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Remimazolam-based total intravenous vs. sevoflurane-based balanced general anesthesia on perioperative outcomes in adult surgical patients: a systematic review and meta-analysis

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Abstract

Background Remimazolam is a novel intravenous anesthetic increasingly used as an alternative to traditional inhalational agents like sevoflurane. This systematic review and meta-analysis compared perioperative outcomes of remimazolam versus sevoflurane in adult patients undergoing general anesthesia.

Methods We searched PubMed, EMBASE, Cochrane, Scopus, and Web of Science through May 2025 for randomized controlled trials (RCTs) and observational studies comparing the two agents. Primary outcomes included intraoperative mean arterial pressure (MAP), heart rate (HR), incidence of hypotension, use of vasopressors, postoperative delirium (POD), postoperative nausea and vomiting (PONV), and antiemetic use. Secondary outcomes included recovery efficiency metrics. Risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI) were pooled using a random-effects model.

Results Fourteen studies with 1,593 patients (nine RCTs, five observational studies) were included. Remimazolam maintained higher MAP intraoperatively (e.g., 30 min after incision: MD = 7.91 mmHg; 95% CI [4.99, 10.83]; $P < 0.0001$; $I^2 = 43.8\%$) and higher HR (e.g., 1 h after incision: MD = 6.23 bpm; 95% CI [3.21, 9.25]; $P < 0.0001$; $I^2 = 0\%$) except in the PACU. Vasopressor use was lower with remimazolam (RR = 0.38; 95% CI [0.15, 0.99]; $P = 0.0485$; $I^2 = 89.7\%$), while IOH incidence was similar. Remimazolam significantly reduced PONV (RR = 0.61; 95% CI [0.42, 0.89]; $P = 0.0101$; $I^2 = 18.6\%$) without increasing POD (RR = 1.08; 95% CI [0.73, 1.59]; $P = 0.7048$; $I^2 = 0\%$). Eye-opening time was shorter (MD = − 121.87 s; 95% CI [−164.20, − 79.55]; $P < 0.0001$; $I^2 = 0\%$), while anesthesia, operation, and extubation times were comparable. RCT-only analyses confirmed most findings with reduced heterogeneity.

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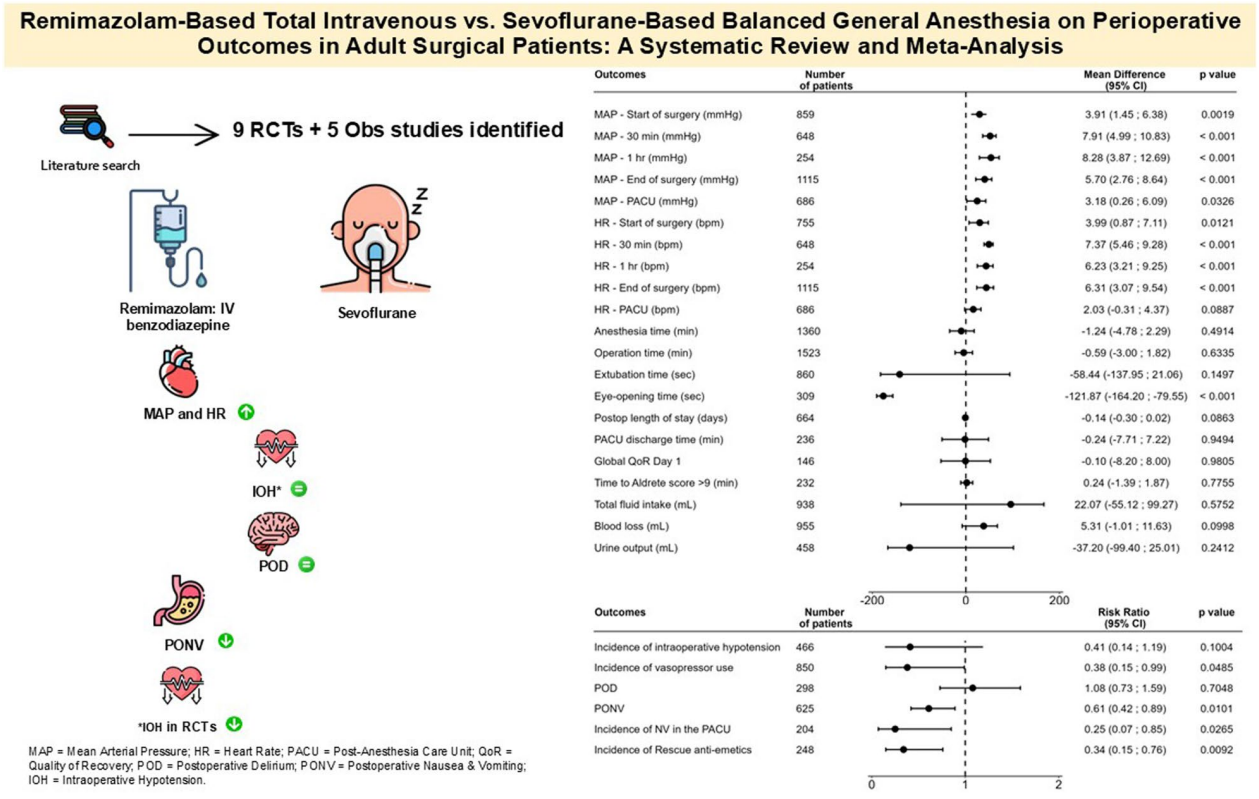
Conclusion Remimazolam-based anesthesia was associated with modestly more stable hemodynamics and reduced PONV without clear differences in recovery or POD. Larger, well-designed multicenter randomized trials are needed to confirm these findings in broader populations.

Registration Our protocol has been registered with PROSPERO under the following registration number: CRD42024523733.

Keywords Remimazolam, Sevoflurane, Hemodynamic stability, Postoperative delirium, Postoperative nausea and vomiting

Graphical Abstract



Introduction

Remimazolam is a recently introduced ultra-short-acting intravenous benzodiazepine that has received approval for the induction and maintenance of anesthesia in China, Korea, and Japan. It has also secured approval for procedural sedation in both the European Union and the United States [1]. Remimazolam acts by selectively binding to the benzodiazepine site of the gamma-aminobutyric acid type A (GABA-A) receptor in the brain with high affinity. Esterases rapidly convert it into a pharmacologically inactive metabolite, resulting in a rapid onset, short duration of action, and rapid recovery [2]. In addition, remimazolam has demonstrated greater hemodynamic stability in multiple clinical trials. For instance, it has been shown to be non-inferior to propofol in maintaining higher blood pressure and heart rate, with fewer patients requiring vasopressors during general anesthesia [3–5]. The availability of flumazenil as a reversal agent adds further clinical value by enabling rapid recovery in cases of prolonged sedation or delayed emergence [6]. Therefore, remimazolam has emerged as a promising alternative to traditional sedative and hypnotic agents used for the induction or maintenance of general anesthesia [7].

On the other hand, sevoflurane is a widely used inhaled anesthetic known for its rapid onset, ease of titration, and short recovery time [8]. Its broad use across surgical populations makes it an ideal reference comparator for newer anesthetic agents [9]. In addition, sevoflurane's well-documented associations with intraoperative hypotension (IOH) and postoperative nausea and vomiting (PONV) offer a practical benchmark for assessing the potential advantages of remimazolam [10, 11].

Several studies have compared the effects of remimazolam and sevoflurane in patients under general anesthesia. A randomized controlled trial involving orthopedic surgery patients found that those maintained with remimazolam exhibited higher mean arterial pressure (MAP) and heart rate (HR) at various time points, with no significant difference between the two groups in postoperative complications [12]. In other studies, remimazolam was associated with a decrease in frequency of vasopressor use [13], a lower incidence of PONV [14], and no increase in postoperative delirium (POD) [15]. In a retrospective propensity score-matched analysis of non-cardiac surgeries, Katsuragawa et al. found that remimazolam did not reduce the overall incidence of IOH compared with sevoflurane; however, it was associated with a shorter cumulative hypotensive duration and less frequent vasopressor use [16].

Although remimazolam has gained recognition as a promising intravenous anesthetic, particularly for patients vulnerable to hemodynamic instability, most existing meta-analyses have focused on its comparison with propofol, predominantly in the setting of procedural sedation or induction of anesthesia [17–23]. These studies have evaluated outcomes such as onset time, sedation efficacy, and recovery characteristics but do not address intraoperative hemodynamics or postoperative recovery during general anesthesia maintenance. Only a few meta-analyses have extended to general anesthesia settings [24–26], and even then, sevoflurane was either absent or pooled with other volatile agents, with fewer studies and a narrower set of perioperative outcomes assessed [27].

To address this important gap, we conducted a systematic review and meta-analysis focusing exclusively on head-to-head comparisons of remimazolam-based total intravenous anesthesia (TIVA) and sevoflurane-based balanced anesthesia in adult surgical patients. By isolating this comparison within the context of general anesthesia maintenance, our study provides a more clinically relevant evaluation of perioperative outcomes, including MAP, HR, vasopressor use, POD, and PONV incidence. Our central hypothesis is that remimazolam, due to its favorable pharmacodynamic and pharmacokinetic profiles, is associated with more stable intraoperative hemodynamics and fewer recovery-related complications compared to sevoflurane. This focused, comparator-specific approach enables more informed clinical decision-making than broad or mixed-comparator analyses.

Methods

Our meta-analysis adhered to the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) guidelines [28]. It also adhered to the AMSTAR 2 checklist [29]. Completed PRISMA and AMSTAR 2 checklists are available in the Supplementary Tables 1 and 2. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and is openly available under the identification number CRD42024523733.

Search strategy

The present investigation was conducted utilizing a comprehensive literature search across five databases: PubMed, EMBASE, Cochrane Library, Scopus, and Web of Science. The initial search, which spanned from inception to January 19, 2025, was subsequently updated on May 17, 2025. To ensure thoroughness, we also manually screened the reference lists of all included studies for potentially relevant articles. The search strategy we employed is detailed in the Supplementary Table 3.

Inclusion and exclusion criteria

The inclusion criteria consisted of randomized trials or observational cohorts comparing the efficacy and safety of general anesthesia maintenance, with remimazolam or sevoflurane in adults undergoing surgery, and reporting at least one of the outcomes of interest. To ensure consistency, only studies using sevoflurane were included, as other volatile agents, such as desflurane, have different pharmacologic and clinical profiles. No restrictions on language were applied. We excluded editorials, letters to the editor, literature reviews, meta-analyses, conference abstracts, studies with no extractable data, and duplicates.

Study selection and data extraction

EndNote was used to eliminate duplicate studies. The title and abstract screening data were imported into a Microsoft Excel spreadsheet and screened for eligibility. We then retrieved and assessed the full texts of those citations deemed potentially eligible. Data from eligible full texts were extracted into a pre-designed Microsoft Excel form. When results were presented only graphically, data were digitized using the WebPlotDigitizer software [30]. The outcomes extracted using Webplotdigitizer are listed in the Supplementary Table 4.

The present investigation extracted the following information: general characteristics (authors, publication year, study location, study design, type of surgery, and sample size); participant characteristics (age, sex, BMI, American Society of Anesthesiologists physical status (ASA-PS)); characteristics of the use of remimazolam and sevoflurane; and outcomes data. Throughout title and abstract screening, full-text assessment, and data extraction, we divided all data into two sets, each reviewed by two independent authors in duplicate (M.A. and D.K., or Z.A. and M.V.N.). We resolved all disagreements either through discussion or by a third reviewer (W.G. or A.M.F.).

Outcomes

Primary outcomes included intraoperative MAP, intraoperative HR, the incidence of IOH, the incidence of vasopressor use, POD, PONV, and the incidence of postoperative rescue antiemetics.

Secondary outcomes included anesthesia, extubation, operation, and eye-opening times; postoperative length of stay (PLOS); total fluid intake; blood loss; urine output; Global Quality of Recovery-15 score at postoperative day 1; and time to Aldrete score > 9. Definitions, types of vasopressors, and follow-up duration of outcomes, as reported by each study, are provided in Supplementary Table 4. All outcomes reported in the manuscript were prespecified in the registered PROSPERO protocol (CRD42024523733).

Quality assessment

The quality assessment of included studies was conducted using the risk of bias in non-randomized studies of interventions (ROBINS-I) and the Cochrane risk of bias 2 (ROB-2) tools [31, 32]. The ROB-2 tool assesses bias in various domains, including randomization, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting of results. The ROBINS-I tool evaluates bias across seven domains: confounding, participant selection, exposure classification, deviations from intended exposures, missing data, outcome measurement, and selective reporting. Included studies were divided into two sets, each reviewed by two independent authors in duplicate (M.A. and D.K., or Z.A. and M.V.N.), and discrepancies resolved by a third reviewer (W.G. or A.M.F.). Visualization of bias assessments was generated using the RobVis tool [33].

Quantitative analysis

A meta-analysis was performed using R Foundation Statistical software (R 4.4.2) and the "meta" extension package, applying a random-effects model to obtain estimates for primary and secondary outcomes.

For continuous variables, such as MAP and HR, the mean difference (MD) and its 95% confidence interval (CI) were calculated. For dichotomous variables such as PONV and IOH incidence, we reported risk ratios (RRs) with 95% CIs. We considered a P-value < 0.05 to be statistically significant. If the median and range were reported, we estimated the mean and standard deviation using the method provided by Wan and colleagues [34]. Studies that reported an outcome with a standard deviation of zero were excluded from the analysis. Heterogeneity among the included studies was evaluated using the I^2 statistic and Cochran's Q test, with a significance threshold of $p < 0.1$ and an I^2 value of 50% or greater indicating substantial heterogeneity.

To provide a more accurate comparison of the effects of remimazolam and sevoflurane, we conducted two post hoc subgroup analyses—one including only RCTs and another excluding studies involving ASA-PS class 4 patients—performed in response to the high heterogeneity observed in the primary analysis.

Leave-one-out sensitivity analysis was performed to assess the robustness of our findings. This involved systematically excluding each study, one at a time, and reanalyzing the data to confirm that no individual study disproportionately influenced the overall results. Publication bias was evaluated using Egger's regression test, which assessed funnel plot asymmetry to detect whether smaller or negative studies were more likely to be missing.

Certainty of evidence assessment

The certainty of evidence for each outcome was assessed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework. Each outcome was independently evaluated across five GRADE domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Additional considerations, such as large effect size and dose-response, were also factored in when applicable.

Results

Our search initially identified 5,270 records. We excluded 1,426 duplicates and, after screening titles and abstracts, 3,793 studies. Fifty-one studies were reviewed during full-text screening, and 13 studies met the inclusion criteria and were included in our meta-analysis. An updated search on May 17, 2025, identified one more study. In total, 14 studies were included in the present meta-analysis, comprising nine randomized controlled trials and five observational studies (three of which employed propensity score matching) [12–16, 35–43]. The PRISMA flow diagram is presented in Fig. 1. A list of retrieved reports in full-text but subsequently excluded is provided in Supplementary Table 5.

The studies were published between 2022 and 2025 and were primarily conducted in South Korea. A total of 1,593 adult surgical patients were included: 796 received remimazolam and 797 received sevoflurane.

In all included studies, remimazolam was used for both induction and maintenance of anesthesia in the remimazolam group. In contrast, most sevoflurane patients were induced with propofol. They received sevoflurane for maintenance, except for two studies that used remimazolam for induction in both groups [42, 43], and for two patients in the sevoflurane group of the study by Katsuragawa et al. [16], who were also induced with remimazolam. Sevoflurane was typically administered in

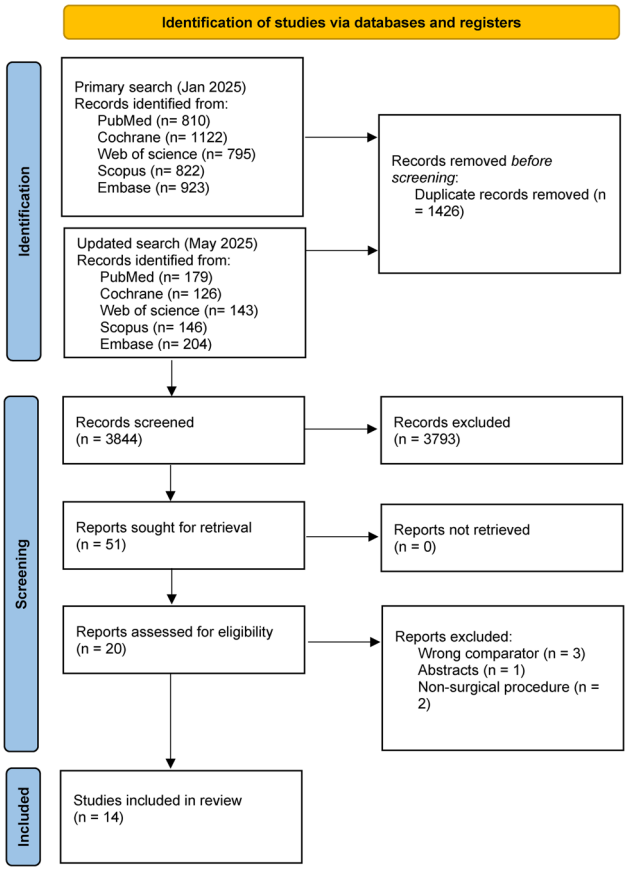


Fig. 1 PRISMA 2020 flow diagram

combination with intravenous remifentanil, reflecting a balanced anesthesia approach.

Surgical procedures spanned multiple non-cardiac specialties, including gastrointestinal, gynecologic, urologic, orthopedic, spine, and otolaryngologic surgery. The ASA-PS scores of patients ranged from 1 to 4, with one study including patients with an ASA-PS Score of 4 [16]. A comprehensive summary of the characteristics of the included studies and the baseline data for the included patients is presented in Table 1 and Supplementary Table 6.

Risk of bias assessment

Using the ROB-2 tool, we identified concerns in four RCTs: Park et al., Sangho Lee et al., Ryu et al., and Ko et al., due to a lack of description of allocation concealment and blinding [12, 13, 36, 40]. The remaining RCTs were found to have a low risk of bias. Using the ROBINS-I tool, we identified a moderate risk of bias in three observational studies: Zhang et al., Katsuragawa et al., and Seong et al. [16, 38, 41] primarily due to the lack of registration of their study protocols. A quality assessment of the methodology is shown in Supplementary Figs. 1 and 2.

Primary outcomes

Intraoperative mean arterial pressure (MAP)

MAP showed a statistically significant difference between the two groups in favor of remimazolam at all time points: At the start of surgery (MD = 3.91 mmHg; 95% CI [1.45, 6.38]; $P = 0.0019$; $I^2 = 55.8\%$). At 30 min after the start of surgery (MD = 7.91 mmHg; 95% CI [4.99, 10.83]; $P < 0.0001$; $I^2 = 43.8\%$). At one hour after the start of surgery (MD = 8.28 mmHg; 95% CI [3.87, 12.69]; $P = 0.0002$; $I^2 = 62.7\%$). At the end of surgery (MD = 5.70 mmHg; 95% CI [2.76, 8.64]; $P = 0.0001$; $I^2 = 77.0\%$). And even in the PACU (MD = 3.18 mmHg; 95% CI [0.26, 6.09]; $P = 0.0326$; $I^2 = 63.0\%$). See Fig. 2 and Supplementary Figs. 3–5.

Intraoperative heart rate (HR)

HR was significantly higher in the remimazolam group compared to the sevoflurane group at all time points, except in the PACU. At the start of surgery, the difference was MD = 3.99 bpm (95% CI [0.87, 7.11]; $P = 0.0121$; $I^2 = 67.6\%$). At 30 min after the start of surgery (MD = 7.37 bpm; 95% CI [5.46, 9.28]; $P < 0.0001$; $I^2 = 0\%$). At one hour after the start of surgery (MD = 6.23 bpm; 95% CI [3.21, 9.25]; $P < 0.0001$; $I^2 = 0\%$). At the end of surgery (MD = 6.31 bpm; 95% CI [3.07, 9.54]; $P = 0.0001$; $I^2 = 74.8\%$). At the PACU (MD = 2.03 bpm; 95% CI [-0.31, 4.37]; $P = 0.0887$; $I^2 = 41.2\%$). See Fig. 3 and Supplementary Figs. 6–8.

Incidence of IOH and vasopressor use

The incidence of IOH was assessed in four studies. There was no statistically significant difference between the two groups (RR = 0.41; 95% CI [0.14, 1.19]; $P = 0.1004$; $I^2 = 90\%$). However, the need for vasopressors, assessed in six studies, was significantly lower in the remimazolam group compared to the sevoflurane group (RR = 0.38; 95% CI [0.15, 0.99]; $P = 0.0485$; $I^2 = 89.7\%$) see Fig. 4.

POD

The incidence of POD was assessed in three studies. There was no statistically significant difference between the two groups (RR = 1.08; 95% CI [0.73, 1.59]; $P = 0.7048$; $I^2 = 0\%$) see Fig. 5A.

PONV and the administration of rescue antiemetics

Eight studies reported the incidence of PONV at different time points. Remimazolam significantly reduced the risk of PONV compared to sevoflurane (RR = 0.61; 95% CI [0.42, 0.89]; $P = 0.0101$; $I^2 = 18.6\%$) see Fig. 5B.

A subgroup analysis of PONV in the PACU revealed a significantly lower incidence in the remimazolam group (RR = 0.25; 95% CI [0.07, 0.85]; $P = 0.0265$; $I^2 = 9.1\%$). See Supplementary Fig. 9.

Similarly to PONV, the incidence of rescue antiemetic administration, assessed in four studies (Supplementary

Table 1 Summary characteristics of the included studies

Study	Study design	Age *mean (SD), or median (IQR)*		ASA-PS *n (%)*								Type of procedure	Anesthesia induction		Anesthesia maintenance	
		R	S	R				S					R	S	R	S
				1	2	3	4	1	2	3	4					
Bahn Lee 2022 Korea	Retrospective cohort propensity score matched	57 (46-64)	57.5 (47-66)	0	42 (81)	10 (19)	0	0	43 (83)	9 (17)	0	Robotic Gastrectomy	Remimazolam 6 mg/kg/h, Remifentanil 0.25-0.5 µg/kg/min	Propofol 1.0-2.0mg/kg, Remifentanil 0.05-0.1 µg/kg/min	Remimazolam 1-2 mg/kg/h, Remifentanil 0.25-2 µg/kg/min	Sevoflurane 0.8-1.0(MAC), Remifentanil
Park 2023 Korea	RCT	50 (5)	49 (4)	30 (100)		0	0	30 (100)		0	0	Gynecological laparoscopy	Remimazolam 1-6 mg/kg/h, Remifentanil 0.5-1.0 µg/kg	Propofol 1.5-2.0 mg/kg, Remifentanil 0.5-1.0 µg/kg	Remimazolam 1-2 mg/kg/h, Remifentanil 0.05-0.2 µg/kg/min	Sevoflurane 2-2.5%, Remifentanil 0.05-0.2 µg/kg/min
Jiwon Lee 2024 Korea	RCT	49.1 (35-67)	49.2 (30-68)	36 (100)			0	36 (100)			0	Cervical spine surgery	Remimazolam 6-12 mg/kg/h, Remifentanil 3.0 ng/ml	Propofol 1-2 mg/kg, Remifentanil 3.0 ng/ml	Remimazolam 1.0-2.0 mg/kg/h, RemifentanilPSI 25-50	Sevoflurane 1.5-2%, RemifentanilPSI 25-50
Zhang 2023 China	Retrospective cohort	64 (57-72)	65 (58-73)	76 (100)		0	0	79 (100)		0	0	Transurethral resection of the prostate	Remimazolam 12 mg/kg/h	Sevoflurane 8% and Midazolam 0.2 mg/kg, Sufentanil 3-4 g/kg	Remimazolam 0.25mg/kg bolus infusion within 30 seconds	Sevoflurane 0.5-4%, Remifentanil 1-2 µg/kg.
Sangho Lee 2024 Korea	RCT	60 (48-69)	60 (45-70)	10 (25.6)	26 (66.7)	3 (7.7)	0	9 (23.1)	28 (71.8)	2 (5.1)	0	Orthopedic surgery	Remimazolam 0.1-0.2 mg/kg, Remifentanil 0.3-0.5 µg/kg	Propofol 1.5-2.0 mg/kg, Remifentanil 0.3-0.5 µg/kg	Remimazolam 1-2 mg, Remifentanil 0.05-0.2 µg/kg/minBIS 30-60	Sevoflurane 0.8-1.2(MAC), Remifentanil 0.05-0.2 µg/kg/minBIS 30-60
Sangho Lee 2023 Korea	RCT	75 (71-78)	72 (69-78)	3 (7.7)	33 (84.6)	3 (7.7)	0	7 (17.9)	30 (76.9)	2 (5.1)	0	Total knee arthroplasty	Remimazolam 0.1 mg/kg, Remifentanil 0.5 µg/kg	Propofol 1.5 mg/kg, Remifentanil 0.5 µg/kg	Remimazolam 1-2 mg/kg/hr, Remifentanil 0.05-0.2 µg/kg/minBIS 30-60	Sevoflurane, Remifentanil 0.05-0.2 µg/kg/minBIS 30-60
Katsuragawa 2023 Japan	Retrospective cohort propensity score matched	72 (64.0-78.0)	71 (62.0-78.0)	0	7 (5)	84 (59.6)	48 (34)	0	4 (2.8)	88 (62.4)	48 (34)	Non-cardiac surgery	Remimazolam in 98.6%, Propofol in 0.7%, Midazolam in 0.7%	Propofol in 69.5%, Midazolam 16.3%, Sevoflurane in12.1%, Remimazolam in 1.4%	Remimazolam, Remifentanil	Sevoflurane, Remifentanil
Yoo 2024 Korea	RCT	55.1 (11.9)	50.9 (10)	19 (95)		1(5)	0	20 (100)		0	0	Laparoscopic cholecystectomy and hemi-colectomy	Remimazolam 6 mg/kg/h, Remifentanil 0.1-0.2 µg/kg/min	Sevoflurane 5%, Remifentanil 0.1-0.2 µg/kg/min	Remimazolam 1-2 mg/kg/h, Remifentanil 0.1-0.2 µg/kg/minBIS 40-60	Sevoflurane 1.6-2%, Remifentanil 0.1-0.2 µg/kg/minBIS 40-60
Ryu 2024 Korea	RCT	71.76 (9.42)	66.18 (11.95)	3 (17.6)	8 (47.1)	6 (35.3)	0	5 (29.4)	8 (47.1)	4 (23.5)	0	Transurethral resection of Bladder Tumor	Remimazolam 12 mg/kg/h, Remifentanil 1 µg/kg	Propofol 1.5-2 mg/kg, Sevoflurane 5%	Remimazolam Remifentanil 0.01-0.20 µg/kgPSI 30-50	Sevoflurane 1.5-2.5%PSI 30-50
Ko 2024 Korea	RCT	61.4 (15.1)	60.8 (11.7)	0	0	15 (100)	0	0	0	15 (100)	0	Coil embolization of Cerebral Aneurysm	Remimazolam 6-12 mg/kg/hRemifentanil 0.5-1.0 µg/kg/min	Propofol 1-2.5 mg/kgRemifentanil 0.5-1.0 µg/kg/min	Remimazolam 1-2 mg/kg/hRemifentanil 0.05 µg/kg/min	Sevoflurane 1 MAC Remifentanil 0.05 µg/kg/min

Table 1 (continued)

Study	Study design	Age *mean (SD), or median (IQR)*		ASA-PS *n (%)*								Type of procedure	Anesthesia induction		Anesthesia maintenance	
		R	S	R				S					R	S	R	S
				1	2	3	4	1	2	3	4					
Seong 2024 Korea	Retrospective cohort	43 (33.5- 50)	44 (34-52)	3 (1.8)	149 (90.9)	12 (7.3)	0	3 (1.8)	149 (90.9)	12 (7.3)	0	laparoscopic gynecologic surgery	Propofol bolus 1.0–2.0 mg/kgRemifentanil infusion 0.05 µg/kg/min	Propofol bolus 1.0–2.0 mg/kgRemifentanil infusion 0.05 µg/kg/min	Remimazolam 6 mg/kg/h until loss of consciousness then 1–2 mg/kg/h after intubation	Sevoflurane 0.8–1.0 MAC BIS 40-60
Seung Cheol Lee 2023 Korea	RCT	55.7 (11.4)	53.9 (14.9)	12 (31)	22 (58)	4 (11)	0	9 (23)	25 (66)	4 (11)	0	Tympanoplasty with Mastoidectomy	Remimazolam 12 mg/kg/h Remifentanil 0.5 µg/kg/min	Remimazolam 12 mg/kg/h Remifentanil 0.5 µg/kg/min	Remimazolam 1–2 mg/kg/h infusion Remifentanil 0.1–1.0 µg/kg/minBIS 40-60	Sevoflurane 1.5–2.5% Remifentanil 0.1–1.0 mcg/kg/min
Cheol lee 2023 Korea	RCT	49.7 (6.4)	49 (8.1)	20 (55)	16 (45)	0	0	15 (44)	19 (56)	0	0	Laparoscopic gynecologic surgery	Remimazolam 6 mg/kg/h	Remimazolam 6 mg/kg/h	Remimazolam 1–2 mg/kg/hBIS 40-60	Sevoflurane 1 MAC BIS 40-60
Kim 2025 Korea	Retrospective cohort propensity score matched	82.3 (6.8)	81.4 (8)	NA	NA	NA	NA	NA	NA	NA	NA	Hip or femur surgery	Remimazolam 6 mg/kg/h	Propofol bolus 1–2 mg/kg	Remimazolam 0.5–2 mg/kg/hBIS 40-60	Sevoflurane 1–2.5% BIS 40-60

RCT Randomized controlled trial, *R* Remimazolam, *S* Sevoflurane, *MAC* Minimum Alveolar Concentration, *BIS* Bispectral Index, *PSI* Patient State Index

Fig. 10), was lower in the remimazolam group (RR = 0.34; 95% CI [0.15, 0.76]; $P = 0.0092$; $I^2 = 0\%$).

Secondary outcomes

Anesthesia, operation, extubation, and eye-opening times

The anesthesia, operation and extubation times were similar between the remimazolam and sevoflurane groups (MD = -1.24 min; 95% CI [-4.78, 2.29]; $P = 0.4914$; $I^2 = 47.4\%$), (MD = -0.59 min; 95% CI [-3.00, 1.82]; $P = 0.6335$; $I^2 = 0\%$), (MD = -58.44 s; 95% CI [-137.95, 21.06]; $P = 0.1497$; $I^2 = 90.8\%$), respectively. See Supplementary Figs. 11–13.

The eye-opening time was included in only three studies, and it was shorter in the remimazolam group (MD = -121.87 s; 95% CI [-164.20, -79.55]; $P < 0.0001$; $I^2 = 0\%$). See Supplementary Fig. 14.

Postoperative length of stay

PLOS was reported in five studies, and there was no significant difference (MD = -0.14 day; 95% CI [-0.30, 0.02]; $P = 0.0863$; $I^2 = 0\%$). See Supplementary Fig. 15.

A subgroup analysis of PACU length of stay also showed that patients receiving remimazolam were not discharged from the PACU before those receiving sevoflurane (MD = -0.24 min; 95% CI [-7.71, 7.22]; $P = 0.9494$; $I^2 = 86.8\%$). See Supplementary Fig. 16.

Postoperative recovery

Three studies assessed the global quality of recovery (QoR) score on postoperative day 1. No significant difference was found between remimazolam and sevoflurane (MD = -0.10; 95% CI [−8.20, 8.00]; $P = 0.9805$; $I^2 = 54.9\%$). See Supplementary Fig. 17.

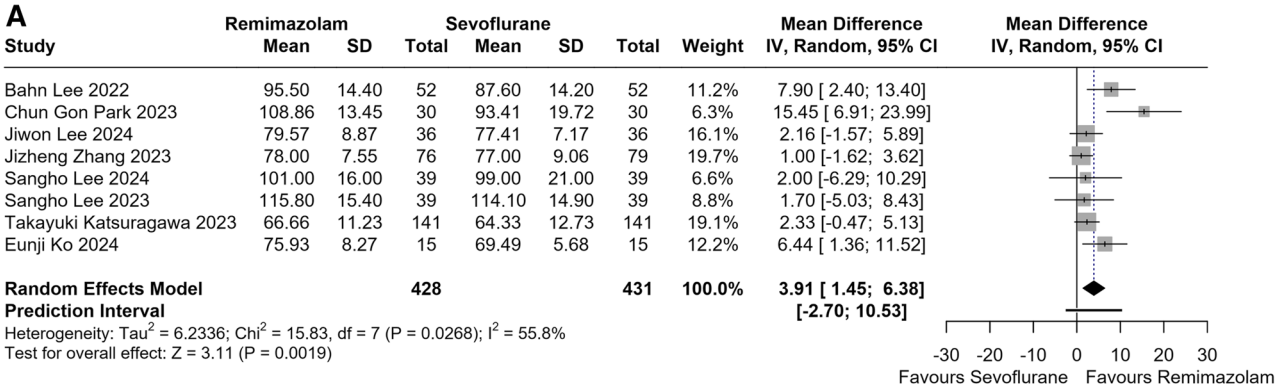
Similarly, time to reach an Aldrete score > 9, reported in three studies, showed no significant difference (MD = 0.24 min; 95% CI [−1.39, 1.87]; $P = 0.7755$; $I^2 = 0\%$). See Supplementary Fig. 18.

Total fluid intake, blood loss, and urine output

The analysis showed that total fluid intake was similar between the two groups (MD = 22.07 mL; 95% CI [-55.12, 99.27]; $P = 0.5752$; $I^2 = 82.5\%$). In addition, blood loss and urine output demonstrated no statistically significant difference between the two groups (MD = 5.31 mL; 95% CI [-1.01, 11.63]; $P = 0.0998$; $I^2 = 32.3\%$), (MD = -37.20 mL; 95% CI [-99.40, 25.01]; $P = 0.2412$; $I^2 = 59.0\%$), respectively. See Supplementary Figs. 19–21.

Subgroup analysis

Subgroup analysis, limited to RCTs, confirmed the primary results for 19 of 27 outcomes. Seven outcomes were not assessed in the RCT-only analysis due to insufficient numbers of studies. See Supplementary Table 7.



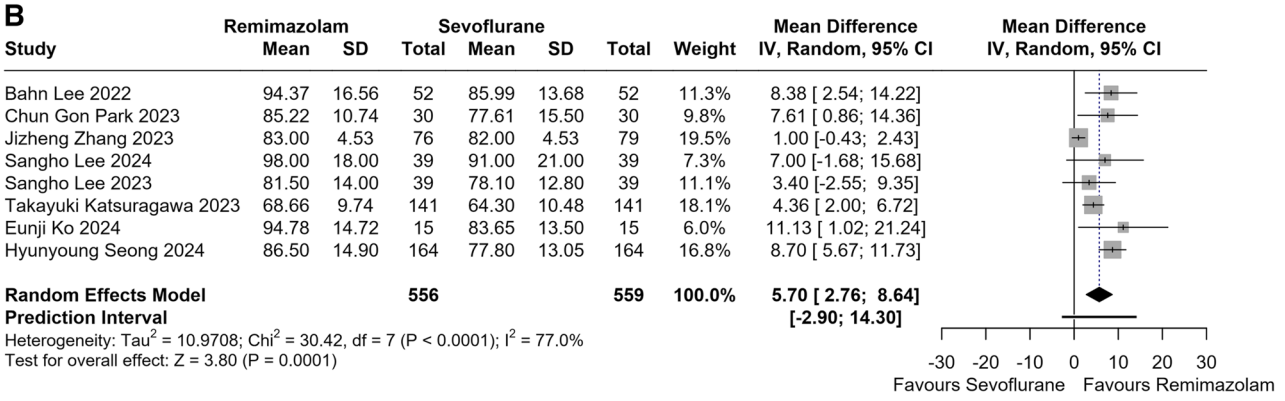


Fig. 2 **A** Forest plot of MAP at the start of surgery comparing remimazolam and sevoflurane (MD, 95% CI; positive values favor remimazolam). **B** Forest plot of MAP at the end of surgery comparing remimazolam and sevoflurane (MD, 95% CI; positive values favor remimazolam)

MAP and HR remained significantly higher in the remimazolam group at all timepoints, even in the PACU. Notably, and in contrast with the primary analysis, the incidence of IOH (RR = 0.32; 95% CI [0.14, 0.75]; $P = 0.0085$; I2 = 52.1%) was significantly lower in the remimazolam group. Other outcomes showed no significant differences. See Supplementary Figs. 22–38.

Heterogeneity was generally lower, particularly for outcomes such as MAP, IOH incidence, and vasopressor use. This suggests that observational studies made a significant contribution to the variability in the primary analysis. However, a few outcomes—such as PONV—showed slightly increased heterogeneity in the RCT-only subgroup, which might indicate some inconsistency even within randomized trials. Overall, limiting the analysis to RCTs helped reduce variability across most outcomes. See Supplementary Table 6.

We conducted a separate meta-analysis excluding the study that included ASA-PS class 4 patients [16]. Contrary to our initial analysis, patients receiving remimazolam did not have higher HRs at the start of surgery. Consistent with the RCT-only subgroup analysis, the incidence of IOH was significantly reduced in the remimazolam group. Other findings remained essentially unchanged. See Supplementary Figs. 39–48.

Sensitivity analysis

A leave-one-out sensitivity analysis revealed that several outcomes were sensitive to the inclusion of specific studies. For example, the statistical significance of MAP and HR in the PACU depended on the presence of individual studies, such as those by Jiwon Lee (2024) or Seong (2024). Similarly, results for PONV and nausea/vomiting in the PACU were influenced by studies, including those by Cheol Lee (2023) and Bahn Lee (2024). These findings suggest that, while the overall direction of the results is consistent, specific study contributions can meaningfully alter the level of statistical significance. See Supplementary Figs. 49–75.

Publication bias

Finally, we assessed publication bias using funnel plots for anesthesia and operation times, the only outcomes with 10 or more studies. For all other outcomes, funnel plots were not performed due to the limited number of included studies. Both plots showed symmetry around the overall effect. This was further supported by Egger's test for the outcomes, which yielded two-tailed p-values greater than 0.05, indicating symmetry and a lower risk of publication bias. See Supplementary Figs. 76–77.

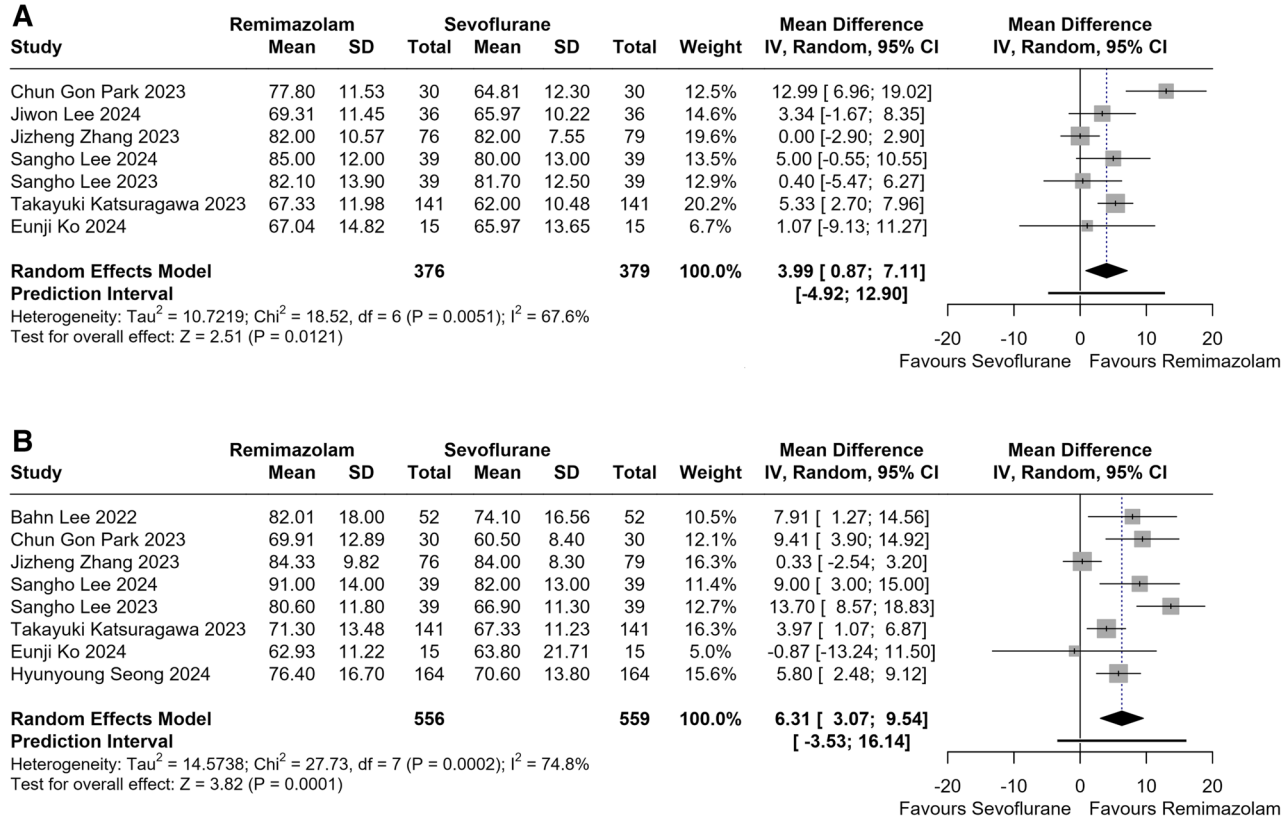


Fig. 3 **A** Forest plot of HR at the start of surgery comparing remimazolam and sevoflurane (MD, 95% CI; positive values favor remimazolam). **B** Forest plot of HR at the end of surgery comparing remimazolam and sevoflurane (MD, 95% CI; positive values favor remimazolam)

GRADE assessment

According to the GRADE evaluation, evidence certainty was moderate for MAP and high for HR, PONV, and recovery metrics, while outcomes affected by heterogeneity or limited sample size (IOH, vasopressor use, and PACU stay) were rated low to moderate. No serious indirectness or publication bias was identified. (See Supplementary Table 8.)

Discussion

Our meta-analysis provides a comprehensive evaluation of the hemodynamic effects and postoperative outcomes associated with remimazolam-based TIVA compared with balanced anesthesia using sevoflurane in adult surgical patients. Our findings demonstrate improved hemodynamic stability with remimazolam, evidenced by consistently higher intraoperative MAP and reduced vasopressor requirements compared with sevoflurane. This aligns with reports of reduced hypotension risk [21, 22, 24, 26, 35, 44, 45]. However, given the heterogeneity and imprecision observed, and the low certainty of evidence for certain outcomes, particularly IOH and vasopressor use, these findings should be interpreted cautiously.

Importantly, although differences in MAP and HR reached statistical significance at multiple time points, their absolute magnitudes were modest. MAP differences ranged approximately from 4 to 8 mmHg, and HR differences from 3 to 9 bpm. In stable, low-risk patients, such differences may not be clinically meaningful. Nevertheless, even small increases in MAP may reduce the likelihood of crossing predefined hypotension thresholds in vulnerable populations, such as elderly patients or those with limited cardiovascular reserve. Similarly, modest increases in HR may be clinically relevant in patients at risk of bradycardia, such as those receiving beta-blocker therapy. Thus, these findings likely reflect a trend toward improved hemodynamic stability rather than large clinically transformative effects.

The clinical relevance of a higher MAP during surgery with remimazolam needs to be balanced against the potential risks of hypertension and associated complications. Intraoperative hypertension, though less studied than hypotension, has been associated with postoperative adverse outcomes such as acute kidney injury [46]. Katsuragawa et al. investigated the incidence of hypertension associated with remimazolam and sevoflurane and reported no significant differences [16]. However, isolated case reports have described unexpected

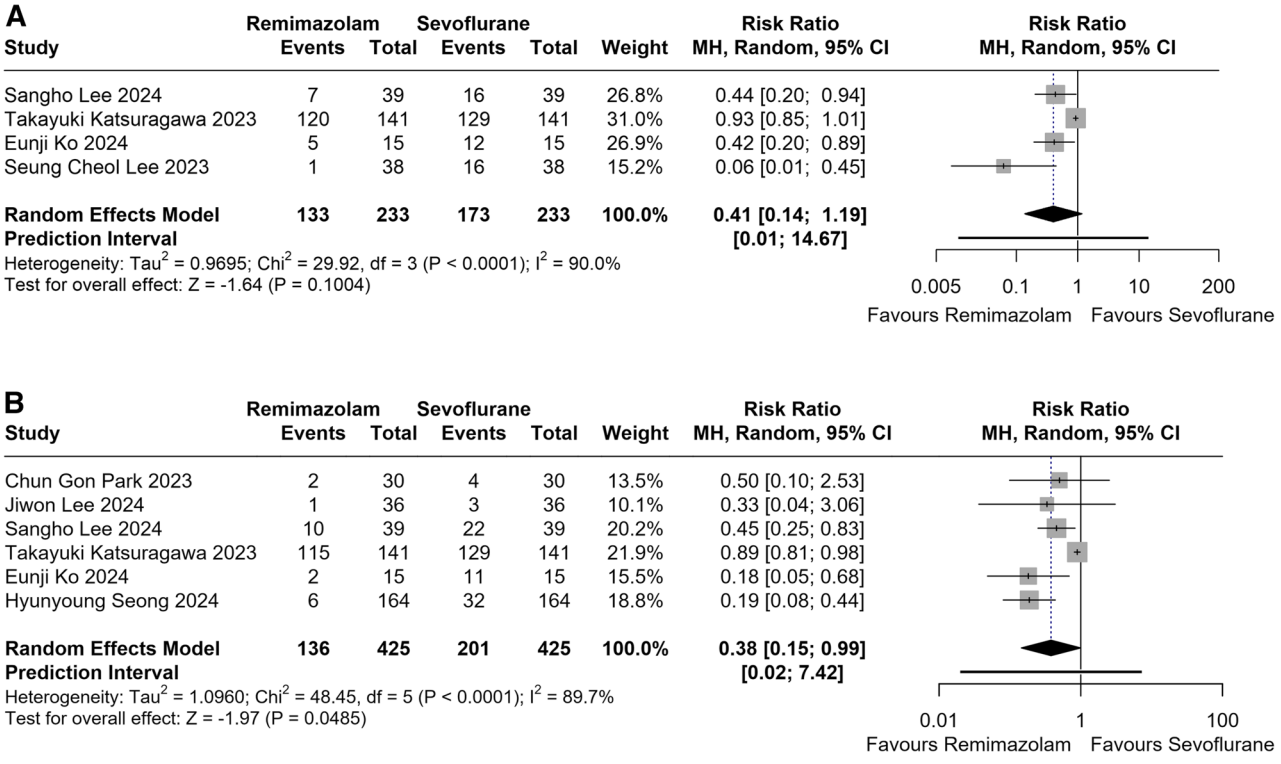


Fig. 4 **A** Forest plot of IOH comparing remimazolam and sevoflurane (RR, 95% CI; values <1 favor remimazolam). **B** Forest plot of vasopressor use comparing remimazolam and sevoflurane (RR, 95% CI; values <1 favor remimazolam)

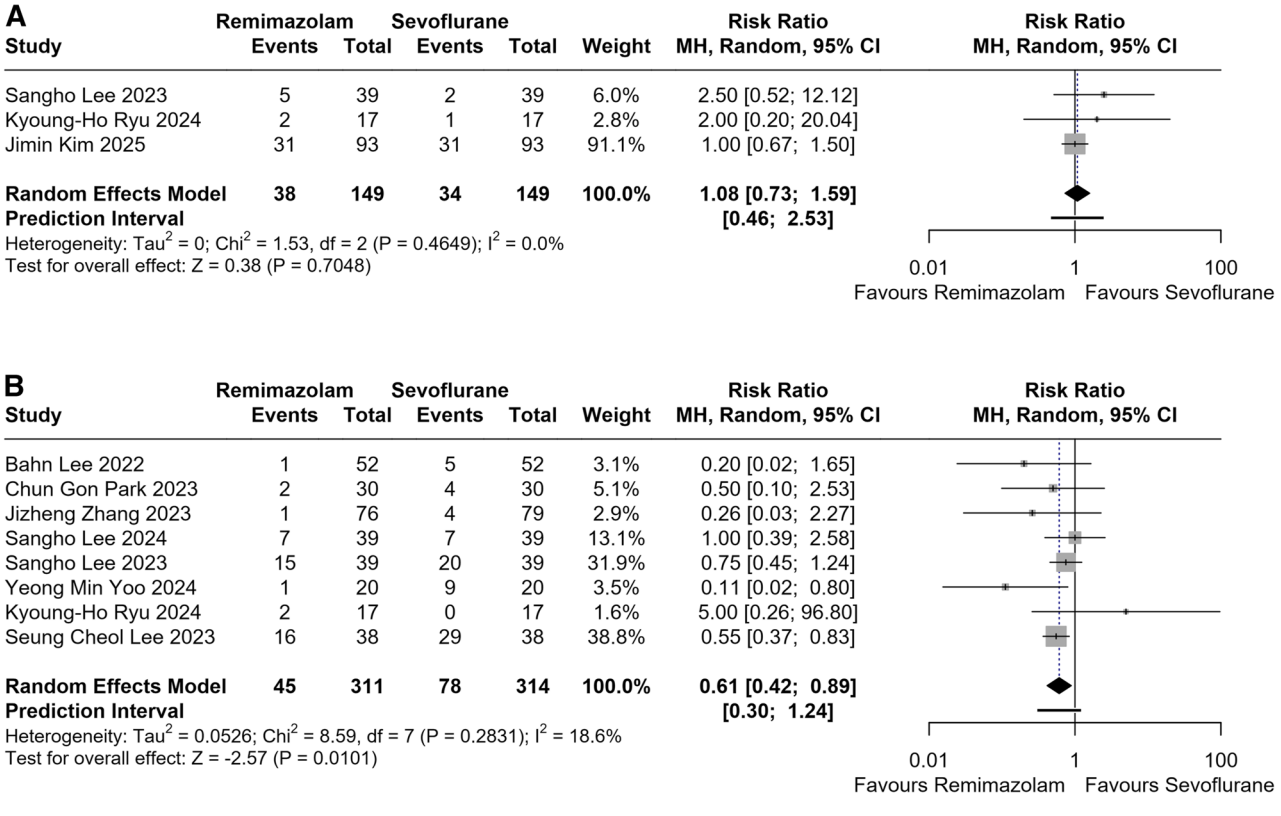


Fig. 5 **A** Forest plot of POD comparing remimazolam and sevoflurane (RR, 95% CI; values <1 favor remimazolam). **B** Forest plot of PONV comparing remimazolam and sevoflurane (RR, 95% CI; values <1 favor remimazolam)

hypertension during induction with remimazolam, suggesting that individual variability in response may play a role [47]. Future research should therefore not only evaluate average MAP trends but also investigate patient-level predictors of hypertensive responses, as well as their potential impact on postoperative outcomes such as renal dysfunction or major cardiovascular events.

The overall incidence of IOH did not reach statistical significance in the primary analysis, though a significant effect emerged in the subgroup restricted to RCTs. This finding should be interpreted cautiously, given the observed heterogeneity, imprecision, and the low certainty of evidence for this outcome. Similarly, while a reduction in vasopressor use was observed in pooled analyses, the certainty of evidence was limited, and further high-quality randomized trials are needed to confirm this potential advantage.

We conducted a separate meta-analysis that excluded patients with ASA-PS class 4. We assumed that patients with severe systemic diseases could potentially have variable responses to anesthesia. Interestingly, while most outcomes remained consistent, the previously observed statistical significance for HR at the start of surgery was lost, likely due to reduced sample size, narrower variability, or the exclusion of extreme HR responders typically found in sicker populations.

In the present study, we found no significant difference in POD. This aligns with the findings of Kim et al., who reported that remimazolam was not associated with an increased risk of POD in elderly patients undergoing hip surgery compared with sevoflurane [15]. Although benzodiazepines are traditionally considered a risk factor for POD, evidence on this association is inconsistent. Remimazolam, however, may represent an exception due to its ultra-short half-life and rapid metabolism via tissue esterases, leading to reduced drug accumulation and side effects. Furthermore, recent evidence suggests remimazolam may exert anti-inflammatory effects. A recent study by Hayoung Lee et al. found that remimazolam was associated with significantly lower postoperative serum levels of inflammatory markers, such as IL-6 and TNF-α, compared with sevoflurane, potentially contributing to its favorable cognitive profile [48]. In contrast, Sangho Lee et al. reported a slightly higher incidence of POD in the remimazolam group compared to the sevoflurane group, possibly due to its benzodiazepine nature [39]. Due to inconsistencies in the existing literature and the limited number of included studies in our review, further large-scale randomized trials are warranted to draw more definitive conclusions.

A statistically significant difference was observed in overall PONV and PONV in the PACU, with a reduced likelihood of requiring rescue antiemetics after the operation. This is consistent with Elbakry et al., who observed a greater incidence of PONV with inhalational anesthesia than with TIVA [49]. Notably, the lower risk of postoperative rescue antiemetics in the remimazolam group suggests reduced use of additional medications, which can improve patient comfort and reduce costs [50], making remimazolam a favorable option in patients at high risk of PONV.

In a randomized controlled trial conducted by Lee et al., remimazolam and propofol were compared during cardiac surgery. They found that flumazenil use in the remimazolam group significantly decreased time to extubation and eye opening compared with propofol [51]. Interestingly, our current study found that the extubation time was similar across both groups. In addition, although the eye-opening time was statistically shorter in patients receiving remimazolam, the absolute difference was modest and did not translate into earlier extubation or shorter PACU or hospital stay. Overall, the recovery profile among patients receiving remimazolam was generally similar to that observed with sevoflurane.

The present investigation determined that both the total volume of fluid administered during anesthesia and the amount of blood loss were comparable between the remimazolam and sevoflurane groups. This is a noteworthy observation because it suggests that the hemodynamic effects of remimazolam are unlikely to be influenced by either the volume of fluids administered or the blood loss during surgery.

Our findings also build upon and extend those of Park et al. [27], who included seven RCTs using sevoflurane and five RCTs using desflurane. Their meta-analysis evaluated a narrower set of outcomes—IOH, PONV, bradycardia, extubation time, PACU stay, and hospital length of stay—and reported results generally consistent with ours. In contrast, our analysis incorporated both randomized and observational studies, focused exclusively on sevoflurane, and assessed additional outcomes, including MAP, vasopressor use, heart rate trends, POD, and recovery variables. This broader evidence base not only confirms prior findings but also provides a more comprehensive and clinically relevant perspective on the perioperative effects of remimazolam compared with sevoflurane.

Beyond its clinical outcomes, the economic implications of remimazolam also warrant consideration. As noted by Ko et al. [13], remimazolam is considerably more expensive than sevoflurane or propofol, with an estimated cost of USD 24.8–37.2 per vial compared with USD 1.8–2.7 for propofol and USD 2–3 for sevoflurane. However, the reduced need for additional vasoactive medications such as norepinephrine or ephedrine may help offset these higher initial costs. Further research is warranted to better define the overall economic impact, including postoperative outcomes, long-term complications, and healthcare resource utilization.

Study limitations

This study was subject to several limitations. First, all studies included in our analysis were conducted in Asia, raising questions about the applicability of our findings to non-Asian populations. In addition, regulatory labeling and clinical adoption patterns differ across regions. Remimazolam was approved early for general anesthesia in Japan and other Asian countries [52], whereas in Europe and the United States, its initial approval focused primarily on procedural sedation before broader perioperative implementation [53]. These regional differences may influence familiarity with the drug, dosing strategies, and its positioning relative to volatile anesthetics such as sevoflurane. In addition, genetic factors such as the higher frequency of CYP2C19 loss-of-function alleles in Asian populations may alter the metabolism and efficacy of anesthetic agents [54, 55]. Although remimazolam metabolism is largely independent of CYP-mediated pathways, interindividual differences in benzodiazepine pharmacodynamic sensitivity may still influence clinical response across populations. Of note, a multicenter European RCT comparing remimazolam with propofol demonstrated reduced post-induction hypotension with remimazolam [56]. While this trial did not compare remimazolam to sevoflurane, it supports the hemodynamic advantages of remimazolam in non-Asian populations. These findings suggest that the cardiovascular profile of remimazolam is unlikely to be ethnicity-specific. However, direct head-to-head comparisons between remimazolam-based TIVA and sevoflurane-based anesthesia in non-Asian populations remain limited, and further multicenter trials in diverse healthcare settings are warranted to confirm generalizability.

Second, the relatively small number of studies, limited sample sizes, and the inclusion of heterogeneous surgical procedures made it difficult to draw definitive conclusions. These factors, along with the lack of standardized outcome definitions, variations in anesthetic dosing protocols, and differences in the use of vasoactive or antihypertensive agents, likely contributed to the moderate to high heterogeneity observed. In particular, intraoperative time points (e.g., the "start" and "end" of surgery), recovery metrics, and definitions of IOH were not consistently defined across studies. Criteria for hypotension included varying MAP thresholds, percentage reductions from baseline, and duration requirements. These differences may have influenced absolute outcome values and contributed to heterogeneity.

Additionally, mean intraoperative MAP values may not fully reflect transient hypotensive episodes that met predefined criteria or prompted vasopressor use. However, because remimazolam and sevoflurane were compared within each study using consistent internal definitions, the relative treatment effects remain interpretable. Standardized definitions in future trials would improve cross-study comparability.

Pooling randomized and observational studies increases statistical power and reflects broader clinical practice; however, it may introduce confounding and limit causal inference. To address between-study variability, we performed several additional analyses, including a subgroup analysis limited to RCTs, an analysis excluding patients with ASA class 4, and leave-one-out sensitivity analyses. The reduction in heterogeneity in the RCT-only analysis for several hemodynamic outcomes suggests that differences in study design and protocol standardization contributed meaningfully to overall variability. However, persistence of moderate heterogeneity for certain endpoints indicates that protocol-level differences—such as induction regimens, depth-of-anesthesia targets, perioperative vasoactive management, and surgical diversity—also played an important role. Leave-one-out analyses further demonstrated that individual studies influenced statistical significance for some outcomes, whereas others, such as IOH, appeared to reflect structural variability rather than single-study effects. Importantly, the overall direction of effect remained consistent across analyses. Additional subgroup stratification was not feasible due to limited overlap in surgical types and relatively homogeneous adult populations. Taken together, these findings support cautious interpretation of outcomes with substantial variability while reinforcing the overall pattern observed across analyses.

Third, variability in depth-of-anesthesia monitoring may have confounded hemodynamic outcomes. While most studies used BIS or PSI, target ranges differed, and some did not report monitoring at all. Because anesthetic depth directly influences blood pressure and heart rate, inconsistent monitoring could partly explain the observed group differences. Moreover, in some trials, propofol was used for induction in the sevoflurane groups. Since propofol causes greater cardiovascular depression than remimazolam, this may have overestimated the hemodynamic advantage of remimazolam-based TIVA.

Finally, follow-up durations varied across studies, which may have contributed to the variability in postoperative outcomes. More robust evidence is required for future studies to utilize standardized protocols, detailed and segmented time points, and direct comparisons of remimazolam-based anesthesia with sevoflurane in larger, more diverse populations. Despite these limitations, we believe our study provides valuable insights and a solid foundation for future research.

In conclusion, our findings indicate that remimazolam-based TIVA, compared to sevoflurane-based inhalational

anesthesia, resulted in a modestly higher MAP and HR at the start, during, and at the end of surgery. Although the available data are limited, no statistically significant difference in POD was observed between remimazolam and sevoflurane; in contrast, remimazolam was associated with lower rates of PONV and reduced need for rescue antiemetics. Postoperative recovery profiles were comparable between the groups. Taken together, these findings suggest that remimazolam may be selectively incorporated into anesthesia protocols for patients at high risk of hemodynamic instability or postoperative nausea. However, given the heterogeneity in study design, anesthetic protocols, and outcome definitions, these results should be interpreted cautiously. Larger randomized trials with standardized methodologies are needed to better establish the clinical relevance of these comparisons.

Abbreviations

GABA-A	Gamma-aminobutyric acid type A
IOH	Intraoperative hypotension
POD	Postoperative Delirium
PONV	Postoperative nausea and vomiting
MAP	Mean arterial pressure
HR	Heart rate
PACU	Post-anesthesia care unit
PLOS	Postoperative length of stay
BMI	Body mass index
ASA-PS	American Society of Anesthesiologists Physical Status
MD	Mean difference
CI	Confidence interval
RR	Risk ratio
IV	Intravenous
TIVA	Total intravenous anesthesia

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-026-03787-y.

Supplementary Material 1.

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None.

Authors' contributions
AMF, WG, MB, and ME contributed to the conceptualization and development of the study protocol. WG, AMF, MVN, DK, ZA, and MA performed study screening, data extraction, and manuscript revisions. WG and AMF curated the data. AMF drafted the initial manuscript. MVN and WG conducted the statistical analyses. WG, MB, LM, ENR, JPC, XZ, RW, ADK, and ME contributed to manuscript writing, critical revision, and final editing. All authors critically reviewed the manuscript for intellectual content and approved the final version for publication.

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Data availability
All data analyzed during this study are derived from published articles. Extracted datasets and analytic code are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval and informed consent were not required for this study because it is a systematic review and meta-analysis based exclusively on previously published studies.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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