9 (34.6%)	22.32±1.53 / 21.83±1.45	16 (61.5%) / 18 (69%)	10 (38.5%) / 8 (31%)	0 / 0	NA / NA	NA / NA
Hu et al. [15]	45.17±10.26 / 46.34±8.91	15 (27.3%) / 16 (29.1%)	NA / NA	NA / NA	NA / NA	NA / NA	NA / NA	NA / NA
Miziara et al. [17]	Demographic data reported as similar between groups							
Mendes et al. [16] (group 1)	45.4±12.5 / 41.9±12.0	NA / NA	29.3±5.6 / 27.6±3.6	5 (27.8%) / NR (35.3%)	13 (72.2%) / NR (57.2%)	0 / NR (7.5%)	NA / NA	NA / NA
Mendes et al. [16] (group 2)	46.6±13.2 / -	NA / -	27.2±4.5 / -	5 (25%) / -	14 (70%) / -	1 (5%) / -	NA / -	NA / -
Mendes et al. [16] (group 3)	45.9±11.4 / -	NA / -	25.6±2.5 / -	7 (36.8%) / -	12 (63.2%) / -	0 / -	NA / -	NA / -
Wu et al. [18]	47.9±9.4 / 49.7±15.1	23 (53.5%) / 21 (48.8%)	24.5±3.5 / 25.6±2.8	20 (46.5%) / 17 (39.5%)	23 (53.5%) / 23 (53.5%)	0 / 3 (7.0%)	1 (2.3%) / 1 (2.3%)	3 (7.0%) / 7 (16.3%)
Xu et al. [19]	54.57±20.35 / 55.71±7.83	8 (29.6%) / 9 (33.3%)	23.79±1.03 / 23.20±1.93	11 (40.7%) / 13 (48.1%)	16 (59.3%) / 14 (51.9%)	0 / 0	NA / NA	NA / NA
Zhang et al. [20]	51.57±11.96 / 51.04±8.35	13 (56.5%) / 11 (45.8%)	NA / NA	NA / NA	NA / NA	0 / 0	1 (4.3%) / 2 (8.3%)	4 (17.4%) / 3 (12.5%)
Zhang et al. [21]	47.5±15.8 / 46.4±13.7	45 (64.3%) / 36 (51.4%)	NA / NA	22 (31.4%) / 14 (20%)	45 (64.3%) / 56 (80%)	3 (4.3%) / 0	5 (7.1%) / 4 (5.7%)	5 (7.1%) / 6 (8.6%)
Zhao et al. [22] (LS)	40.3±10.3 / 39.3±11.2	14 (46.7%) / 15 (50%)	22.4±1.6 / 22.5±1.7	15 (50%) / 16 (53.3%)	15 (50%) / 14 (46.7%)	0 / 0	NA / NA	NA / NA
Zhao et al. [22] (HS)	39.5±10.6 / -	16 (53.3%) / -	22.8±1.5 / -	14 (46.7%) / -	16 (53.3%) / -	0 / -	NA / -	NA / -

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; E/C, esketamine/control; HS, high-dose esketamine group; LS, low-dose esketamine group; NA, not available; NR, not reported. A dash indicates that no separate comparator value was reported.

	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Deng et al. (2024)	+	+	+	+	+	+
Hu et al. (2024)	+	+	+	+	-	-
Mendes et al. (2011)	+	+	+	+	+	+
Miziara et al. (2016)	+	+	+	+	+	+
Wu et al. (2025)	+	+	+	+	+	+
Xu et al. (2023)	+	+	+	+	+	+
Zhang et al. (2022)	+	+	+	+	+	+
Zhang et al. (2025)	+	+	+	+	+	+
Zhao et al. (2024)	+	-	+	-	+	-

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
- Some concerns
+ Low

Figure 2. Risk-of-bias assessment of included randomized controlled trials.

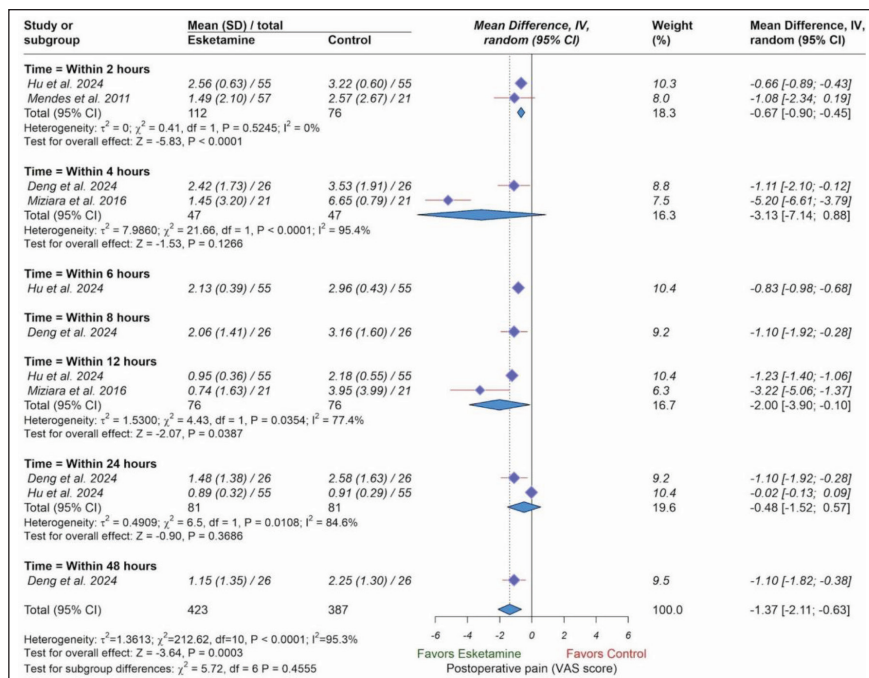


Figure 3. Forest plot of postoperative pain at different postoperative time points.

not considered a reliable common effect and is reported descriptively; no firm conclusion about sufentanil sparing can be drawn. The proportion of patients requiring postoperative rescue analgesia also did not differ (3 studies; RR 0.84; 95% CI 0.60 to 1.17; $p = 0.30$; Figure 4b).

Recovery parameters

The pooled estimate for awakening time showed no statistically significant difference (MD -0.50 minutes; 95% CI -2.89 to 1.90; $p = 0.68$; $I^2 = 97.1\%$), with a significant test for subgroup differences ($p < 0.0001$). PACU stay also did not differ statistically (3 studies;

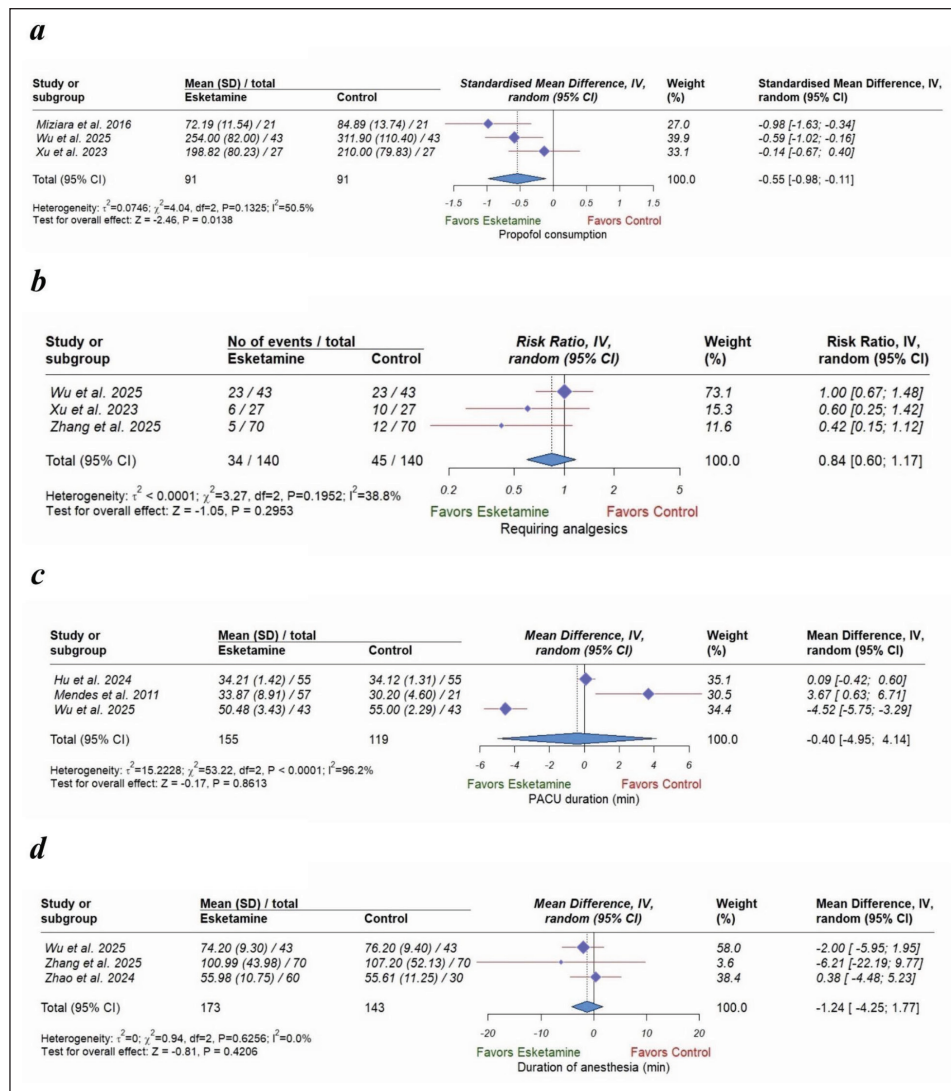


Figure 4. Forest plots of key secondary outcomes: (a) total propofol consumption; (b) postoperative rescue analgesic requirement; (c) PACU stay duration; and (d) total anesthesia duration.

MD -0.40 minutes; 95% CI -4.95 to 4.14; $p = 0.86$; $I^2 = 96.2\%$; Figure 4c), nor did total anesthesia duration (3 studies; MD -1.24 minutes; 95% CI -4.25 to 1.77; $p = 0.42$; $I^2 = 0\%$; Figure 4d). Because heterogeneity exceeded 90% for awakening time and PACU stay, these pooled estimates are exploratory and may obscure clinically important study-level differences in definitions and discharge practices.

Adverse events

Esketamine was not associated with a statistically significant increase in common perioperative adverse events. Pooled analyses showed no statistically significant difference in agitation (2 studies; RR 1.42; 95% CI 0.16 to 12.37; $p = 0.75$), dizziness (2 studies; RR 1.09; 95% CI 0.52 to 2.28; $p = 0.81$), drowsiness (2 studies; RR 1.13; 95% CI 0.45 to 2.82; $p = 0.80$), hallucinations (5 studies; RR 2.11; 95% CI 0.47 to 9.47; $p = 0.33$; Figure 5a), postoperative nausea (4 studies; RR 0.82; 95% CI 0.50 to 1.37; $p = 0.46$; Figure 5b), postoperative vomiting (4 studies; RR 0.77; 95% CI 0.37 to 1.60; $p = 0.48$; Figure

5c), PONV (7 studies; RR 0.69; 95% CI 0.41 to 1.15; $p = 0.16$; Figure 5d), nightmares (4 studies; RR 1.16; 95% CI 0.30 to 4.45; $p = 0.83$), pruritus (4 studies; RR 0.67; 95% CI 0.21 to 2.09; $p = 0.49$), respiratory distress (3 studies; RR 0.29; 95% CI 0.04 to 2.17; $p = 0.23$), or double vision (2 studies; RR 3.00; 95% CI 0.32 to 28.10; $p = 0.34$).

Surgical parameters

Esketamine did not significantly affect surgical duration (7 studies; MD -0.29 minutes; 95% CI -2.56 to 1.99; $p = 0.81$; $I^2 = 0\%$). Subgroup analysis by administration timing showed no statistically significant interaction ($p = 0.73$). Estimated blood loss was also comparable (2 studies; MD 0.00 ml; 95% CI -2.73 to 2.73; $p = 1.00$; $I^2 = 0\%$).

Hemodynamic stability

For harmonization, baseline referred to the preinduction measurement; the early intraoperative phase referred to measurements after induction and before or shortly after pneumoperitoneum; the mid-intraoperative phase

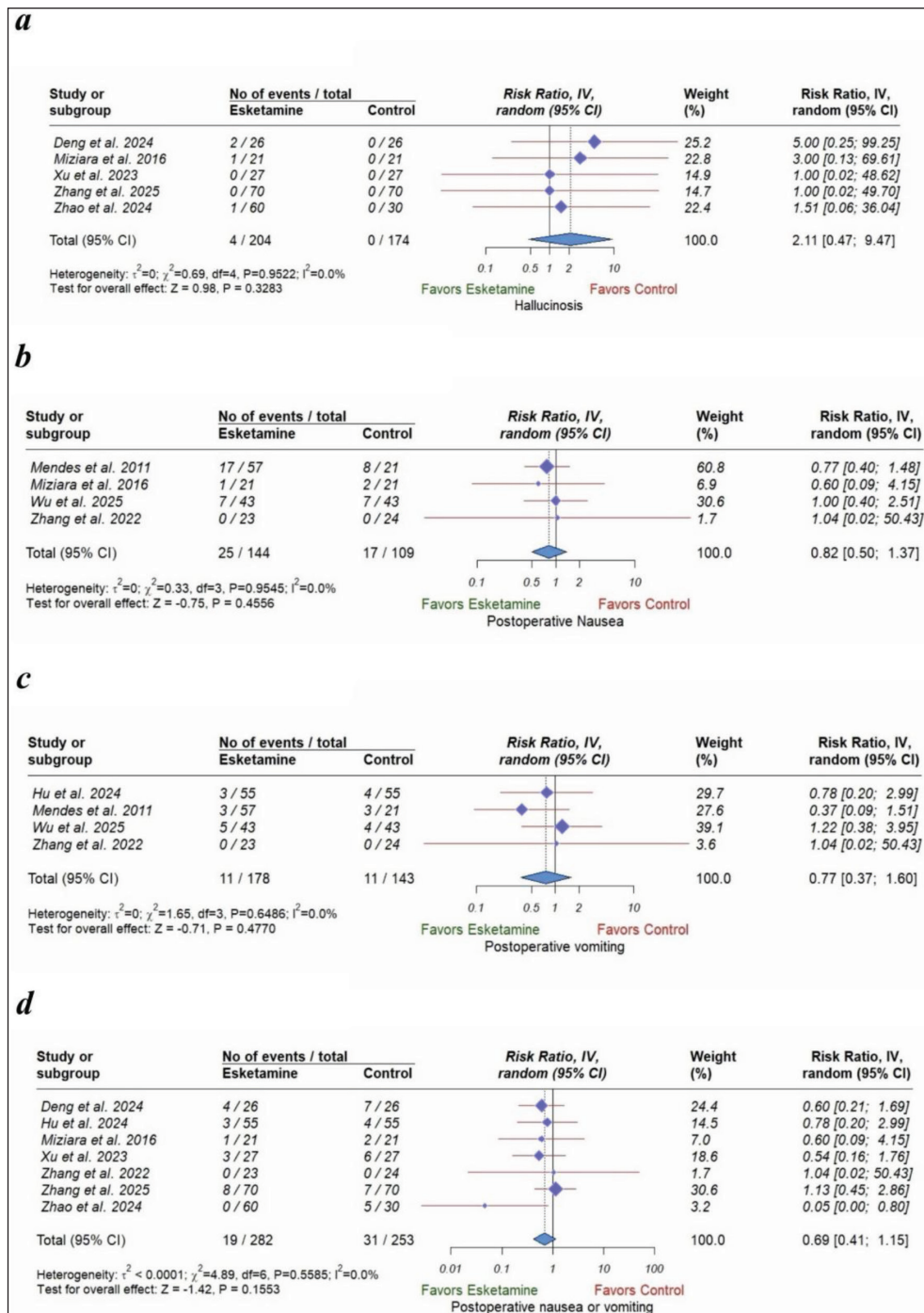


Figure 5. Forest plots of adverse events: (a) hallucinations; (b) postoperative nausea; (c) postoperative vomiting; and (d) postoperative nausea and vomiting.

referred to established pneumoperitoneum; the end-of-surgery phase referred to the period immediately before extubation; and awakening referred to immediate postextubation or PACU assessment. Because source trials used different clock times, these labels represent clinical phases rather than identical minute-based measurements. Esketamine was associated with a lower heart rate in the early intraoperative phase (MD -6.01 beats/minute; 95% CI -9.63 to -2.38; $p = 0.0012$; $I^2 = 0\%$) and lower MAP in the early phase (MD -5.47 mmHg; 95% CI -9.23 to -1.71; $p = 0.0043$; $I^2 = 0\%$) and mid-intraoperative phase (1 study; MD -5.80 mmHg; 95% CI -10.85 to -0.74). No statistically

significant differences were observed at baseline, the end of surgery, or awakening for either parameter, although the subgroup difference was significant for MAP ($p = 0.02$).

Sensitivity analysis

Leave-one-out sensitivity analyses did not materially change the direction or statistical conclusion for awakening time, surgical duration, hallucinations, nausea, vomiting, nightmares, PONV, or pruritus. However, these analyses did not resolve the considerable heterogeneity in awakening time and should not be interpreted as evidence of a common underlying effect.

Discussion

This systematic review and meta-analysis suggests that perioperative esketamine produces statistically significant but generally modest reductions in postoperative pain after LC, with the clearest and most consistent signal within 2 hours. Effects at later rest and movement time points were directionally favorable but were frequently based on only two trials and accompanied by substantial or considerable heterogeneity. NMDA receptor antagonism provides biological plausibility through attenuation of central sensitization, spinal wind-up, and opioid-induced hyperalgesia [7]. Esketamine has greater NMDA-receptor affinity than the R-enantiomer, which may permit analgesic effects at subanesthetic doses [9].

Lower remifentanyl and propofol requirements were also observed, although the overall remifentanyl estimate was heterogeneous and the most consistent signal arose from the intraoperative-infusion subgroup. These findings are broadly aligned with perioperative evidence that ketamine-class agents can reduce opioid requirements without a clear increase in common adverse events when subanesthetic doses are used [23,24]. A recent meta-analysis across surgical procedures reported improved early quality of recovery and reduced pain during the first two postoperative days without an overall increase in adverse events [24]. The administration-regimen signal also accords with procedure-level LC trials that reported improvements in perioperative stability and recovery-related outcomes [15,22].

The neutral findings for awakening time and PACU stay may reflect two factors. First, modern ambulatory anesthesia pathways already compress recovery time and may limit the opportunity for additional improvement [25]. Second, the extreme heterogeneity indicates that outcome definitions, background anesthetic regimens, co-interventions, and discharge criteria differed substantially. A random-effects model accounts for between-study variation in the statistical model but does not make clinically dissimilar effects interchangeable. Accordingly, these recovery estimates should be interpreted narratively rather than as precise common effects [25,26].

The safety synthesis did not identify a clear increase in common adverse events, but estimates for rare psychomimetic outcomes were imprecise and do not exclude modest risk increases. This is broadly consistent with pooled perioperative ketamine and esketamine evidence, in which subanesthetic adjunctive regimens have not consistently increased nausea, vomiting, or hallucinations [24,25]. The composite PONV estimate favored esketamine (RR 0.69), but its 95% CI (0.41-1.15) crossed the null; this possible benefit remains unconfirmed and may be underpowered. Some broader meta-analyses have suggested reductions in postoperative delirium, but certainty varies by population and procedure [27]. Recent LC-specific trials have begun to evaluate delirium-related outcomes, which remains an important direction for future research [21].

Beyond NMDA antagonism, ketamine-class drugs may exert anti-inflammatory and stress-response effects that could contribute to analgesia and hemodynamic findings [28,29]. The observed early reductions were modest

(approximately 6 beats/minute for heart rate and 5 mmHg for MAP), transient, and absent at later phases. They may reflect attenuation of the sympathetic response to nociception rather than direct cardiovascular depression. However, the available studies did not consistently report hypotension, bradycardia, or vasopressor use; therefore, these changes cannot be assumed to be clinically inconsequential, and routine hemodynamic monitoring remains appropriate.

Procedure-specific LC guidance recommends basic multimodal analgesia with paracetamol plus a nonsteroidal anti-inflammatory drug or a COX-2-selective inhibitor, intravenous dexamethasone, and local anesthetic wound infiltration or intraperitoneal instillation, while reserving opioids for rescue [30]. Transversus abdominis plane and erector spinae plane blocks are generally positioned as second-line options because of technical complexity and local anesthetic systemic-toxicity considerations. Within this framework, esketamine may be considered an opioid-sparing adjunct when the basic multimodal bundle is constrained, such as by an NSAID contraindication or a need to minimize intraoperative opioid exposure [10,30,31].

Dexmedetomidine and intravenous lidocaine have substantial evidence bases as systemic adjuncts in laparoscopic surgery. A meta-analysis of dexmedetomidine in laparoscopic procedures found reductions in postoperative opioid use, pain, nausea, and vomiting, although bradycardia and hypotension remain potential risks [32]. Intravenous lidocaine has also been associated with lower pain scores and opioid consumption after LC in meta-analyses, and randomized trials continue to refine its role [33,34]. Transversus abdominis plane block can reduce pain and opioid requirements compared with conventional control, although its incremental benefit over simpler port-site infiltration may be smaller and technique-dependent [35]. Esketamine is therefore one of several potential adjuncts rather than a replacement for established multimodal care.

The clinical interpretation of pain-score differences requires comparison with a minimal clinically important difference (MCID). In postoperative patients, approximately 10 mm on a 100-mm visual analog scale, equivalent to 1.0 point on a 0–10 scale, has been proposed as the MCID [36]. The pooled within-2-hour difference (-0.67 points) and most 24- to 72-hour estimates (-0.47 to -0.98 points) were below this threshold. The within-12-hour estimate (-2.00 points) exceeded it but was based on two studies with substantial heterogeneity ($I^2 = 77.4\%$). Thus, the statistically significant average pain reductions may not be perceptible or worthwhile for the average patient. MCID is context-dependent, and opioid- and propofol-sparing effects may still contribute to overall value, but the analgesic findings should not be described as uniformly clinically meaningful.

Limitations

The evidence base was geographically concentrated, with most trials conducted in China and two in Brazil; this may limit generalizability across perioperative pathways, anesthetic practices, and discharge criteria.

In addition, the restriction to English-language reports may have introduced language-related selection bias by excluding eligible regional studies with systematically different findings. Because no outcome included at least 10 studies, formal assessment of funnel-plot asymmetry was not appropriate, and unpublished negative trials cannot be excluded.

Doses, timing, routes, background anesthetic regimens, co-analgesics, and measurement schedules varied substantially. Extreme heterogeneity affected pain at some later time points, sufentanil consumption, awakening time, and PACU stay. A random-effects model does not eliminate this inconsistency, and additional dose-, region-, or co-intervention-based subgroup analyses were not reliable with only two to five studies per outcome. Consequently, estimates with I^2 greater than 90% should be considered exploratory rather than definitive common treatment effects. Rare safety events, including hallucinations and agitation, were imprecisely estimated, and most trials had short follow-up; chronic postsurgical pain, longer-term function, and patient-reported recovery were not consistently measured.

Future directions

Future trials should use pragmatic, multicenter designs that embed esketamine within contemporary enhanced-recovery pathways and compare it directly with established adjuncts, including dexmedetomidine, intravenous lidocaine, and regional techniques when feasible. Dose-finding studies are needed to identify the minimum effective analgesic and opioid-sparing regimen while monitoring neuropsychiatric symptoms with standardized instruments. Future LC studies should also incorporate validated delirium screening, sleep outcomes, patient-reported quality of recovery, and longer-term pain and functional outcomes. Mechanistic substudies that measure inflammatory markers and stress hormones could help link clinical effects to proposed pathways and identify patients most likely to benefit.

Clinical implications

These findings do not establish routine use of perioperative esketamine for all adults undergoing LC. Esketamine may be considered as one component of multimodal analgesia when opioid minimization is a priority, but the average pain benefit was modest and the optimal regimen remains uncertain. The most consistent opioid-sparing signal arose from intraoperative infusion, yet this finding should be balanced against the small subgroup, broader heterogeneity, and the need for hemodynamic and neuropsychiatric monitoring. This cautious positioning is consistent with procedure-specific guidance that prioritizes basic multimodal nonopioid strategies and reserves opioids for rescue [30].

Conclusion

Perioperative low-dose esketamine in adults undergoing LC modestly reduced postoperative pain and may reduce remifentanyl and propofol requirements without a clear increase in common adverse events. However, the

average early pain reduction was below a commonly used minimal clinically important difference, and rare safety outcomes were imprecisely estimated. Small outcome-specific evidence bases, substantial heterogeneity, regimen variability, and English-language restriction limit certainty and generalizability. Well-designed multicenter trials are needed before an optimal regimen or routine role can be established.

List of Abbreviations

ASA	American Society of Anesthesiologists
BMI	Body mass index
CI	Confidence interval
COX-2	cyclooxygenase-2
LC	Laparoscopic cholecystectomy
MAP	Mean arterial pressure
MCID	Minimal clinically important difference
MD	Mean difference
MeSH	Medical Subject Headings
NMDA	N-methyl-D-aspartate
NSAID	Nonsteroidal anti-inflammatory drug
PACU	Postanesthesia care unit
PCA	Patient-controlled analgesia
PCIA	Patient-controlled intravenous analgesia
PONV	Postoperative nausea and vomiting
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RoB 2	Revised Cochrane Risk of Bias tool for randomized trials
RR	Risk ratio
SMD	Standardized mean difference
TAP	Transversus abdominis plane
VAS	Visual analog scale

Conflict of interests

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Supplementary content (If any) is available online.

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