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Incidence and predictors of postoperative delirium following remimazolam administration: a systematic review and meta-analysis of 29 randomized trials

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Abstract

Background Postoperative delirium is a significant and common complication in surgical patients, particularly in vulnerable populations such as the elderly. Remimazolam, a novel benzodiazepine, has been introduced as an anesthetic agent with a favorable pharmacokinetic profile. However, its potential association with postoperative delirium remains unclear. This study aims to systematically synthesize available evidence on the incidence of delirium following remimazolam administration in surgical patients. We sought to identify significant moderators of delirium incidence and to explore predictors of delirium through meta-regression analysis.

Methods A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar, up to May 20, 2024. The search was updated on Feb 2nd, 2025. Randomized trials were selected based on predefined criteria, and data on patient characteristics, surgical details, and delirium incidence were extracted. A meta-analysis was performed to calculate the pooled incidence rate of delirium, and subgroup and meta-regression analyses were conducted to identify incidence rate moderators.

Results A total of 29 RCTs, including 2,435 patients, were analyzed. The pooled incidence of postoperative delirium following remimazolam administration was 5% (95%CI: 3–7%). ASA III-IV patients had a delirium rate of 19% (95%CI: 15–23%) compared to 1% (95%CI: 0–1%) for ASA I-II. Age was a key factor, with children showing the highest rate (11%, 95%CI: 3–19%), followed by elderly patients (8%, 95%CI: 4–13%), while adults had the lowest (1%, 95%CI: 0–2%). Delirium incidence was highest in oncologic (16%, 95%CI: 0–34%) and orthopedic surgeries (12%, 95%CI: 9–14%), and lowest in gastrointestinal and endoscopic procedures (0%, 95%CI: 0–1%). High-dose remimazolam was linked to the lowest delirium incidence, while moderate doses had higher rates. Meta-regression identified surgery type as the primary predictor, with orthopedic surgery having the highest risk compared to laparoscopic and abdominal procedures (coefficient = 0.081, $p = 0.03$).

Conclusions Postoperative delirium occurs in 5% of surgical patients following remimazolam administration. Key moderators include ASA classification, age, surgery type, and anesthetic dosing. Remimazolam may be safely used in surgical patients, particularly when higher doses are administered, but caution is warranted in high-risk populations such as elderly patients and those undergoing complex surgical procedures.

Keywords Delirium, Remimazolam, Incidence Rate, Moderators

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Introduction

Postoperative delirium is a common and serious complication that affects surgical patients, particularly those who are elderly or have significant comorbidities [1]. Delirium is characterized by acute cognitive impairment, fluctuating levels of consciousness, and disorganized thinking, which can lead to increased morbidity, prolonged hospital stays [2], and higher healthcare costs [3]. Despite advances in anesthesia and surgical techniques, the incidence of postoperative delirium remains substantial, necessitating the ongoing investigation of risk factors and preventive strategies [4].

Remimazolam, a novel benzodiazepine, has gained attention for its rapid onset and offset of action, making it an attractive option for procedural sedation and general anesthesia [5]. Its pharmacokinetic profile, characterized by organ-independent metabolism and a reduced risk of accumulation, suggests that remimazolam may offer advantages over traditional anesthetic agents, particularly in vulnerable populations [6]. However, the safety profile of remimazolam, particularly concerning its potential to induce postoperative delirium (ranging from 19–32%) [7–9], has not been fully elucidated.

Previous studies have provided mixed results regarding the association between remimazolam and delirium, with some suggesting an increased risk [7, 8], especially in certain subpopulations such as the elderly or those undergoing complex surgeries [7]. The existing literature lacks a comprehensive synthesis of the available evidence, particularly in understanding how patient characteristics, surgery types, and remimazolam dosing influence delirium risk.

In this context, we conducted a systematic review and meta-analysis to assess the incidence rate of postoperative delirium following remimazolam administration in surgical patients. We also aimed to identify significant moderators of delirium incidence and to explore the potential predictors of delirium rate through meta-regression analysis. Our findings are intended to inform clinical practice by providing insights into the safe use of remimazolam and identifying populations that may require closer monitoring or alternative anesthetic strategies.

Materials and methods

Design and literature search

This work has been reported in line with the PRISMA [10] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR [11] (Assessing the methodological quality of systematic reviews) Guidelines. Since it is not mandated in most guidelines, a protocol in-priori was not registered on PROSPERO [12]. We searched PubMed, Scopus, Web of Science, Cochrane Library, clinicaltrials.gov, and Google Scholar (first 200 citations) [13] up to May 20, 2024. The search was updated on Feb 2nd, 2025. The search strategy, outlined in Table S1, was adjusted per searched databases. Citations were filtered based on their titles and abstracts. No restrictions were applied regarding the original language of publication. Manual searches included reviewing reference lists and related articles on PubMed [14]. Given the fact that this is a secondary analysis of already published data, the need for ethical approval was not required.

Selection strategy

Studies were selected using the PICOS framework [15]. Single-armed and comparative randomized controlled trials (RCTs) of surgical patients (regardless of the type of surgery) receiving remimazolam (of any dose or route) were included only if data regarding post-administration delirium were provided. Meanwhile, we excluded the following studies: (1) non-original research and non-randomized studies, (2) no report of remimazolam, (3) no reporting of delirium, (4), (5) duplicate studies, and (6) overlapping datasets.

Data collection and outcomes

The senior author designed the data collection sheet using Microsoft Excel. The first part covered trials' information (authors' names, year of publication, design, year of investigation, registration, and follow-up), patients' characteristics (sample size, age, gender, and ASA class), and remimazolam data (route of administration, initial dose, maintenance dose, and co-administered drugs) and surgical information (type of surgery, surgery time, anesthetic time). Based on age, patients were categorized into children (< 18 years), adults (18–60 years), and elderly (> 60 years). Remimazolam dosing was categorized into three levels based on previously reported pharmacokinetic data and clinical usage patterns [16–18]. Low-dose induction was defined as < 0.2 mg/kg, moderate-dose induction ranged from 0.2 to 0.3 mg/kg, and high-dose induction was > 0.3 mg/kg. For maintenance, low-dose infusion was defined as < 0.5 mg/kg/h, moderate-dose infusion ranged from 0.5 to 1 mg/kg/h, and high-dose infusion was > 1 mg/kg/h. These classifications were used to facilitate subgroup analyses and assess potential dose-dependent effects on postoperative delirium, while negating multicollinearity observed with numerous multi-level variables such as dosing.

The second part covered our outcome of interest which is the incidence rate of delirium post-remimazolam administration. Data on the diagnostic criteria of delirium were also extracted. Although we were interested in determining emergence time [19, 20] and delirium

duration [21], these data were scarcely reported in the literature; thus, a meta-analysis of these outcomes was not feasible.

Risk of bias assessment

The revised Cochrane RoB-II tool (revised in 2019) was used to assess the methodological quality of included trials [22]. Each RCTs will be assessed on the level of five domains: randomization, deviation from intended interventions, missing outcome data, outcome measurement bias, and selective reporting. Finally, each trial will be given a quality of low risk of bias, some concerns, or high risk of bias.

Statistical analysis

Statistical analyses used STATA, following a predefined plan without adjustments. We used the pooled effect size [ES] and its corresponding 95% confidence interval (CI) to report the pooled incidence rate. We employed a random-effects model and used the last observation carried forward method to handle data heterogeneity and minimize missing data risks [23]. Heterogeneity was quantified using the I^2 statistic, with significant heterogeneity defined as $I^2 > 40\%$ [24]. Sensitivity analyses tested the robustness of results with Galbraith plots identifying outliers, and publication bias was assessed with funnel plots and asymmetry tests (if > 5 trials are reported) [25]. In studies reporting zero delirium events, a continuity correction of 0.5 was applied to both the numerator and denominator, and the Freeman–Tukey double arcsine transformation was used to stabilize variance; sensitivity analyses confirmed that these methods did not alter the overall findings.

Subgroup analyses examined variables like follow-up, risk of bias, country, surgery type, age group, baseline ASA class, remimazolam use and induction/maintenance dose, and co-administered drugs. Meta-regression assessed the impact of study-level covariates (induction and maintenance dose of remimazolam, ASA class, age, surgery time, operative time, anesthesia time, follow-up time, surgery type, co-anesthetics, and risk of bias), adjusting for multicollinearity, which was evaluated using variance inflation factors (> 5 indicates problematic multicollinearity) [26]. Model fit was assessed with the adjusted R-squared (higher values reflect better fit). Variables reported by at least five trials were eligible for subgroup and meta-regression (significant heterogeneity is mandatory) [27].

Results

Literature search results

The literature search and screening process yielded 512 citations, with 115 duplicates identified using EndNote (Fig. 1). After removing duplicates, 397 articles remained,

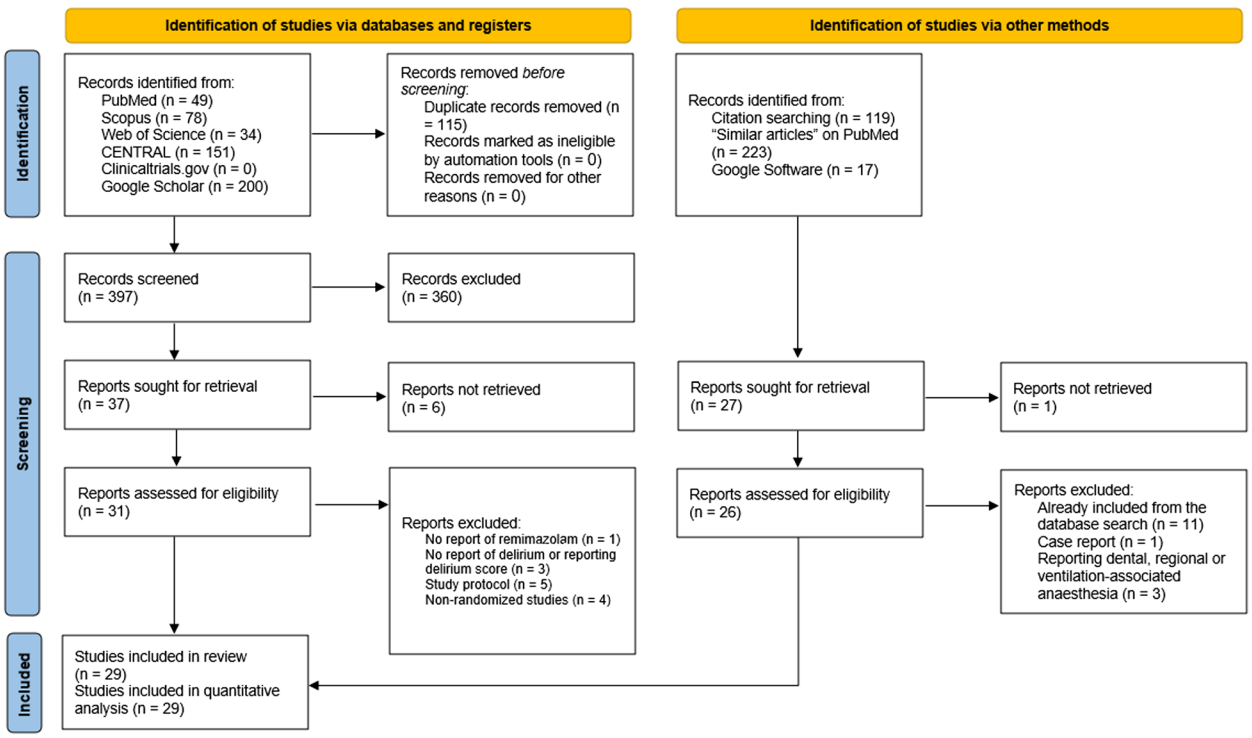

Fig. 1 A flow chart showing the recruitment process of patients in this study

from which 360 were excluded during title/abstract screening. We could not retrieve the full-text for six articles, leaving 31 for full-text review. Of these, nine were excluded due to reasons such as lack of information on remimazolam (n = 1) or delirium ($n = 3$), study protocols ($n = 5$), or non-randomized studies ($n = 4$). The manual search revealed no additional articles, resulting in 18 RCTs being eligible for data synthesis [8, 9, 19–21, 28–40]. An updated search was done on Feb 2nd, 2025, yielding 11 newly published RCTs on this topic [17, 41–50], with 29 finally synthesized RCTs. A Chinese paper was translated to English prior to data extraction [50]. Noteworthy, in the updated search, we excluded four RCTs because they included regional anesthesia [51], dental anesthesia [52], mechanical ventilation [53], or for being inaccessible due to the lack of a full text [54].

Baseline characteristics of examined RCTs and patients

A total of 29 RCTs were included in the final analysis, with a combined sample size of 2435 patients. The majority of the included studies were conducted in China ($n = 23$), followed by Korea ($n = 4$), Japan ($n = 2$), and Germany ($n = 1$) (Table 1). Most trials were single-center studies, except for one bi-center RCT and one multicenter study. The follow-up duration varied widely, ranging from intraoperative assessments to 12 days postoperatively.

The mean age of included patients ranged from 3 to 86 years, representing a diverse population spanning pediatric, adult, and elderly groups (Table 2). Gender distribution varied across studies, with male representation ranging from 38 to 81%. Patients underwent a broad range of surgical procedures, which were categorized into gastrointestinal and endoscopic surgery ($n = 7$), general surgery and oncology ($n = 3$), laparoscopic and abdominal surgery ($n = 7$), orthopedic surgery (n = 4), cardiovascular and neurovascular surgery ($n = 4$), urological and gynecological surgery (n = 3), and ENT surgery ($n = 3$).

Regarding anesthetic management, remimazolam was used for induction only in 8 studies, for maintenance only in 6 studies, and for both induction and maintenance in 13 studies. The induction dose varied between 0.1 mg/kg to 1.5 mg/kg, while maintenance doses ranged from 0.05 mg/kg/h to 12 mg/kg/h. Several co-administered drugs were reported, including opioids (remifentanil, sufentanil, fentanyl), muscle relaxants (cisatracurium, rocuronium), and volatile anesthetics (sevoflurane, desflurane).

Delirium was assessed using multiple diagnostic criteria. The Confusion Assessment Method (CAM) was used in 9 trials, DSM-IV in 2 trials, Mini-Mental State Examination (MMSE) in 1 trial, Nursing Delirium Screening Scale (NuDESC) in 2 trials, and the Pediatric Anesthesia Emergence Delirium (PAED) scale in 2 trials, while 11 trials relied on patient medical records (Table 2). The included patient populations also differed in terms of baseline risk, with most trials enrolling ASA I–II patients (12 studies), while others included higher-risk populations, with ASA III–IV patients comprising the study population in 2 trials.

The mean surgical time ranged from 11.9 to 212.7 min, and anesthesia duration varied between 16.5 and 238.6 min. These baseline characteristics highlight the heterogeneity in patient populations, surgical settings, and anesthetic management strategies across the included RCTs, reinforcing the need for robust subgroup analyses (Table 2).

Risk of bias of included studies

Of the 29 included RCTs, 24 had an overall low risk of bias, while the remaining five trials had some concerns secondary to the lack of information regarding randomization process and protocol registration (Fig. 2).

Pooled incidence rate of delirium

A total of 22 studies reported the incidence rate of delirium post-remimazolam administration. The meta-analysis revealed a pooled rate of 5% [95% CI: 3–7%] (Fig. 3). A substantially high level of heterogeneity was observed as expected [$\tau^2 = 0.001$; $I^2 = 93.51\%$; $p = 0.001$]. However, the leave-one-out sensitivity analysis revealed no significant change in the observed incidence rate following the exclusion of each study separately (Figure S1). The Galbraith plot showed 3 outliers; however, excluding them did not affect the overall rate (Figure S2). The funnel plot showed that all of included studies were at one side of the graph, and the trim-and-fill method added 15 trials to the left side (Figure S3). However, this is expected since this is a meta-analysis of proportions and studies are expected to have a pooled proportion more than 0%. The Egger's regression test showed no significant risk of bias ($p = 0.531$).

Subgroup analyses

Statistically significant differences in the incidence rate of post-operative delirium were observed based on patients' age ($p = 0.001$), surgery type ($p = 0.001$), remimazolam induction ($p = 0.001$) and maintenance dose ($p = 0.03$), country ($p = 0.02$), delirium diagnostic criteria ($p = 0.001$), ASA class ($p = 0.001$), co-administered anesthetics ($p = 0.001$), and follow-up ($p = 0.001$) (Table 3). No significant differences were observed based on risk of bias or remimazolam use (anesthesia induction, maintenance, or both).

At a country-level, postoperative delirium rate was lowest in Korea (4 RCTs; 1%; 95%CI: 0–3%, $I^2 = 0\%$) and highest in Japan (2 RCTs, 10%; 95%CI: 0–22%,

Table 1 Baseline characteristics of included randomized trials reporting postoperative delirium in patients receiving remimazolam

Author (YOP)	Design	Country	YOI	Sample		Remimazolam			FU
				Total	Remi	Use	Induction	Maintenance	
Chen (2024) [29]	RCT	China	Oct 2020—Nov 2022	240	122	Induction	0.17 mg/kg	0.15 mg/kg	During Surgery
Liu (2024) [9]	RCT	China	Oct 2023—Jan 2024	100	50	Induction and Maintenance	0.1–0.2 mg/kg	0.4–1.2 mg/kg/h	During Surgery
Lee (2023) [34]	RCT	China	Sep 2022—Jan 2023	78	39	Induction and Maintenance	0.1 mg/kg	1–2 mg/kg/h	2 Days
Cai (2024) [19]	RCT	China	-	119	40 (infusion)	Maintenance	-	1 mg/kg/h	During Surgery
					39 (bolus)		-		During Surgery
Yang (2023) [21]	RCT	China	Nov 2021—Jun 2022	320	147	Induction and Maintenance	0.2–0.3 mg/kg	-	3 Days
Liu (2023) [35]	Bi-center RCT	China	Feb—Jun 2022	216	107	Induction	0.1 mg/kg	-	During Surgery
Zhang (2024a) [48]	RCT	China	Jul 2021—Jun 2022	129	71	Induction and Maintenance	0.1 mg/kg	0.3–0.7 mg/kg/h	During Surgery
Zheng (2022) [40]	RCT	China	Nov 2020—Oct 2021	120	41	Induction and Maintenance	0.1 mg/kg	0.05 mg/kg	During Surgery
					39	Induction and Maintenance	0.15 mg/kg	0.05 mg/kg	During Surgery
					40	Induction and Maintenance	0.2 mg/kg	0.05 mg/kg	During Surgery
Huang (2023) [31]	RCT	China	Sep 2021—Jun 2022	120	60	Induction and Maintenance	0.3 mg/kg	0.3 mg/kg/h	During Anesthesia
Luo (2023) [37]	RCT	China	Oct—Dec 2021	115	38	Induction and Maintenance	0.3 mg/kg	1–3 mg/kg/h	12 Days
Jeon (2023) [33]	RCT	Republic of Korea	Dec 2021—Apr 2023	122	60	Induction and Maintenance	6 mg/kg/h	1–2 mg/kg/h	During Surgery
Cai (2024) [28]	RCT	China	Feb 2021—Feb 2022	90	30	Induction	1.5 mg/kg	-	10 Minutes
Shimizu (2023) [38]	RCT	Japan	-	66	32	Induction and Maintenance	12 mg/kg/h	1–2 mg/kg/h	3 Hours
Yang (2022) [20]	RCT	China	-	104	51	Post-anesthetic	0.2 mg/kg	-	During Surgery
Guo (2022) [30]	RCT	China	Jan—Aug 2021	82	39	Induction	0.15 mg/kg	-	During Surgery
Lu (2022) [36]	Multicenter RCT	China	Sep 2020—Sep 2021	400	200	Induction and Maintenance	300 mg/h	2.5 mg	During Surgery
Huang (2023) [32]	RCT	China	-	138	67	Induction	10 mg/kg/h	-	During Surgery
Fang (2024) [41]	RCT	China	-	728	364	Induction and Maintenance	0.2–0.25 mg/kg	-	3 Days
Zhou (2024) [49]	RCT	China	-	102	51	Induction and Maintenance	0.2–0.4 mg/kg	0.2–0.4 mg/kg/h	3 days

Table 1 (continued)

Author (YOP)	Design	Country	YOI	Sample		Remimazolam			FU
				Total	Remi	Use	Induction	Maintenance	
Lu (2025) [45]	RCT	China	Sep-Oct 2023	86	43	Post-anesthetic	0.1 mg/kg	-	3 days
Zhang (2024b) [55]	RCT	China	Mar-Oct 2023	128	65	Induction and Maintenance	0.3 mg/kg	1–1.5 mg/kg/h	3 days
Fechner (2024) [8]	RCT	Germany	Jul 2018—Apr 2020	365	270	Induction	0.1 mg/kg	-	PACU
Lee (2024) [44]	RCT	Korea	Aug 2022—Apr 2023	54	26	Induction and Maintenance	6 mg/kg/h	1–2 mg/kg/h	After emergence from anesthesia
Luo (2024) [46]	RCT	China	May 2023—Nov 2023	112	56	Induction and Maintenance	0.3 mg/kg	1–2 mg/kg/h	After extubation
Ryu (2024)[56]	RCT	Korea	Dec 2021—Sep 2022	36	17	Induction and Maintenance	12 mg/kg/h	-	Day 1
Minghong (2025) [57]	RCT	China	Mar 2021—Mar 2023	135	45	Induction	0.2 mg/kg	-	Day 0
					45	Induction	0.3 mg/kg	-	
					45	Induction	0.4 mg/kg	-	
Harimochi (2024) [42]	RCT	Japan	Jun 2022—Aug 2023	60	28	Induction and Maintenance	6 mg/kg/h	0.68 mg/kg/h	ICU
Ko (2024) [43]	RCT	Korea	Mar-Nov 2023	30	15	Induction and Maintenance	6–12 mg/kg/h	1–2 mg/kg/h	Day 1
Duan (2024) [58]	RCT	China	Dec 2022—Jun 2023	106	53	Maintenance	-	0.1–0.3 mg/kg/h	Day 7

YOP year of publication, *YOI* year of investigation, *RCT* randomized controlled trial, *FU* follow-up, *ICU* intensive care unit

$I^2 = 52.11\%$). In terms of age, adults had the lowest rate (7 RCTs, 1%; 95%CI: 0–2%, $I^2 = 0.09\%$), while children had the highest rate (4 RCTs, 11%; 95%CI: 3–19%, $I^2 = 67.47\%$).

Oncologic (3 RCTs, 16%; 95%CI: 0–34%, $I^2 = 89.82\%$) and orthopedic (4 RCTs, 12%; 95%CI: 9–14%, $I^2 = 0.01\%$) surgeries were associated with the highest rates, while GI and endoscopic surgery was associated with the lowest rate (7 RCTs, 0%: 95%CI: 0–1%, $I^2 = 0.03$) (Fig. 4).

High induction (6 RCTs, 0%; 0–1%, $I^2 = 46.88\%$) and maintenance (8 RCTs, 1%; 95%CI: 0–2%, $I^2 = 0.02\%$) doses of remimazolam were associated with the lowest rates of postoperative delirium, while moderate doses were associated with the highest rates (induction = 3%; 95%CI: 2–4%; maintenance = 12%; 95%CI: 4–19%), respectively (Figs. 5 and 6).

Significant variability was observed with the diagnostic criteria used for delirium, where the PAED score was associated with the highest rate of delirium diagnosis, followed by CAM scale (9 RCTs, and NuDESC scale (2 RCTs, 7%; 95% CI: 0–19%, $I^2 = 98.75\%$). Meanwhile, the lowest rate was observed in trials using patients' records for defining delirium (11 RCTs, 1%; 95%CI: 0–1%, $I^2 = 0\%$) (Fig. 7).

ASA was a very strong determinant of postoperative delirium, with patients having milder forms of the disease (class I-II) exhibiting the lowest rates of delirium (12 RCTs, 1%; 95%CI: 0–1%, $I^2 = 0\%$), while those with the severe forms (class III-IV) exhibiting the highest rates (2 RCTs, 19%; 95% CI: 15–23%, $I^2 = 0.02\%$) (Fig. 8).

In terms of timing, significant variability was noted, with the highest rates being observed in post-anesthesia care unit (2 RCTs, 19%; 95%CI: 15–23%, $I^2 = 0.02\%$). The rates at 3-day and 7-day post-anesthesia were comparable (7%; 95%CI: 1–13% and 8%; 95%CI: 0–15%), respectively.

Regarding co-administered anesthetic drugs, fentanyl was associated with the lowest rate of postoperative delirium (4 RCTs, 0%; 95%CI: 0–1%, $I^2 = 0.95\%$), while Rocuronium was associated with the highest rate (2 RCTs, 15%; 95%CI: 6–23%, $I^2 = 0.01\%$). Remifentanil, propofol, and sevoflurane had the same rate of 7%, but with significant heterogeneity.

Table 2 Patients' and anesthesia-related characteristics in randomized trials investigating postoperative delirium in patients receiving remimazolam

Author (YOP)	Age		Gender		Surgery	ASA	Surgery time (hr)	Anesthesia time (hr)	Anesthetic Drugs		Delirium Diagnosis
	Mean	SD	Male	Female					Induction	Maintenance	
Chen (2024) [29]	71.9	5	66	56	GI & Endoscopic Surgery	I-II	30	-	RZ, sufentanil	-	Patient records
Liu (2024) [9]	71.62	5.47	22	28	General Surgery & Oncology	I-III	212.7	238.6	Sufentanil, RZ, cisatracurium	RZ, Remifentanil	CAM
Lee (2023) [34]	75	11.8	6	33	Orthopedic Surgery	I-III	105	145	RZ, rocuronium, remifentanil	RZ	Patient records
Cai (2024) [19]	3	2.1	30	10	Laparoscopic & Abdominal Surgery	I-II	25	38.5	Fentanyl, propofol, Cisatracurium	RZ, Sevoflurane	PAED
	2.8	1.8	29	10		I-II	28	42			
Yang (2023) [21]	68	15.7	61	86	Orthopedic Surgery	II-III	138	177	RZ, alfentanil	Desflurane, RZ	CAM
Liu (2023) [35]	67.6	5.75	51	56	GI & Endoscopic Surgery	I-II	24.7	-	Sufentanil, RZ	RZ	Patient records
Zhang (2024) [48]	-	-	-	-	Cardiovascular & Neurovascular Surgery	-	-	-	RZ	RZ, Remifentanil	CAM
Zheng (2022) [40]	45.58	13.13	27	14	GI & Endoscopic Surgery	I-II	11.93	-	RZ, Fentanyl	RZ (bolus)	MMSE
	45.28	11.39	17	22			10.18	-			
	45.25	11.36	26	14			12	-			
Huang (2023) [31]	62.6	8.9	0	60	General Surgery & Oncology	II-III	-	98	RZ, Sufentanil, and Cistracurium	RZ, remifentanil, sevoflurane	NuDESC
Luo (2023) [37]	43.5	15.6	14	24	Urological & Gynecological Surgery	I-II	42.2	-	RZ, flumazenil	RZ, flumazenil	DSM-V
Jeon (2023) [33]	70.9	4.3	38	22	Laparoscopic & Abdominal Surgery	II-III	40.3	79.7	RZ	RZ	DSM-V
Cai (2024) [28]	3.82	2.68	25	5	General Surgery & Oncology	I-II	23.5	-	Sevoflurane	Sevoflurane	PAED
Shimizu (2023) [38]	43.5	10.4	22	10	ENT Surgery	I-II	107	157	Remifentanil, RZ	Remifentanil, RZ	Patient records
Yang (2022) [20]	5	1.4	30	21	ENT Surgery	I-II	34	60	Sevoflurane	Sevoflurane, RZ	PAED
Guo (2022) [30]	70.4	3.9	25	14	GI & Endoscopic Surgery	I-II	17.3	-	Alfentanil, RZ	RZ (bolus)	Patient records
Lu (2022) [36]	70.6	4.7	78	122	GI & Endoscopic Surgery	I-III	10.8	16.5	RZ, Fentanyl	RZ, Fentanyl	Patient records
Huang (2023) [32]	43	10	48	19	Urological & Gynecological Surgery	I-II	54	79	RZ	Cisatracurium, fentanil	Patient records
Fang (2024) [41]	73	68–80	121	243	Orthopedic Surgery	I-III	70	93	RZ, Sufentanil, cisatracurium	RZ, Remifentanil	CAM
Zhou (2024) [49]	61.24	12.15	23	28	GI & Endoscopic Surgery	I-III	75.45	82.76	RZ, remifentanil	RZ	CAM
Lu (2025) [45]	42	11.7	10	33	ENT Surgery	I-II	53.6	-	Propofol, Sufentanil, Cisatracurium	Sevoflurane	CAM
Zhang (2024b) [55]	49.08	9.4	33	32	Not Categorized	I-II	42.32	48.98	RZ, sufentanil	RZ, remifentanil	Patient records
Fechner (2024) [8]	68	10.8	195	75	Not Categorized	III-IV	166	-	RZ, remifentanil	Remifentanil	NuDESC
Lee (2024) [44]	66	61–69	20	6	Cardiovascular & Neurovascular Surgery	-	142	-	RZ, Remifentanil	RZ, Remifentanil	Patient records

Table 2 (continued)

Author (YOP)	Age		Gender		Surgery	ASA	Surgery time (hr)	Anesthesia time (hr)	Anesthetic Drugs		Delirium Diagnosis
	Mean	SD	Male	Female					Induction	Maintenance	
Luo (2024) [46]	42.8	10.4	12	44	Laparoscopic & Abdominal Surgery	I-II	54.2	85	RZ, sufentanil, Cisatracurium	RZ, Remifentanil	Patient records
Ryu (2024) [56]	71.76	9.42	12	5	Urological & Gynecological Surgery	I-III	15	39	RZ, Remifentanil	RZ, remifentanil	CAM
Minghong (2025) [57]	68.5	5.2	67	68	Laparoscopic & Abdominal Surgery	II-III	59.2	65.8	RZ, sufentanil	Remifentanil, propofol	Patient records
	68.7	5.1				II-III	56.3	67.6			
	68.8	5				II-III	57.8	64.1			
Harimochi (2024) [42]	86	83–89	7	21	Cardiovascular & Neurovascular Surgery	III-IV	75	178	RZ, remifentanil, rocuronium	RZ, flumazenil	CAM
Ko (2024) [43]	61.4	15.1	11	4	Cardiovascular & Neurovascular Surgery	-	127.5	185	RZ, remifentanil	RZ	Patient records
Duan (2024) [58]	77.4	6.1	24	29	Orthopedic Surgery	II-III	78.7	84.6	-	RZ	CAM

YOP year of publication, *SD* standard deviation, *hr* hour, *ASA* American Academy of Anesthesiologists, *GI* gastrointestinal, *ENT* ear, nose, and throat, *NuDESC* The Nursing Delirium Screening Scale, *CAM* Confusion Assessment Method, *PAED* Pediatric Anesthesia Emergence Delirium, *MMSE* Mini-Mental State Examination, *PACU* post-anesthesia care unit

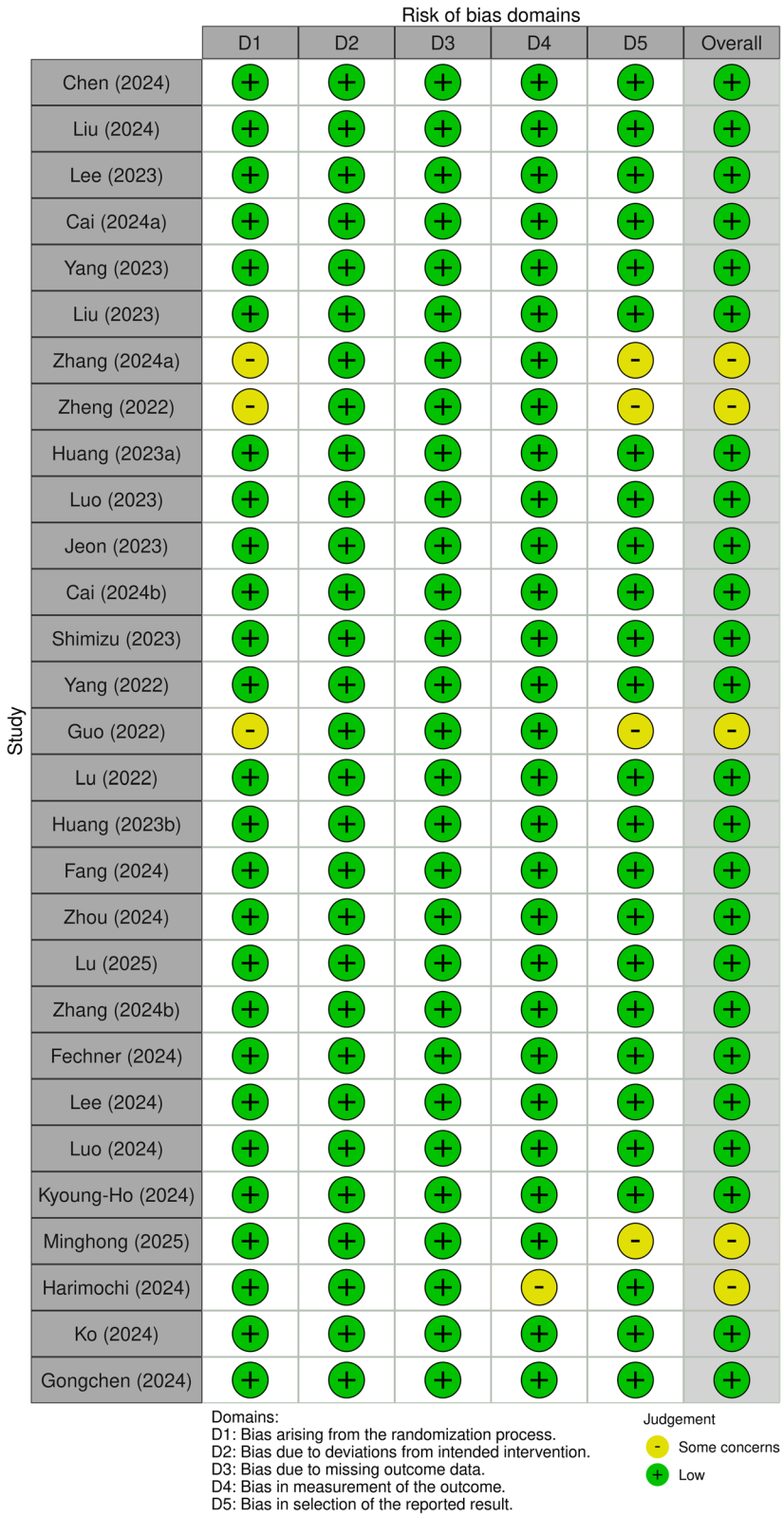

Fig. 2 A summary of the risk of bias of included randomized controlled trials using Cochrane's revised risk of bias tool

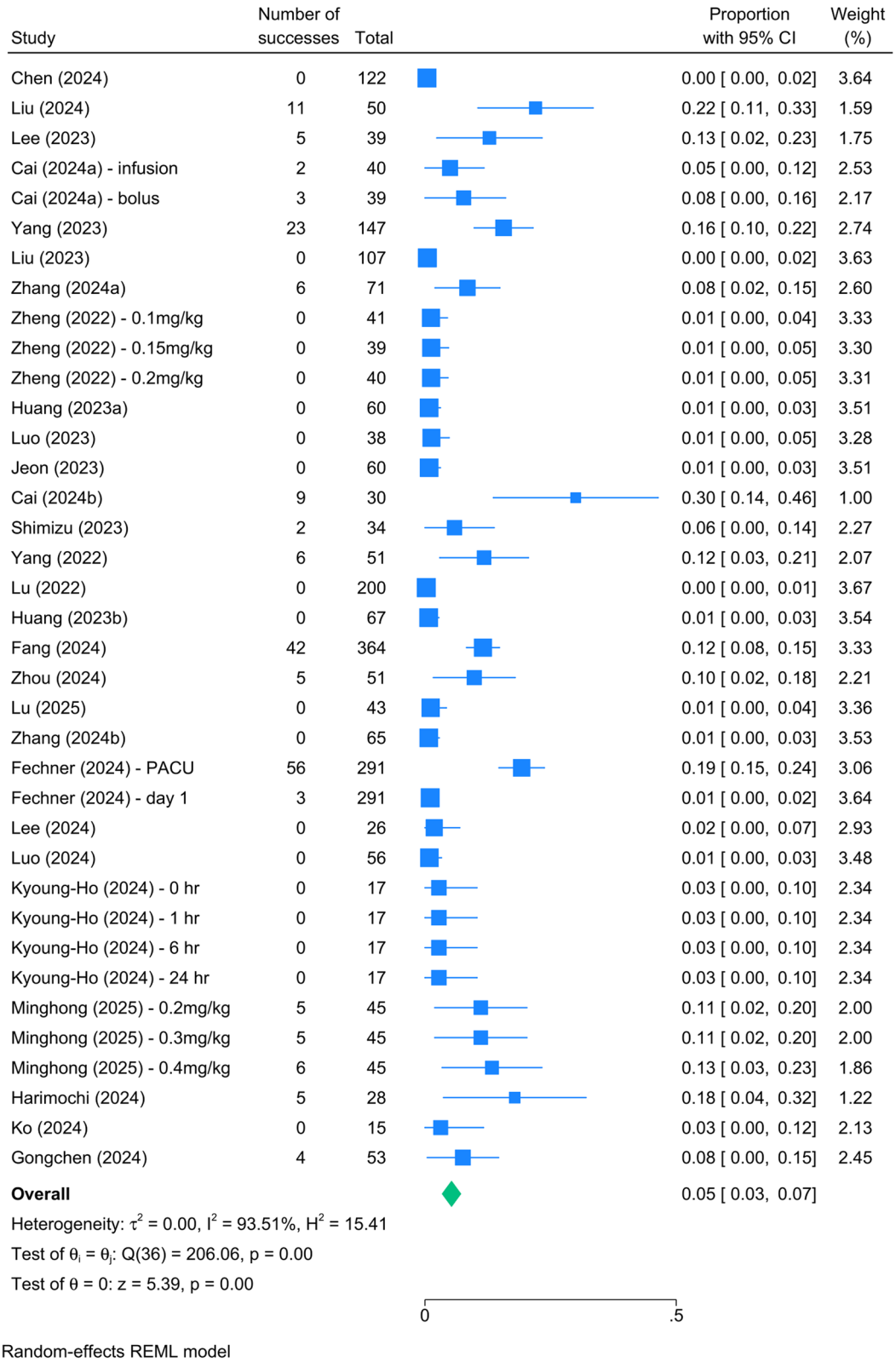

Fig. 3 Forest plot of the pooled incidence rate of remimazolam-associated delirium across all included randomized trials

Table 3 The pooled proportion rate of postoperative delirium following remimazolam, stratified by study-level, patient-level, and intervention-level characteristics

		Studies	Proportion (95% CI)	I^2 (%)	*P*-value
Age	Adults	7	1% (0–2%)	0.090	0.001
	Adults + Elderly	6	5% (0–10%)	94.410	
	Elderly	12	7% (4–10%)	95.090	
	Children	4	11% (3–19%)	67.470	
Surgery	GI & Endoscopic Surgery	7	0% (0–1%)	0.03	0.001
	Urological & Gynecological Surgery	6	1% (0–3%)	0.02	
	Cardiovascular & Neurovascular Surgery	4	6% (1–11%)	43.43	
	General Surgery & Oncology	3	16% (0–34%)	89.82	
	Orthopedic Surgery	4	12% (9–14%)	0.01	
	ENT Surgery	3	5% (0–11%)	63.33	
	Laparoscopic & Abdominal Surgery	7	6% (2–10%)	75.45	
	Not Categorized	3	7% (0–19%)	98.87	
Risk of bias	Low risk	24	5% (3–7%)	94.89	0.640
	Some concerns	4	6% (2–10%)	75.02	
Remimazolam Use	Anesthesia induction only	6	8% (2–14%)	98.38	0.550
	Anesthesia maintenance only	18	4% (2–6%)	87.25	
	Induction plus maintenance	3	7% (2–11%)	0.01	
	Post-anesthetic	2	6% (0–16%)	79.72	
Remimazolam Induction Dose	Low dose	11	2% (1–2%)	88.82	0.001
	Medium dose	11	3% (2–4%)	85.40	
	High dose	6	0% (0–1%)	46.88	
Remimazolam Maintenance Dose	Low dose	4	2% (0–3%)	0.05	0.030
	Moderate dose	4	12% (4–19%)	65.26	
	High dose	8	1% (0–2%)	0.02	
Country	China	21	5% (3–8%)	94.00	0.020
	Germany	1	10% (0–28%)	98.28	
	Japan	2	10% (0–22%)	52.11	
	Korea	4	1% (0–3%)	0.00	
Delirium Diagnostic Criteria	CAM	9	8% (4–11%)	71.33	0.001
	DSM-IV	2	1% (0–3%)	0.03	
	MMSE	1	1% (0–3%)	0.03	
	NuDESC	2	7% (0–19%)	98.75	
	PAED	2	11% (3–19%)	67.47	
	Patient records	11	1% (0–1%)	0.00	
ASA	I-II	12	1% (0–1%)	0.03	0.001
	I-III	6	9% (3–15%)	89.81	
	II-III	5	8% (3–13%)	86.67	
	III-IV	2	19% (15–23%)	0.02	

Table 3 (continued)

		Studies	Proportion (95% CI)	I^2 (%)	*P*-value
Follow-up	0 Hour	2	15% (0–42%)	88.53	0.001
	1 Hour	2	2% (0–6%)	0.00	
	3 Hours	1	6% (0–14%)	-	
	6 Hours	1	3% (0–10%)	-	
	1 day	3	1% (0–2%)	0.05	
	2 days	1	13% (2–23%)	-	
	3 days	5	7% (1–13%)	92.33	
	7 days	1.000	8% (0–15%)	-	
	12 days	1	1% (0–5%)	-	
	After extubation	1	1% (0–3%)	-	
	During anesthesia	1	1% (0–3%)	-	
	During surgery	11	4% (2–6%)	91.94	
	PACU	2	19% (15–23%)	0.02	
Co-administered Drugs	Remifentanil	15	7% (4–10%)	88.21	0.001
	Propofol	3	7% (3–11%)	54.85	
	Sufentanil	9	5% (1–9%)	95.42	
	Cisatracurium	6	5% (1–9%)	91.17	
	Rocuronium	2	15% (6–23%)	0.01	
	Sevoflurane	5	7% (1–13%)	86.82	
	Fentanyl	4	0% (0–1%)	0.95	
	Alfentanil	1	16% (10–22%)	-	
	Desflurane	1	16% (10–22%)	-	
	Flumazenil	2	8% (0–24%)	79.75	

CI confidence interval, I^2 measure of heterogeneity, *P* p-value of between group differences, *ASA* American Academy of Anesthesiologists, *GI* gastrointestinal, *ENT* ear, nose, and throat, *NuDESC* The Nursing Delirium Screening Scale, *CAM* Confusion Assessment Method, *PAED* Pediatric Anesthesia Emergence Delirium, *MMSE* Mini-Mental State Examination, *PACU* post-anesthesia care unit

Meta-regression analysis

The univariate regression showed that surgery type, remimazolam maintenance dose, operative time, anesthesia duration, and delirium diagnostic criteria were significant determinants of postoperative delirium rate (Table 4). However, in the adjusted multivariate meta-regression model, surgery type was the sole determinant of delirium rate after controlling for all confounders, with orthopedic surgery showing higher likelihood compared to laparoscopic and abdominal surgery (coefficient = 0.081, $p = 0.03$).

Discussion

This systematic review and meta-analysis provide a comprehensive evaluation of the incidence of postoperative delirium following remimazolam administration in surgical patients. The analysis, which synthesizes data from 29 RCTs and includes 2,435 patients, reveals a pooled delirium incidence rate of 5%. The heterogeneity observed across studies is largely explained by variations in patient demographics, anesthetic protocols, surgical procedures, and delirium assessment methodologies. A detailed exploration of subgroup and meta-regression analyses reveals that baseline ASA classification, age, surgery type, and remimazolam dosing strategies are critical determinants of postoperative delirium risk. The analysis also indicates that higher doses of remimazolam for both induction and maintenance are associated with a lower incidence of delirium, suggesting a dose-related protective effect against postoperative cognitive dysfunction.

Recent systematic reviews on remimazolam

Several recent systematic reviews have examined remimazolam's role in various clinical settings, including procedural sedation, intensive care unit (ICU) sedation, and general anesthesia. One systematic review compared remimazolam and propofol for sedation in gastrointestinal endoscopic procedures, highlighting remimazolam's superior safety profile in terms of reduced respiratory depression and hypotension (Barbosa). While these

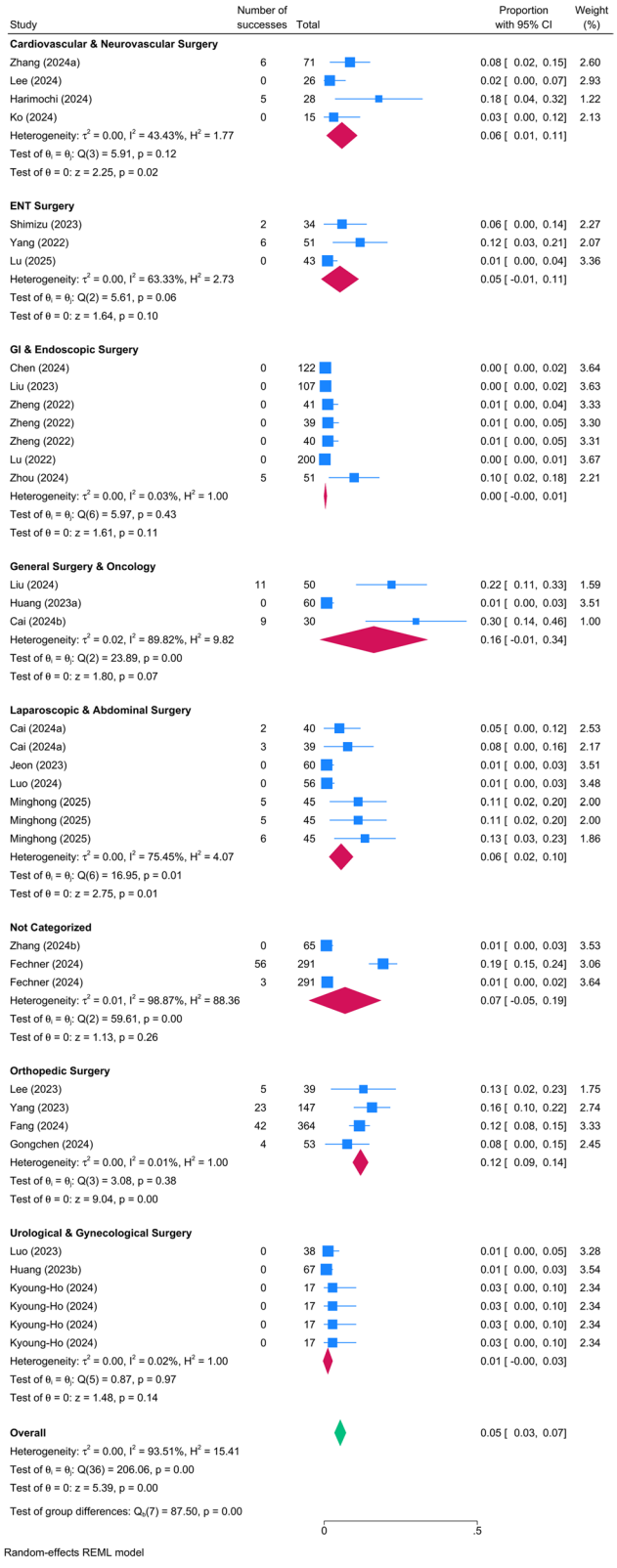

Fig. 4 Forest plot showing the pooled rate of postoperative delirium following remimazolam administration in randomized trials, stratified by surgery type

findings are relevant to procedural sedation, the present study extends these observations to general anesthesia, demonstrating a lower risk of postoperative delirium in surgical patients.

Another meta-analysis focused on the geriatric population emphasized remimazolam's hemodynamic stability and lower incidence of respiratory complications in elderly patients undergoing procedural sedation (Lee). The current analysis provides further evidence supporting its safety in older surgical patients, although the risk of postoperative delirium remains elevated in this subgroup.

A systematic review comparing remimazolam and propofol in general anesthesia settings reported no significant difference in postoperative delirium rates between the two agents (Suga). However, that analysis was based on a smaller dataset, whereas the current study incorporates a larger and more diverse sample, allowing for a more detailed subgroup analysis. The findings suggest that remimazolam may confer a protective effect against delirium in specific patient populations, particularly when used at higher doses for both induction and maintenance.

Key moderators of delirium incidence

ASA classification emerges as a significant predictor of postoperative delirium, with patients classified as ASA III-IV exhibiting a substantially higher delirium risk compared to ASA I-II patients. The ASA classification reflects the overall health status of patients, with higher classes indicating greater comorbidities and physiological stress during surgery, which likely increases the susceptibility to delirium [59]. This underscores the role of systemic comorbidities in postoperative cognitive outcomes and highlights the need for tailored perioperative management strategies in high-risk populations [60].

Age is another critical determinant, with pediatric patients showing the highest incidence of delirium, followed by elderly patients, while adults experience the lowest rates. This finding aligns with the known vulnerability of developing and aging brains to neurocognitive disturbances [61]. Our results are consistent with the vulnerability of both very young [62] and older populations [63] to cognitive disturbances post-surgery. In children, the developing brain may be more sensitive to the effects of anesthesia [64], while in the elderly, age-related cognitive decline and comorbidities likely contribute to an increased risk of delirium [65].

The type of surgery also plays a major role in delirium risk, with oncologic and orthopedic procedures associated with the highest incidence rates, whereas gastrointestinal and endoscopic surgeries demonstrate the lowest. The physiological stress and inflammatory

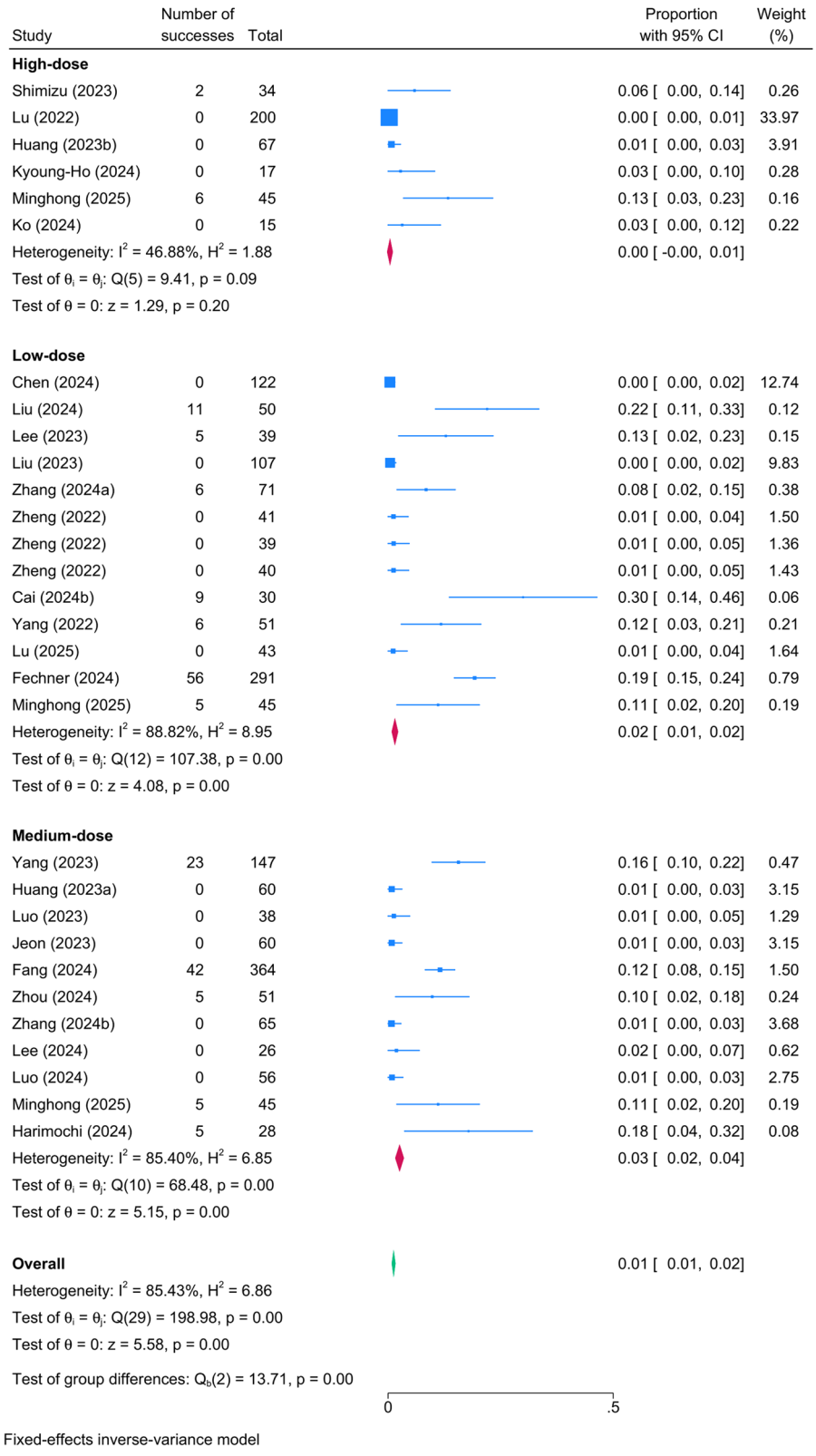

Fig. 5 Forest plot showing the pooled rate of postoperative delirium following remimazolam administration in randomized trials, stratified by remimazolam induction dose

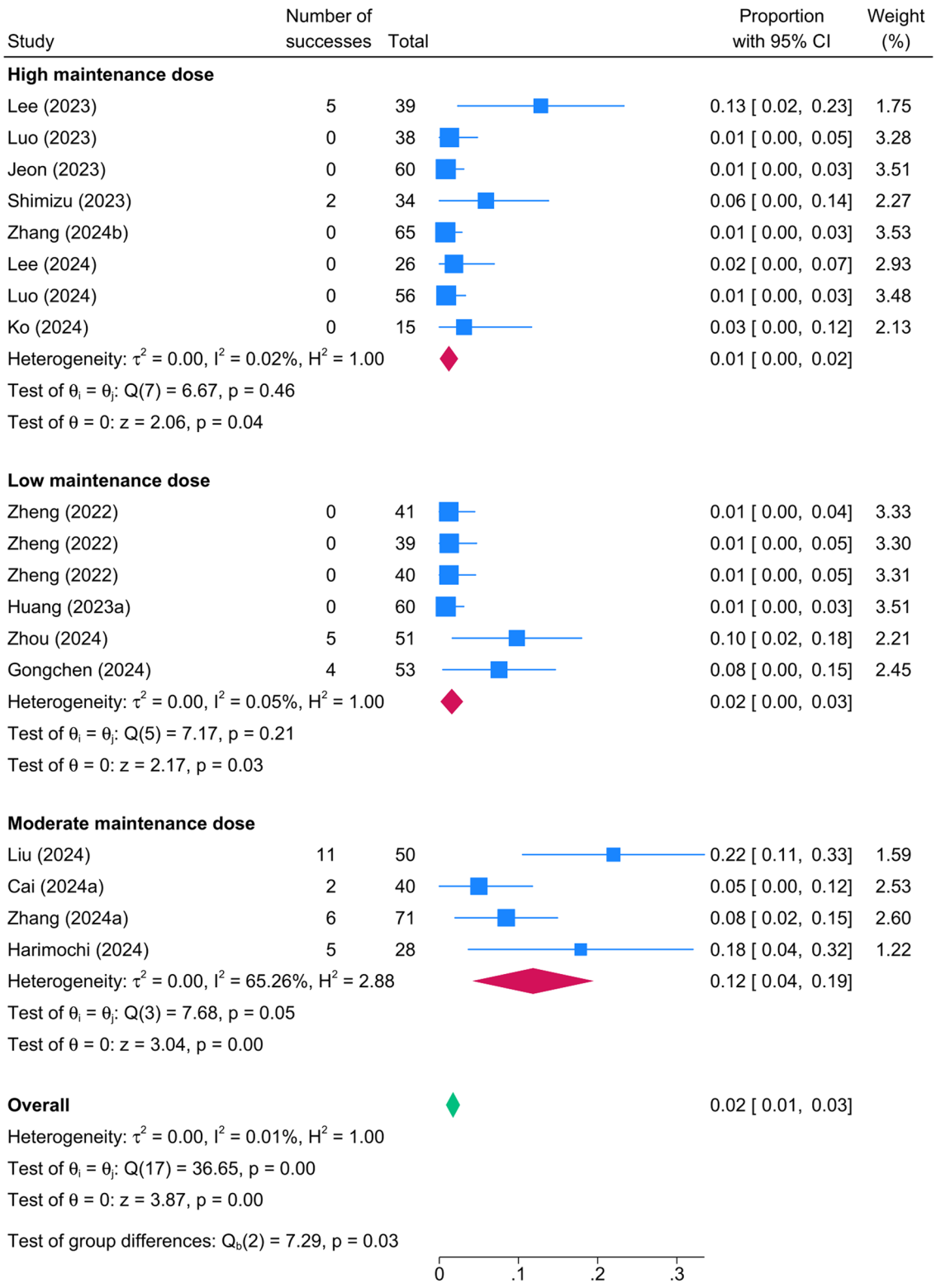

Fig. 6 Forest plot showing the pooled rate of postoperative delirium following remimazolam administration in randomized trials, stratified by remimazolam maintenance dose

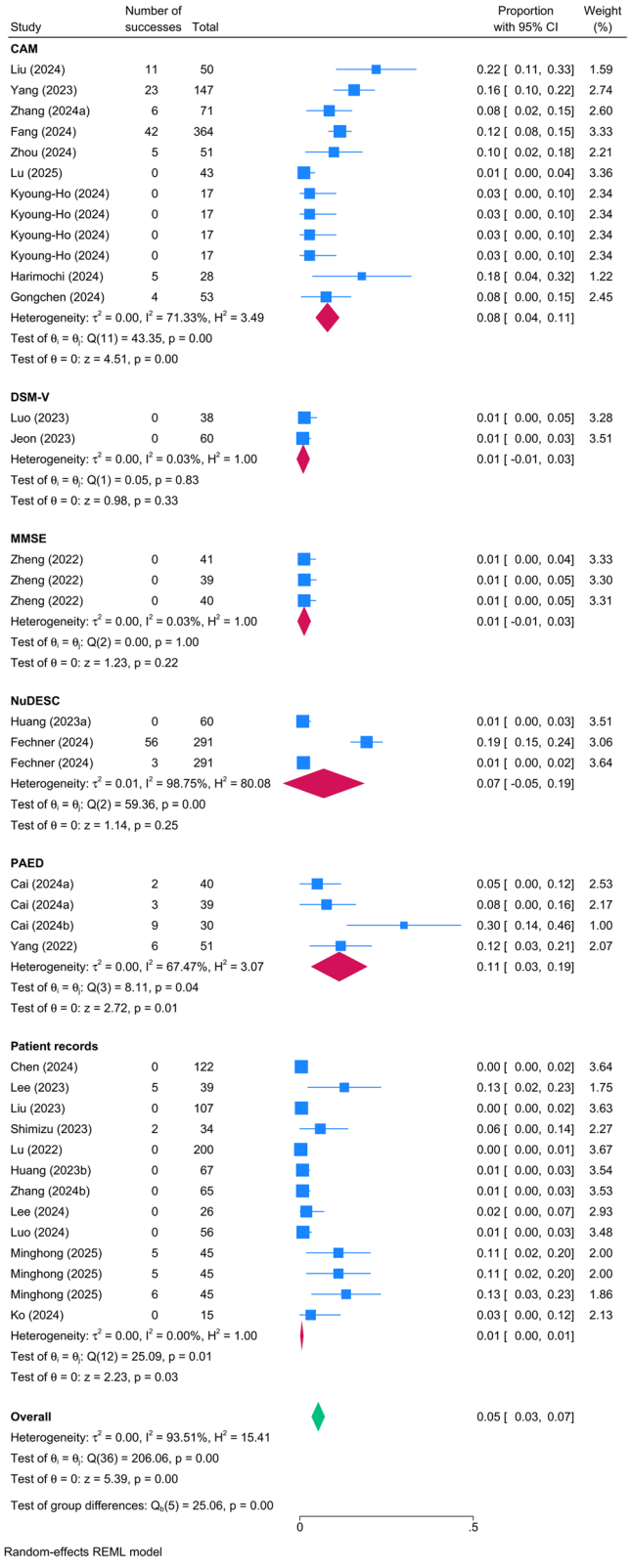

Fig. 7 Forest plot showing the pooled rate of postoperative delirium following remimazolam administration in randomized trials, stratified by derlirium diagnostic criteria

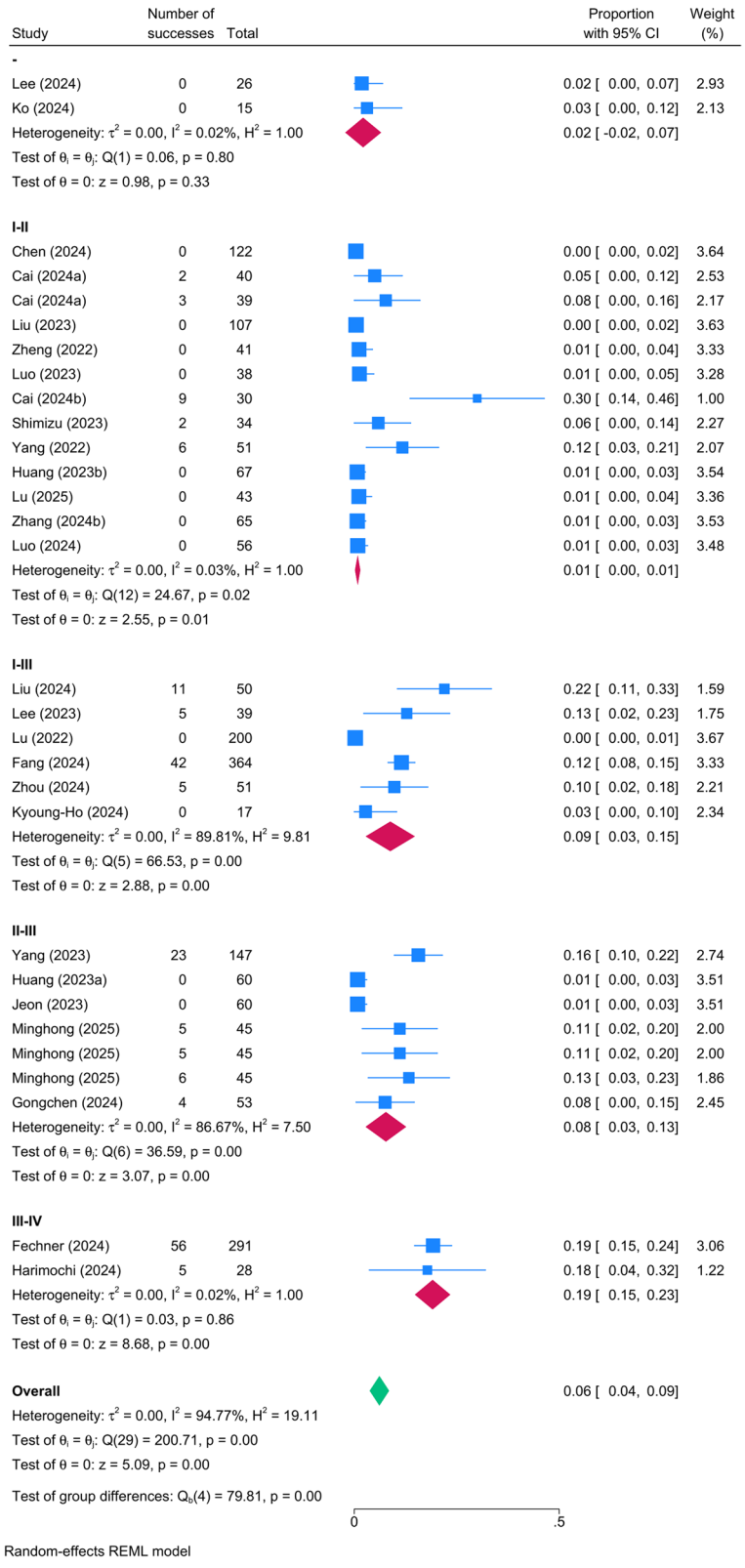

Fig. 8 Forest plot showing the pooled rate of postoperative delirium following remimazolam administration in randomized trials, stratified by baseline ASA (American Society of Anesthesiologists) class

Table 4 Univariate and multivariate adjusted meta-regression of the determinants of the proportion rate of postoperative delirium in patients receiving remimazolam

	Univariate Meta-Regression						Multivariate Meta-Regression					
	Coefficient	P	Low CI	High CI	R^2 (%)	I^2 (%)	Coefficient	P	Low CI	High CI	R^2 (%)	I^2 (%)
Surgery Type [Reference: Laparoscopic & Abdominal Surgery]					48.31	80.85					100	0
GI & Endoscopic Surgery	−0.036	0.093	−0.078	0.006			−0.039	0.322	−0.116	0.038		
Urological & Gynecological Surgery	−0.031	0.205	−0.078	0.017			−0.047	0.364	−0.148	0.054		
Cardiovascular & Neurovascular Surgery	0.008	0.788	−0.051	0.067			0.163	0.164	−0.067	0.394		
General Surgery & Oncology	0.026	0.423	−0.038	0.091			0.079	0.102	−0.016	0.173		
Orthopedic Surgery	0.070	0.012	0.015	0.125			0.081	0.036	0.005	0.156		
ENT Surgery	−0.003	0.925	−0.063	0.057			0.021	0.617	−0.062	0.104		
ASA Class III-IV (%)	0.001	0.001	0.001	0.002	41.91	92.22	0.000	0.899	−0.002	0.002		
Age Group [Reference: Elderly]					4.12	92.55						
Adults	−0.044	0.073	−0.092	0.004			−0.032	0.356	−0.101	0.036		
Adults + Elderly	−0.016	0.543	−0.067	0.035			0.003	0.960	−0.101	0.106		
Children	0.042	0.272	−0.033	0.117			−0.002	0.974	−0.116	0.112		
Follow-up [per day]	−0.001	0.898	−0.008	0.007	0.00	93.75	----Excluded----					
Remimazolam Use [Reference: Anesthesia Induction]					0.00	93.37	----Excluded----					
Maintenance Anesthesia	−0.003	0.942	−0.087	0.081			----Excluded----					
Induction + Maintenance	−0.024	0.314	−0.072	0.023			----Excluded----					
Remimazolam Induction Dose [Reference: Low]					0.00	93.50	----Excluded----					
Moderate dose	−0.017	0.551	−0.071	0.038			----Excluded----					
High dose	−0.035	0.301	−0.102	0.031			----Excluded----					
Remimazolam Maintenance Dose [Reference: Low]					0.00	0.01						
Moderate dose	0.081	0.000	0.038	0.125			0.044	0.480	−0.078	0.167		
High dose	−0.004	0.697	−0.022	0.015			−0.012	0.872	−0.161	0.137		
Operative time [per hour]	0.001	0.000	0.000	0.001	60.81	85.82	0.001	0.225	−0.001	0.003		
Anesthesia time [per hour]	0.001	0.005	0.000	0.001	32.85	82.26	0.000	0.582	−0.001	0.001		
Risk of bias [Low vs. some concerns]	0.014	0.581	−0.035	0.063	0.00	93.76	----Excluded----					
Country [Reference: China]					0.00	92.86	----Excluded----					
Korea	−0.031	0.227	−0.082	0.019			----Excluded----					
Germany	0.039	0.323	−0.039	0.117			----Excluded----					
Japan	0.047	0.387	−0.059	0.152			----Excluded----					
Delirium Definition Criteria [Reference: Patient records]					15.35	91.54						
CAM	0.045	0.049	0.000	0.090			0.041	0.588	−0.106	0.187		
PAED	0.072	0.051	0.000	0.144			0.000	omitted				
NuDESC	0.029	0.365	−0.034	0.092			0.000	omitted				
DSM-IV	−0.024	0.533	−0.098	0.051			0.012	0.551	−0.028	0.052		
MMSE	−0.022	0.501	−0.086	0.042			0.000	omitted				

Table 4 (continued)

	Univariate Meta-Regression						Multivariate Meta-Regression					
	Coefficient	**P**	**Low CI**	**High CI**	**R^2 (%)**	**I^2 (%)**	**Coefficient**	**P**	**Low CI**	**High CI**	**R^2 (%)**	**I^2 (%)**
Co-administered Drugs [Reference: None]												
Remifentanil	0.031	0.104	−0.006	0.068	8.62	92.25						
Propofol	0.024	0.395	−0.031	0.080	0.00	93.61	----Excluded----					
Sufentanil	−0.005	0.828	−0.046	0.037	0.00	92.90	----Excluded----					
Cisatracurium	−0.005	0.830	−0.051	0.041	0.00	93.59	----Excluded----					
Rocuronium	0.099	0.080	−0.012	0.211	6.38	93.27	0.085	0.092	−0.014	0.184		
Sevoflurane	0.011	0.701	−0.044	0.066	0.00	93.74	----Excluded----					
Fentanyl	−0.041	0.077	−0.086	0.004	5.28	91.55	0.000	omitted				
Alfentanil	0.108	0.059	−0.004	0.220	12.43	92.80	0.000	omitted				
Desflurane	0.108	0.059	−0.004	0.220	12.43	92.80	0.000	omitted				
Flumazenil	0.006	0.904	−0.088	0.100	0.00	93.84	----Excluded----					

P p-value, *CI* confidence interval, *NuDESC* The Nursing Delirium Screening Scale, *CAM* Confusion Assessment Method, *PAED* Pediatric Anesthesia Emergence Delirium, *MMSE* Mini-Mental State Examination

response associated with complex surgical interventions likely contribute to these differences [66]. These complex and invasive procedures likely induce greater physiological stress, inflammation, and blood–brain barrier disruption, all of which are known contributors to delirium [67].

The dose–response relationship of remimazolam provides additional insights into its impact on postoperative delirium. Higher doses of remimazolam for both induction and maintenance are associated with a lower incidence of delirium, suggesting that adequate dosing may help mitigate cognitive disturbances. These findings contrast with traditional concerns about benzodiazepine-associated cognitive impairment and indicate that remimazolam's pharmacokinetics, including rapid metabolism and minimal accumulation, may play a role in reducing delirium risk [55].

Potential mechanisms underlying remimazolam-associated delirium may be multifactorial. Remimazolam, as a benzodiazepine, exerts its effects by enhancing the activity of γ-aminobutyric acid (GABA) at GABA-A receptors, which play a critical role in neuronal excitability and cognitive function [68]. Variability in GABA receptor subtypes and distribution across different patient populations—especially in pediatric and elderly individuals—could contribute to differing susceptibilities to delirium [69]. Additionally, remimazolam's rapid metabolism and short context-sensitive half-life, while generally advantageous for quick recovery, might lead to fluctuations in sedation depth in vulnerable patients, potentially triggering cognitive disturbances [70]. Furthermore, the observed dose–response relationship—where higher doses were associated with a lower incidence of delirium—may indicate that maintaining a stable and adequate level of sedation reduces the likelihood of abrupt changes in neural activity that predispose to delirium. These pharmacokinetic and pharmacodynamic properties, along with individual patient factors such as comorbidities and baseline cognitive reserve, likely interact to influence the risk of postoperative delirium.

Clinical implications

The findings of this study have important implications for the use of remimazolam in surgical anesthesia. The identification of key moderators of delirium risk suggests that anesthetic management should be individualized based on patient characteristics. In high-risk populations, such as those with high ASA classifications or undergoing complex oncologic or orthopedic surgeries, close postoperative monitoring for cognitive disturbances may be warranted [60].

Optimizing remimazolam dosing strategies may also enhance its safety profile. The observed reduction in delirium incidence with higher doses highlights the importance of appropriate dose selection to minimize neurocognitive side effects while maintaining hemodynamic stability. The findings also support the broader use of remimazolam in surgical settings where minimizing hemodynamic fluctuations is a priority, particularly in elderly patients and those with significant comorbidities [61].

Strengths and limitations

This study benefits from a rigorous methodology, adherence to PRISMA guidelines, and the inclusion of a large and diverse evidence base. The use of advanced statistical techniques, including meta-regression and sensitivity analyses, enhances the validity of the findings. The exclusion of non-randomized studies strengthens the overall reliability of the conclusions.

Despite these strengths, some limitations must be acknowledged. The presence of significant heterogeneity across studies remains a challenge, although robust statistical methods were employed to account for this variability. We acknowledge that the high level of heterogeneity ($I^2 = 97.88\%$) in our pooled analysis raises concerns regarding the reliability of the overall estimate. This variability likely reflects several underlying factors. Differences in patient characteristics—including age distribution, baseline ASA classification, and comorbidities—may contribute significantly, as delirium incidence was markedly higher in elderly and high-risk populations. Moreover, variations in surgical type, with some procedures (e.g., orthopedic and oncologic surgeries) inherently associated with a higher stress response and risk of cognitive impairment, further amplify this heterogeneity. Differences in remimazolam administration (induction vs. maintenance vs. combined use), dosing strategies, and the use of co-administered anesthetic drugs also likely play a role. Additionally, the use of various delirium diagnostic criteria (such as CAM, DSM-IV, MMSE, NuDESC, and PAED) across studies introduces further variability in outcome assessment. Although these factors collectively contribute to the observed heterogeneity, sensitivity analyses and meta-regression have helped identify significant moderators, particularly the type of surgery. It is important to interpret the pooled estimate in this context, understanding that while the overall figure provides a useful summary, the risk of postoperative delirium is highly dependent on patient and procedural factors.

The reliance on different delirium assessment tools across studies introduces potential inconsistencies, and while efforts were made to standardize data extraction, this remains an inherent limitation of systematic reviews and meta-analyses. Furthermore, the possibility of publication bias cannot be entirely ruled out, despite the use

of the trim-and-fill method to adjust for asymmetry in the funnel plot.

Future research directions

Future research should focus on prospective randomized controlled trials comparing remimazolam with other anesthetic agents in high-risk surgical populations. Investigating the underlying mechanisms of remimazolam's potential neuroprotective effects through pharmacogenetic studies could provide valuable insights. Additionally, longitudinal studies assessing long-term cognitive outcomes following remimazolam-based anesthesia would help clarify its impact on postoperative cognitive recovery [55].

In conclusion, this systematic review and meta-analysis indicate that postoperative delirium following remimazolam administration occurs in approximately 5% of surgical patients, with significant variability across patient subgroups and surgical settings. The findings suggest that remimazolam, particularly at higher doses, may offer a protective effect against delirium in certain populations. The identification of key moderators, including ASA classification, age, surgery type, and remimazolam dosing, highlights the importance of individualized anesthetic management strategies. Future research should further explore these associations to refine perioperative anesthesia protocols and optimize patient outcomes.

Abbreviations

ES	Effect Size
CI	Confidence Interval
SD	Standard Deviation
P	P-value
SE	Standard Error
ASA	American Society of Anesthesiologists
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
AMSTAR	Assessing the methodological quality of systematic reviews
PICOS	Population, Intervention, Comparison, Outcome, and Study Design
ROB	Risk of Bias
YOI	Year of Investigation
YOP	Year of Publication
RCT	Randomized Controlled Trial

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-025-03018-w.

Supplementary Material 1.

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None to declare.

Authors' contributions

Conceptualization: Chao Li and Lai Wei Data curation: Hong Gong and Xingxing Yuan Formal analysis: Chao Li Investigation: Chao Li and Lai Wei Methodology: Hong Gong and Xingxing Yuan Project administration: Lai Wei Resources: Lai Wei Software: Chao Li Validation: Chao Li and Lai Wei Visualization: Hong Gong and Xingxing Yuan Writing – original draft: Hong Gong and Xingxing Yuan Writing – review & editing: Chao Li and Lai Wei.

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Data availability

The datasets generated during and/or analyzed during the current study are not publicly available due to legal constraints and institutional policies but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Given the nature of this research which involved pooling of data from already published studies, there was no need for patient consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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