Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

# Remimazolam and Postoperative Delirium in Patients with Hyperlipidemia: A Retrospective Cohort Study with Target Trial Emulation Analysis

Yuling Tang[1,2,*], Menghong Long[1,2,*], Yuhang Gao[1,2], Ana Kowark[3], Mark Coburn[3], Hengjun Wan[1,2], Yiyun Li[1,2], Xiaoxia Duan[1]

[1]Department of Anesthesiology, The Affiliated Hospital, Southwest Medical University, Luzhou, Sichuan, People's Republic of China; [2]Anesthesiology and Critical Care Medicine Key Laboratory of Luzhou, Southwest Medical University, Luzhou, Sichuan, People's Republic of China; [3]Department of Anaesthesiology and Intensive Care Medicine, University Hospital Bonn, Bonn, Germany

*These authors contributed equally to this work

Correspondence: Xiaoxia Duan, Department of Anesthesiology, The Affiliated Hospital, Southwest Medical University, Luzhou, Sichuan, People's Republic of China, Tel +86 13568635458, Email duanxiaoxia@swmu.edu.cn

Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: https://youtu.be/TdoQevv5tFg



**Purpose:** Hyperlipidemia increases postoperative delirium (POD) risk via neuroinflammation; however, effective pharmacological interventions to mitigate POD in this population remain limited. Remimazolam has been reported to reduce perioperative stress and modulate neuroinflammatory responses. We investigated the effect of remimazolam on POD incidence in surgical patients with hyperlipidemia.

**Patients and Methods:** In this retrospective cohort study, we enrolled 1123 patients with hyperlipidemia who underwent surgery under general anesthesia with or without remimazolam at a single institution. The primary outcome measure was POD incidence within 3 days postoperatively. To assess the impact of remimazolam on POD, a target trial emulation framework was applied to enhance control of confounders and strengthen causal inference. We additionally investigated the dose–response relationship between remimazolam exposure and POD.

**Results:** POD incidence in the remimazolam group was 13.8%, which was 7.2% lower than that in the non-remimazolam group (P<0.01). Additionally, delirium severity (median score: 9 vs 10, P<0.01) and cognitive impairment incidence at 6 months postoperatively (4.4% vs 8.3%, P<0.05) were lower in the remimazolam group. The target trial emulation further confirmed the protective effects of remimazolam on POD (adjusted risk difference [aRD]: −5.3%, P=0.016), delirium severity (aRD: −2.238, P<0.001), and cognitive dysfunction incidence at 6 months postoperatively (aRD: −3.97%, P=0.019). Dose–response analysis showed a significant reduction in POD incidence when the total remimazolam dose was ≥10.29 mg or the maintenance rate was ≥0.51 mg $kg^{-1}$ $h^{-1}$.

**Conclusion:** Remimazolam significantly reduced POD incidence and severity in patients with hyperlipidemia and improved cognitive function at 6 months postoperatively. However, prospective studies are needed to confirm these findings.

**Keywords:** remimazolam, postoperative delirium, hyperlipidemia, target trial emulation, dose–response, neuroprotection

## Introduction

Postoperative delirium (POD) is a common and serious perioperative complication,[1] characterized by impaired attention, altered consciousness, and fluctuating cognition.[2] Research has indicated that POD is closely linked to extended hospitalization, increased mortality risk,[3] and persistent cognitive deterioration.[4] Its incidence is high among patients with metabolic disorders,[5] particularly hyperlipidemia, which can enhance the central nervous system vulnerability to perioperative injury and further promote POD by activating microglia and neuronal inflammasomes, thereby exacerbating neuroinflammation,[6] promoting oxidative stress,[7] and impairing cerebral vascular endothelial function.[8]

https://doi.org/10.2147/DDDT.S568452
Received: 18 September 2025
Accepted: 18 January 2026
Published: 24 January 2026

A correlation between hyperlipidemia and POD has been demonstrated;[9] however, the use of traditional sedatives such as propofol or midazolam may cause lipid fluctuations[10] or delayed emergence[11] in patients with metabolic abnormalities, highlighting the limited evidence-based guidance regarding optimal anesthetic selection in this specific population. Remimazolam tosylate, a new ultra-short-acting benzodiazepine, offers hemodynamic stability, non-accumulative pharmacokinetics, and metabolism independent of hepatic and renal function,[12] potentially making it more advantageous in reducing delirium risk. Remimazolam has been shown to significantly reduce neuroinflammation and neuronal damage by inhibiting microglial activation[13] and reducing inflammation mediated through the nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome pathway,[14] suggesting that its anti-inflammatory effects may be particularly beneficial in countering the pro-inflammatory state of hyperlipidemia.

While remimazolam has shown efficacy in decreasing POD incidence among older patients with hip fractures[15] and enhancing postoperative cognitive recovery,[16] its impact on hyperlipidemic surgical populations remains unexplored. Therefore, in this study, we aimed to evaluate the effect of remimazolam on POD incidence and severity in surgical patients with hyperlipidemia and to explore dose–response relationships using a target trial emulation framework.

# Materials and Methods

## Ethics Consideration

This study was approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University (KY2025006) and registered with ChiCTR (ChiCTR2500097885). This study is retrospective, and all patient information used in the research has been strictly de-identified, thus, the informed consent forms was waived. The design principles of randomized controlled trials (Supplementary Table 1) and the STROBE guidelines for observational studies were strictly followed during the study implementation.[17] All patients data were anonymized and maintained with strict confidentiality in compliance with the principles of the Declaration of Helsinki.

## Study Population and Subgroups

Adult patients (age ≥18 years) who underwent surgery under general anesthesia between March 1, 2024, and February 28, 2025, at the Affiliated Hospital of Southwest Medical University were eligible. The inclusion criteria were preoperative combined hyperlipidemia; American Society of Anesthesiologists (ASA) class I–III; non-cranial, non-cardiac surgery; and a postoperative hospital stay of ≥3 days.

Hyperlipidemia was defined according to the 2023 Chinese Guidelines for Lipid Management,[18] based on dyslipidemia characterized by elevated total cholesterol (TC ≥5.2mmol·$L^{-1}$), elevated triglycerides (TGs ≥1.7mmol·$L^{-1}$), reduced high-density lipoprotein cholesterol (HDL-C <1.0 mmol·$L^{-1}$), or elevated low-density lipoprotein cholesterol (LDL-C ≥3.4mmol·$L^{-1}$).

Patients with the following contraindications were excluded: 1) preoperative delirium or mental illness; 2) allergy to or contraindications for benzodiazepines; 3) severe cardiovascular disease or hepatic or renal insufficiency; and 4) a history of drug abuse or use of psychotropic drugs.

Participants were categorized into two groups based on the administration status of remimazolam tosylate (Jiangsu Hengrui Medicine Co., Ltd.; National Pharmaceutical Licence No. H20190034). Patients who received remimazolam tosylate intraoperatively were assigned to the remimazolam group, whereas those who did not were categorized in the non-remimazolam group.

## Clinical Data Collection

Patient-related information was collected from the hospital's electronic medical record system (Donghua Standard Edition Digital Hospital; iMedical HIS 9.0.1). Demographic information included sex, age, body mass index (BMI), ASA classification, education level (categorized into low and high levels using a 6-year cut-off), and alcohol dependence (males: >20 g of alcohol per day; females: >15 g per day).[19] Medical history included hypertension, diabetes mellitus, coronary artery disease, arrhythmia, and cerebrovascular disease. The patients' lipid profiles (TC, TGs, LDL-C, and HDL-C) were also collected.

Intraoperative information included operative time, intraoperative hypertension (intraoperative blood pressure ≥30% above baseline value for 5 min),[20] intraoperative hypotension (intraoperative mean arterial pressure ≤65 mmHg for 5 min),[21] intraoperative hypothermia (core temperature <36°C),[22] and delayed awakening (failure to regain consciousness within 30–60 min after discontinuation of general anesthesia).[23] For patients receiving intraoperative remimazolam, the mode of remimazolam administration (induction alone or induction-maintenance co-administration) and total dose used were recorded.

## Primary Outcome

The primary outcome was 3-day POD incidence, assessed using the 3-Minute Diagnostic Interview for Confusion Assessment Method (3D-CAM),[24] which includes the following four features: 1) acute mental status change, 2) attention deficit, 3) fluctuating levels of consciousness, and 4) disorganized or disordered thinking. Delirium was diagnosed when features 1 and 2 were positive, along with either features 3 or 4. Assessments were completed by two trained researchers between 6:00 PM and 8:00 PM the day before surgery and on postoperative days 1–3. Outcome events had been collected prospectively, and a retrospective analysis was performed in this study.

## Secondary Outcomes

Secondary outcomes included length of hospital stay, post-anesthesia care unit (PACU) stay time, delirium severity, cognitive dysfunction incidence at 3 and 6 months postoperatively, and all-cause mortality at 6 months postoperatively. Delirium severity was measured using the quantitative scale established by Vasunilashorn et al,[25] a scoring system that transforms 3D-CAM assessments into a continuous variable score ranging from 0 to 20, with higher scores indicating greater symptom severity. Postoperative follow-ups were conducted via telephone at 3 and 6 months. Cognitive function was assessed using a modified version of the Telephone Interview for Cognitive Status,[26] and survival status was confirmed during the 6-month follow-up.

## Statistical Analysis

Data normality was assessed using the Shapiro–Wilk test. Normally distributed continuous variables are expressed as mean ± standard deviation and were compared using independent samples *t*-tests, while non-normally distributed data are expressed as median with interquartile range and were analyzed using Mann–Whitney *U*-tests. Categorical variables are presented as counts and were compared using chi-square tests.

To evaluate the association between remimazolam use and POD risk, we constructed multivariate logistic regression models and reported odds ratios (ORs) with 95% confidence intervals (CIs). Kaplan–Meier curves were generated to compare cumulative POD incidence between the remimazolam and non-remimazolam groups, and Log rank tests were applied to estimate hazard ratios along with 95% CIs.

Restricted cubic spline analyses were performed to evaluate dose–response relationships for remimazolam doses in the overall remimazolam group, induction-only subgroup, and induction–maintenance subgroup; the maintenance rate of remimazolam in the induction–maintenance population; and POD risk (four nodes). Covariates adjusted for in these models included age, education level, BMI, alcohol dependence, sex, diabetes, cerebrovascular disease, hypertension, arrhythmia, coronary heart disease, operative time, intraoperative hypothermia, intraoperative hypotension, intraoperative hypertension, and delayed emergence. To explore the potential moderating effect of remimazolam, we included an interaction term between remimazolam dose and each covariate added separately to the regression model and a statistically significant range of dose moderation was determined using the Johnson–Neyman method.

To emulate a target trial estimating the effect of remimazolam on postoperative outcomes, the observed administration (or non-administration) of remimazolam for each individual was re-assigned to generate two hypothetical scenarios using a static intervention framework:[27] (1) what if all participants received remimazolam, and (2) what if no participants received remimazolam. In the primary analysis, we estimated the effect of remimazolam on POD.

Secondary outcomes included the POD severity score, length of hospital and PACU stays, postoperative cognitive function at 3 and 6 months, and all-cause mortality at 6 months. Baseline confounders included age, education level, BMI, alcohol dependence, sex, diabetes, cerebrovascular disease, hypertension, arrhythmia, coronary heart disease,

operative time, intraoperative hypothermia, intraoperative hypotension, intraoperative hypertension, and delayed emergence.

The aforementioned statistical estimand belongs to the category of a "modified treatment policy",[28,29] which assesses outcomes when the application of a treatment or intervention is modified from reality. Casual interpretation required the following assumptions: (1) conditional exchangeability, indicating no unobserved/unmeasured confounding in the relationship between the set of treatments and the outcome or between censoring and outcome, conditional on covariates or covariates and treatment, respectively; (2) positivity, which ensures each individual has a non-zero probability of receiving a treatment conditional on observed covariates; and (3) consistency, ensuring the observed outcome for an individual under a specific treatment aligns with their potential outcome under that same treatment.

We obtained this statistical estimand using a doubly robust, nonparametric targeted minimum loss-based estimator.[30] A five-fold cross-fitted version of this estimator was utilized, which involves fitting regressions for both the outcome and treatment mechanisms. These regressions were conducted using an ensemble of machine learning algorithms,[31] including generalized linear, random forest, Lasso, XGBoost, and generalized additive models.

All patients with hyperlipidemia included in the analysis were categorized into subgroups based on abnormal critical values of TGs, TC, LDL-C, and HDL-C. Additionally, subgroup analyses of the estimated POD incidence between the remimazolam and non-remimazolam groups in the different lipid subgroups were conducted using the target trial emulation method. Sensitivity analysis was performed after excluding patients with cerebrovascular disease in the target trial emulation framework to verify the robustness of the results.

Statistical analyses were performed using R 4.4.2 (R Core Team, Vienna, Austria) and IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA), and graphs were plotted using GraphPad Prism 10.4 (GraphPad Software, San Diego, CA, USA). Statistical significance was set at $P<0.05$.

# Results

## General Patient Information

Overall, 1344 patients with hyperlipidemia were initially included. After excluding those with incomplete data and loss to follow-up, 1123 patients were included in the final analysis cohort, comprising 586 and 537 in the remimazolam and control groups, respectively (Figure 1).

TC (5.27 vs 5.13 $mmol \cdot L^{-1}$, $P<0.05$) and LDL-C levels (3.56 vs 3.42 $mmol \cdot L^{-1}$, $P<0.05$) were higher in the remimazolam group than in the non-remimazolam group. No significant differences were observed between the two groups in demographics, comorbidities, and surgical parameters ($P>0.05$; Table 1).

## Effect of Remimazolam on Postoperative Delirium Incidence

Among the 1123 patients included in the study, POD occurred in 194, yielding an overall incidence of 17.3%. Multivariate logistic regression analysis showed that remimazolam administration was associated with a significantly reduced risk of POD (OR=0.552, 95% CI: 0.392–0.776, P=0.001) and was identified as an independent protective factor. Several variables were significantly correlated with an increased POD risk, including higher BMI (OR=1.068, 95% CI: 1.021–1.118, P=0.004), pre-existing arrhythmia (OR=3.071, 95% CI: 2.168–4.349, P<0.001), intraoperative hypertension (OR=2.119, 95% CI: 1.043–4.307, P=0.038), and longer operative time (OR=1.007, 95% CI: 1.006–1.019, P<0.001, Figure 2A). POD incidence was significantly lower in the remimazolam group (n=81; incidence rate 13.8%) than in the non-remimazolam group (n=113; incidence rate 21.0%, P<0.05; Figure 2B). Kaplan–Meier survival analysis revealed a significantly lower cumulative POD incidence in the remimazolam group (log-rank P<0.05), with a hazard ratio of 0.418 (95% CI: 0.330–0.529, Figure 2C).

Using a target trial emulation method adjusted for confounders and calculating the adjusted estimated incidence rate and its 95% CIs, the estimated incidence of POD showed that remimazolam reduced absolute risk by 5.3% (95% CI: −9.6% to −0.8%, P=0.016, Figure 2D), a result consistent with the previous analysis.

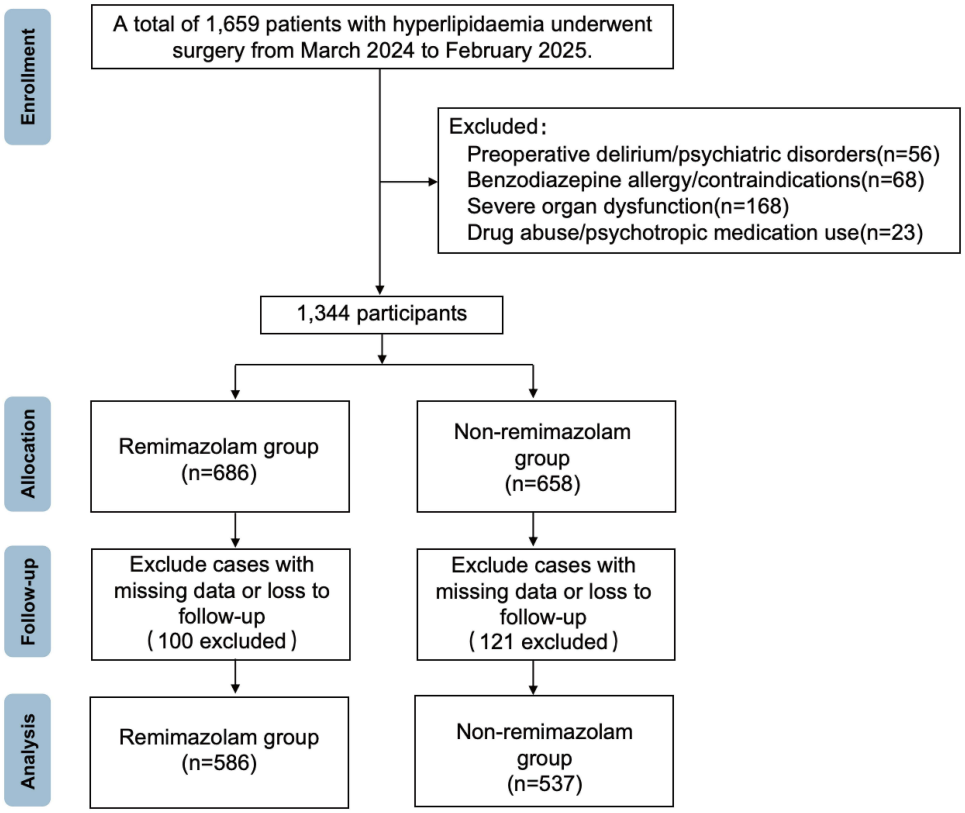



**Figure 1** Flow chart of patient screening.

## Effect of Remimazolam on Delirium Severity and Cognitive Function at 6 Months Postoperatively

The time of onset, duration of days, and delirium severity in patients with POD are shown in Figure 3A. Patients receiving remimazolam showed significantly better outcomes in two key measures than did those in the control group: median POD severity score on postoperative day 1 (9 vs 10, P<0.01, Figure 3B) and incidence of cognitive impairment at 6 months (4.4% vs 8.3%, P<0.05, Figure 3C). Length of hospital stay (median, 8 vs 8 days, P=0.945, Figure 3D), cognitive impairment incidence at 3 months (2.7% vs 3.9%, P=0.316, Figure 3E), PACU stay duration (median, 23 vs 23 min, P=0.509, Figure 3F), and 6-month all-cause mortality (1.1% vs 2.6%, P=0.121, Figure 3G) were not significantly different.

The results of the emulation analysis of the target trial were consistent with the observational data, further confirming that remimazolam significantly decreased the POD severity score on the first day (adjusted mean difference: −2.238, 95% CI: −2.881 to −1.595, P<0.001) and lowered the risk of 6-month cognitive impairment (adjusted risk difference [aRD]: −3.97%, 95% CI: −7.30% to −0.65%, P=0.019); however, no significant differences were observed in 3-month post-operative cognitive function, length of hospital and PACU stays, and 6-month postoperative all-cause mortality (Figure 3H).

## Remimazolam Dose and Maintenance Rate Thresholds

In the overall population, a linear negative correlation was observed between remimazolam dose and POD risk (P for nonlinearity=0.708), with OR values decreasing continuously at doses >10.29 mg (Figure 4A). The dose–response curve in the induction-only population showed a U-shape; although the trend of the curve suggested nonlinearity, the statistical test did not reject the assumption of linearity (P for nonlinearity=0.062), and the OR value of <1 for the induction dose was in the range of 10.06–18.94 mg (Figure 4B). The induction–maintenance group showed an inverted U-shaped curve (P for nonlinearity<0.005), and the OR value dropped below 1 at a dose of 17.57 mg (Figure 4C). The maintenance


https://doi.org/10.2147/DDDT.S568452

**Table 1** Baseline Characteristics of the Hyperlipidemic Population

| Variables | Overall (n=1123) | Remimazolam Group (n=586) | Non-Remimazolam group (n=537) | P value |
|---|---|---|---|---|
| Age, median (IQR) | 60 (16) | 60 (15) | 60 (16) | 0.677 |
| Sex women, N (%) | 582 (51.8%) | 301 (51.4%) | 281 (52.3%) | 0.765 |
| BMI, median (IQR), kg $m^{-2}$ | 24.22 (4.27) | 24.03 (4.45) | 24.24 (4.25) | 0.729 |
| Education level, N (%) | | | | 0.711 |
| Low (<6 years) | 227 (20.28%) | 121 (20.68%) | 106 (19.7%) | |
| High (≥6 years) | 896 (79.8%) | 465 (79.4%) | 431 (80.3%) | |
| Diabetes, N (%) | 179 (15.9%) | 96 (16.4%) | 83 (15.5%) | 0.684 |
| CVD, N (%) | 142 (12.6%) | 79 (13.5%) | 63 (11.7%) | 0.419 |
| Hypertension, N (%) | 362 (32.2%) | 175 (29.9%) | 187 (34.8%) | 0.084 |
| Arrhythmia, N (%) | 395 (35.2%) | 204 (34.9%) | 191 (35.6%) | 0.851 |
| CHD, N (%) | 66 (5.9%) | 37 (6.3%) | 29 (5.4%) | 0.528 |
| Alcohol dependence, N (%) | 97 (8.6%) | 53 (9%) | 44 (8.2%) | 0.671 |
| ASA Classification, N (%) | | | | 0.511 |
| ≤II | 577 (51.4%) | 307 (52.4%) | 270 (50.3%) | |
| ≥III | 546 (48.6%) | 279 (47.6%) | 267 (49.7%) | |
| TGs, median (IQR), mmol $L^{-1}$ | 1.74 (1.07) | 1.75 (1.04) | 1.72 (1.10) | 0.609 |
| TC, median (IQR), mmol $L^{-1}$ | 5.22 (1.6) | 5.27 (1.42) | 5.13 (1.72) | <0.05 |
| LDL, median (IQR), mmol $L^{-1}$ | 3.49 (1.18) | 3.56 (1.09) | 3.42 (1.31) | <0.05 |
| HDL, median (IQR), mmol $L^{-1}$ | 1.21 (0.55) | 1.24 (0.55) | 1.18 (0.56) | 0.108 |
| Operative time, median (IQR), min | 100 (100) | 100 (100) | 100 (95) | 0.903 |
| Intraoperative | | | | |
| Hypothermia | 25 (2.2%) | 16 (2.7%) | 9 (1.7%) | 0.312 |
| Hypotension | 65 (5.8%) | 31 (5.3%) | 34 (6.3%) | 0.523 |
| Hypertension | 56 (5%) | 32 (5.5%) | 24 (4.5%) | 0.494 |
| Delayed emergence | 33 (2.9%) | 15 (2.6%) | 18 (3.4%) | 0.482 |

**Notes**: The Shapiro–Wilk test for normality is used for quantitative data. The Mann–Whitney *U*-test is used for non-normal quantitative data, and the chi-square test is utilised for qualitative data.

**Abbreviations**: ASA, American Society of Anesthesiologists; BMI, body mass index; CVD, cerebrovascular disease; CHD, coronary heart disease; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; TC, total cholesterol; TGs, triglycerides.

infusion rate analysis similarly showed an inverted U-shaped relationship (P for nonlinearity<0.005), with a critical value of 0.51 mg $kg^{-1}$ $h^{-1}$ (Figure 4D).

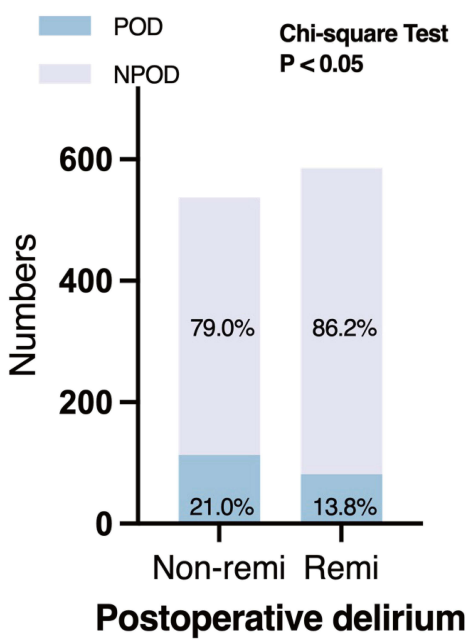
Based on the dose thresholds determined through restrictive cubic spline analysis, the results of a stratified analysis of the different remimazolam dosing regimens using the target trial emulation framework validated the dose–response relationship observed in the restrictive cubic spline analysis. In the total remimazolam-use group, POD incidence was significantly lower at doses ≥10.29 mg (14.48% vs 19.88%; aRD: −5.40%, 95% CI: −9.60% to −1.20%, P=0.012). This trend was also observed in the induction group. When the maintenance infusion rate was ≥0.51 mg $kg^{-1}$ $h^{-1}$ (aRD: −12.92%, 95% CI: −17.14% to −8.71%, P<0.01), the estimated POD incidence was only 7.04%. The induction–maintenance combination regimen of remimazolam further reduced delirium risk compared with that of the induction regimen alone (10.62% vs 16.37%, aRD: −5.7%, 95% CI: −10.9% to −0.6%, P=0.029), suggesting a full course of drug administration with a clinical advantage (Figure 4E).

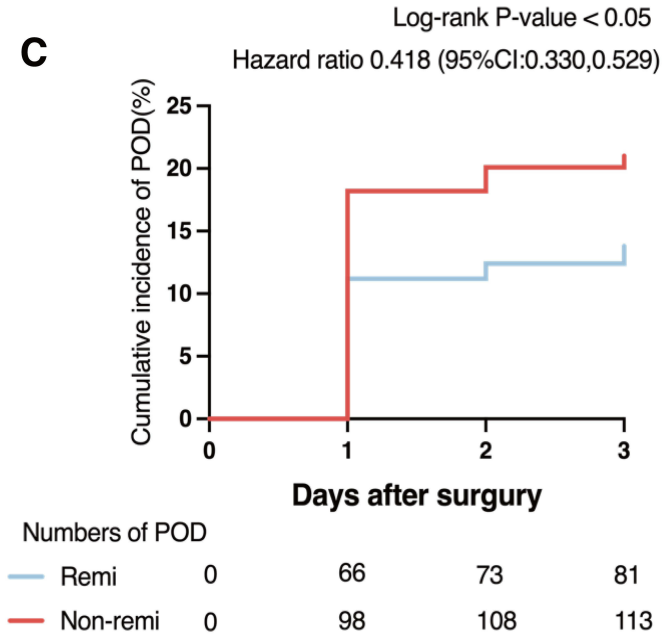
## Moderating Effects of Remimazolam in Postoperative Delirium Development in Patients with Cardiac Arrhythmias

The analyses showed that the interaction term between total remimazolam dose and arrhythmia was statistically significant (β=−0.002, standard error=0.001, t value: −2.455, P=0.014, Supplementary Table 2).

**A**

| Variables | OR | 95%CI | P Value |
|---|---|---|---|
| Remimazolam | 0.552 | (0.392,0.776) | 0.001 |
| Age | 1.002 | (0.987,1.017) | 0.820 |
| Sex | 0.958 | (0.677,1.354) | 0.807 |
| BMI | 1.068 | (1.021,1.118) | 0.004 |
| Education level | 1.326 | (0.844,2.084) | 0.220 |
| Diabetes | 1.375 | (0.884,2.138) | 0.157 |
| CVD | 1.356 | (0.847,2.168) | 0.204 |
| Hypertension | 1.390 | (0.969,1.992) | 0.073 |
| Arrhythmia | 3.071 | (2.168,4.349) | <0.001 |
| CHD | 1.184 | (0.602,2.327) | 0.625 |
| Alcohol dependence | 0.676 | (0.355,1.287) | 0.233 |
| Operative time | 1.007 | (1.006,1.009) | <0.001 |
| Intraoperative | | | |
| Hypothermia | 0.827 | (0.229,2.982) | 0.772 |
| Hypotension | 0.645 | (0.291,1.429) | 0.280 |
| Hypertension | 2.119 | (1.043,4.307) | 0.038 |
| Delayed emergence | 0.473 | (0.150,1.486) | 0.200 |


**D**

| Primary outcome | Estimates: Remi group | Non-remi group | aRD | 95%CI | P Value |
|---|---|---|---|---|---|
| Postoperative delirium | 14.59% | 19.88% | -5.30% | (-9.6%,-0.8%) | 1.60% |

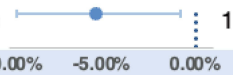
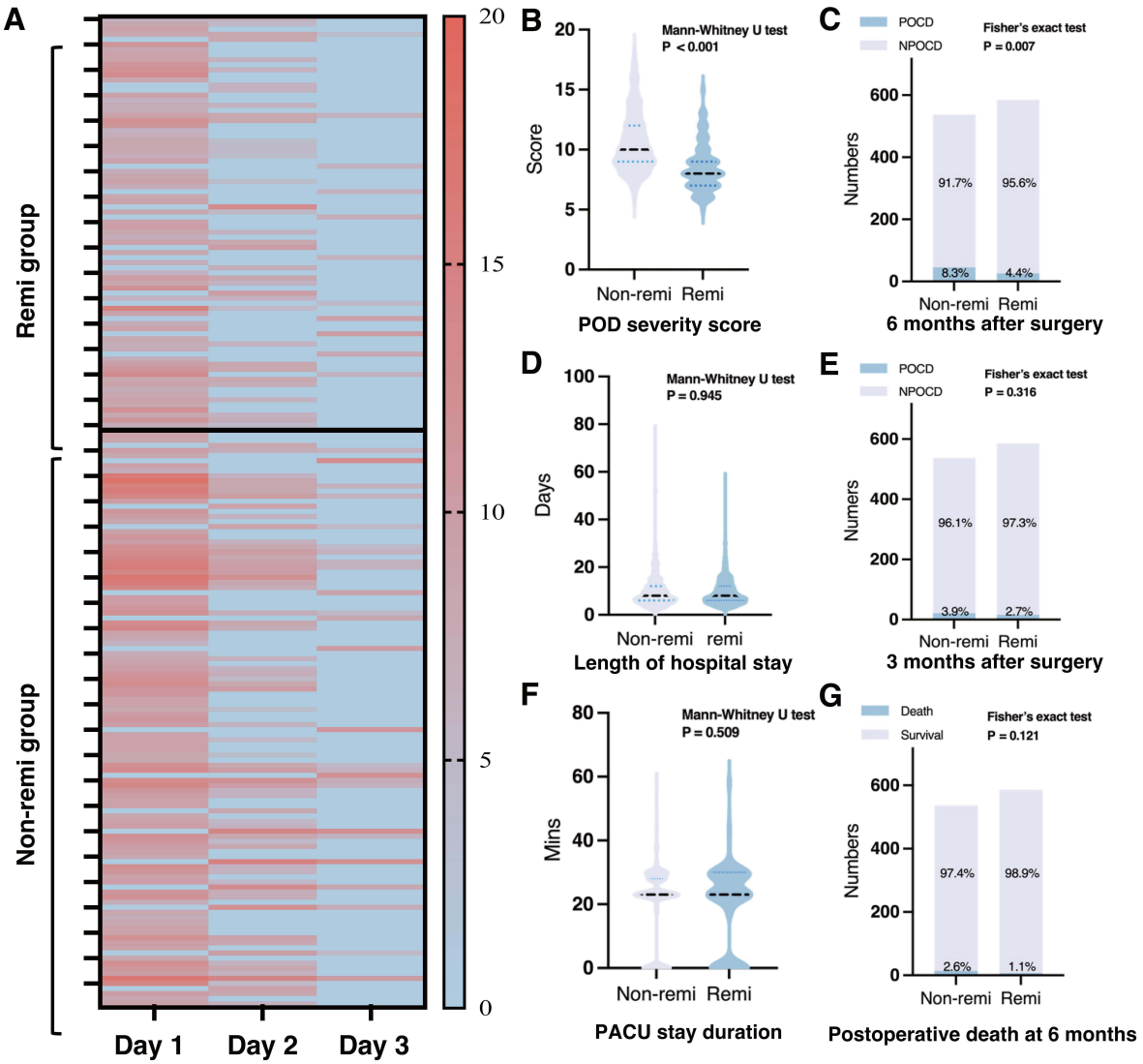



**Figure 2** (**A**) Forest plot of multivariate logistic regression results: Remimazolam reduces the risk of POD, arrhythmia, BMI, intraoperative hypertension, and duration of surgery increases the risk. (**B**) Stacked histogram: The incidence of POD in the remimazolam group was 7.2% lower than that in the non-remimazolam group. (**C**) Kaplan–Meier analysis: the cumulative morbidity rate was lower in the remimazolam group. (**D**) Target trial emulation: The estimated absolute risk of POD incidence in the remimazolam group was 5.3% lower than that in the non-remimazolam group.

**Abbreviations**: BMI, body mass index; POD, Postoperative delirium.


https://doi.org/10.2147/DDDT.S568452




H

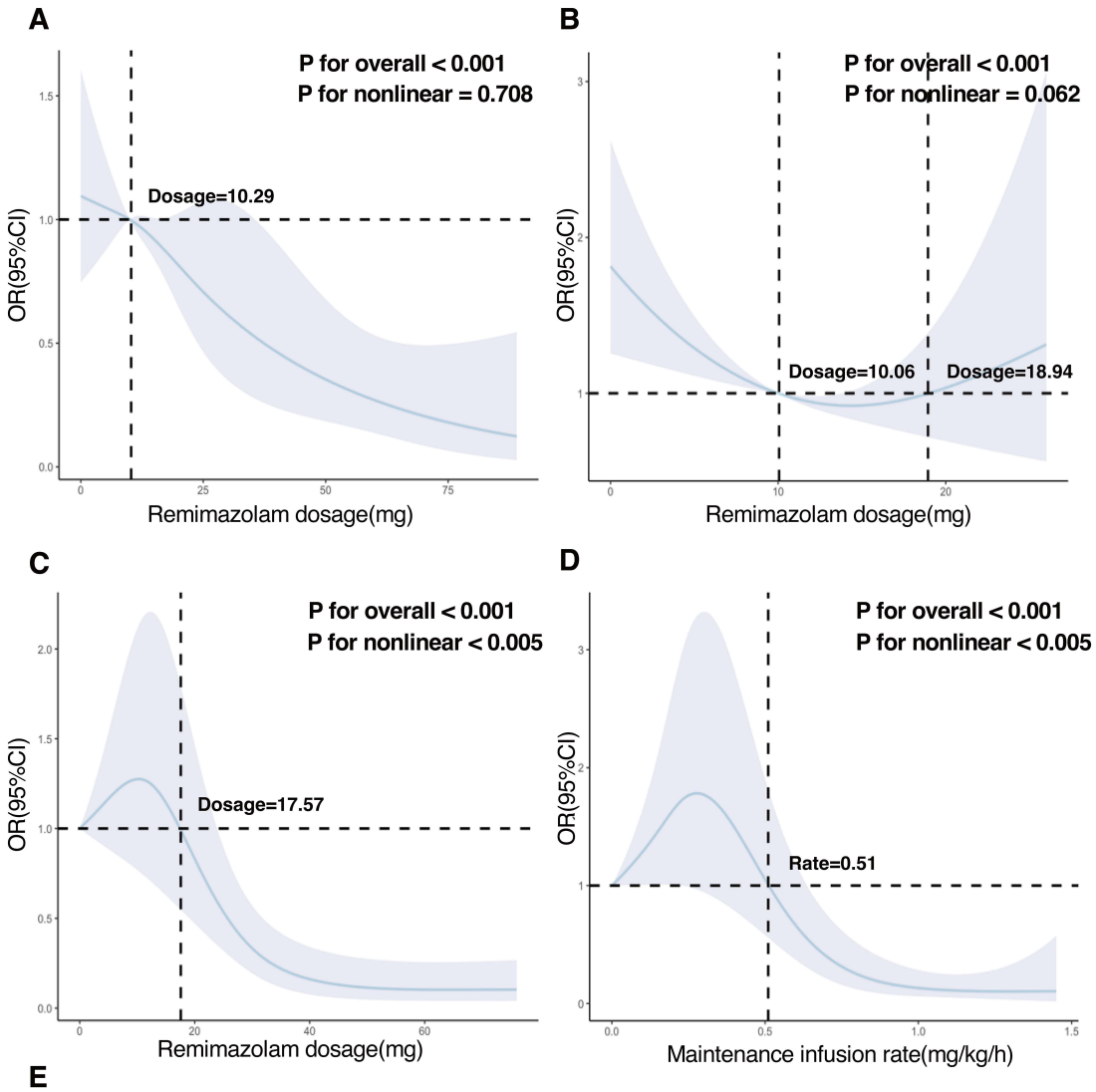
| Secondary outcomes | Estimates: Remi group | Non-remi group | aMD | 95%CI | P Value |
|---|---|---|---|---|---|
| Length of stay（days） | 9.59 | 9.98 | -0.393 | (-1.134,0.347) | 0.298 |
| PACU stay time（mins） | 20.84 | 19.95 | 0.966 | (-0.621,2.552) | 0.233 |
| Postoperative delirium severity | 8.48 | 10.72 | -2.238 | (-2.881,-1.595) | <0.001 |
| | | | aRD | 95%CI | P Value |
| POCD 3 months after surgery | 2.81% | 4.07% | -1.26% | (-3.57%,-1.04%) | 0.283 |
| POCD 6 months after surgery | 5.37% | 9.34% | -3.97% | (-7.30%,-0.65%) | 0.019 |
| Postoperative 6-month all-cause mortality | 1.38% | 2.96% | -1.59% | (-3.47%,2.86%) | 0.097 |



**Figure 3** (**A**) Heat map: Time of onset, duration of days, and severity of delirium in patients with POD. (**B**) Comparison of POD severity. (**C**) Comparison of the incidence of cognitive impairment at 6 months. (**D**) Comparison of the length of hospital stay. (**E**) Comparison of the incidence of cognitive impairment at 3 months. (**F**) Comparison of PACU stay duration. (**G**) Comparison of 6-month all-cause mortality. (**H**) Target trial emulation: Lower severity score of POD on the first day and incidence of postoperative 6-month cognitive impairment in the remimazolam group.

**Abbreviations**: POD, Postoperative delirium; PACU, Post-anesthesia care unit.


https://doi.org/10.2147/DDDT.S568452




E

| | Estimates of POD | aRD | 95%CI | P Value |
|---|---|---|---|---|
| **Group by administration method** | | | | |
| Induction-maintenance group | 10.62% | -5.70% | (-10.9%,-0.6%) | 0.029 |
| Induction group | 16.37% | | | |
| **Group by dosage** | | | | |
| Total remimazolam group(mg) | | | | |
| <10.29 | 19.88% | -5.40% | (-9.60%,-1.20%) | 0.012 |
| ≥10.29 | 14.48% | | | |
| Induction-only group(mg) | | | | |
| <10.06,>18.94 | 19.53% | -4.95% | (-9.15%,-0.76%) | 0.021 |
| 10.06-18.94 | 14.58% | | | |
| Induction-maintenance group(mg) | | | | |
| <17.57 | 19.42% | -8.40% | (-12,58%,-4.22%) | <0.01 |
| ≥17.57 | 11.01% | | | |
| Maintenance rate group(mg/kg/h) | | | | |
| <0.51 | 19.96% | -12.92% | (-17.14%,-8.71%) | <0.01 |
| ≥0.51 | 7.04% | | | |



**Figure 4** (**A**) Total remimazolam group: Dose is linearly and negatively correlated with POD, with a critical dose of 10.29 mg. (**B**) Induction-only group: Dose–response is U-shaped, with an optimal dose range of 10.06–18.94 mg. (**C**) Induction-maintenance group: Dose–response is an inverted U-shaped relationship, with a critical dose of 17.57 mg. (**D**) Maintenance infusion rate: An inverted U-shaped relationship, with a critical rate of 0.51 mg $kg^{-1}$ $h^{-1}$. (**E**) Emulated stratified analysis of the target trial: Dose thresholds show that the high dose (≥threshold group) and the combined induction-maintenance regimen significantly reduce the risk of POD.
**Abbreviation**: POD, Postoperative delirium.


https://doi.org/10.2147/DDDT.S568452

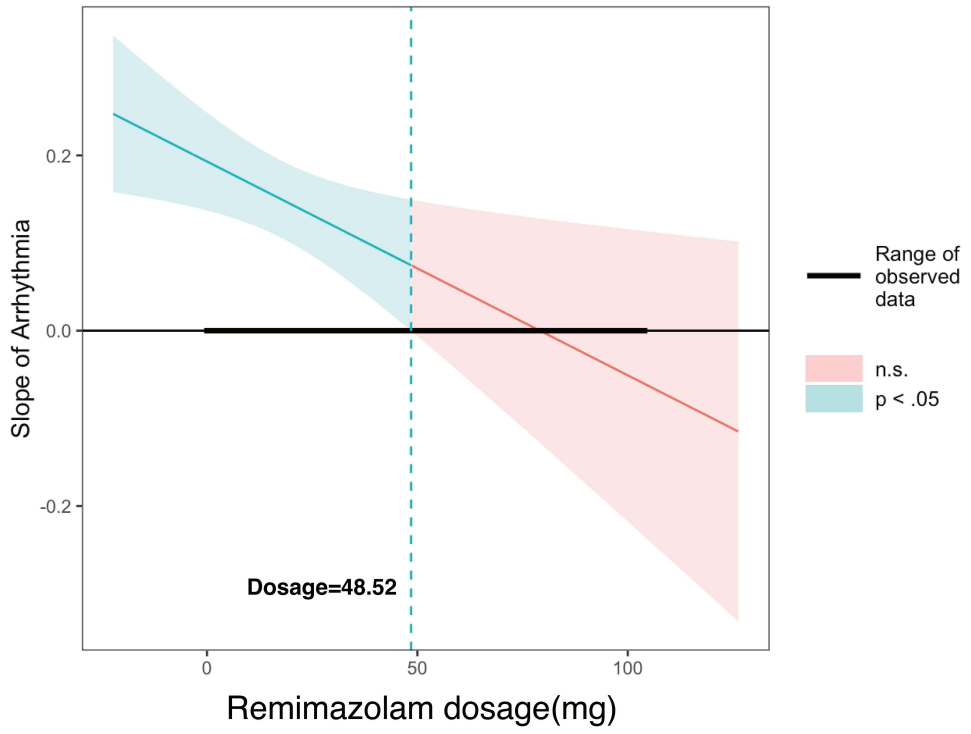



**Figure 5** Johnson–Neyman analysis. The red area of the graph indicates a nonsignificant (n.s.) moderating effect, and the blue area shows a significant negative moderating effect of remimazolam dose on arrhythmia versus POD (P<0.05). The X-axis shows the dose of remimazolam, and the Y-axis represents the value of the simple slope effect of arrhythmia on POD.
**Abbreviation**: POD, Postoperative delirium.

Further analysis using the Johnson–Neyman method revealed that remimazolam had a significant negative moderating effect on POD risk in patients with arrhythmia when the remimazolam dose ranged from 0 to 48.52 mg (P<0.05; Figure 5).

## Subgroup Analysis of Four Dyslipidemias

In the subgroup analysis, remimazolam significantly reduced POD risk in four dyslipidemia subgroups: TG ≥1.7 mmol·L$^{-1}$ (RR=0.585, 95% CI: 0.400–0.854, P=0.006), TC ≥5.2 mmol·L$^{-1}$ (RR=0.609, 95% CI: 0.421–0.882, P=0.009), LDL-C ≥3.4 mmol·L$^{-1}$ (RR=0.609, 95% CI: 0.419–0.887, P=0.01), and HDL-C <1.0 mmol·L$^{-1}$ (RR=0.671, 95% CI: 0.477–0.944, P=0.02, Supplementary Figure 1).

## Sensitivity Analysis

After excluding individuals with preoperative cerebrovascular disease, 981 patients were included in the emulated sensitivity analysis of the target trial. The results aligned with those of the main analysis. Moreover, the statistical significance remained unchanged, indicating the robustness of the findings (Supplementary Figure 2).

# Discussion

The perioperative use of remimazolam in patients with hyperlipidemia significantly reduced POD incidence, delirium severity, and cognitive impairment incidence at 6 months postoperatively. Furthermore, a significant dose-dependent protective effect was observed at a total dose ≥10.29 mg and a maintenance infusion rate ≥0.51 mg kg$^{-1}$ h$^{-1}$. The protective effect of remimazolam was significant in the dyslipidemia subgroup and had a negative moderating effect on POD occurrence in patients with cardiac arrhythmia.

This study suggests a relationship between remimazolam and POD, delirium severity, and long-term cognitive function, as well as highlighting its role in patients with dyslipidemia. Our previous prospective cohort study revealed

that POD incidence was 8.9% higher and the duration of delirium was longer in patients with hyperlipidemia than in those without.[9] Lin et al[32] also demonstrated that an increase in serum TGs, TC, and LDL-C concentrations was a risk factor for POD development.

Recent studies have shown that the use of remimazolam during general anesthesia in older patients with lower limb fractures reduces POD risk and is independently associated with POD incidence.[15,33] This is consistent with our results, further supporting the potential protective effects of remimazolam on POD development. In contrast to prior observational studies, we used a target trial emulation method, constructed a counterfactual framework, and employed double robust estimation based on real-world data, effectively controlling for confounding bias commonly seen in observational studies, thereby providing a less biased assessment of the true therapeutic effect of remimazolam.

The pathological elevation of TGs and TC in hyperlipidemia can disrupt the blood–brain barrier, induce inflammation and oxidative stress, accelerate the formation of arterial plaques, and increase the risk of neurodegenerative diseases.[34] However, previous studies have reported that remimazolam can reduce neuroinflammation and improve cognitive function,[13,14] which explains the significant protective effect of remimazolam in the subgroup analysis of individuals with abnormal lipid profiles in this study.

This dose-dependent protective effect may be attributed to remimazolam's unique pharmacological profile. As a short-acting benzodiazepine sedative, remimazolam is hydrolyzed by tissue carboxylesterase and offers a short elimination half-life, a small steady-state volume of distribution, and a relatively high clearance rate.[35] Remimazolam may have some anti-inflammatory properties and cognitive protection,[14] which are more fully exploited at higher doses, reducing the potential risk of delirium from other anesthetics or insufficient depth of anesthesia. Our study also suggests that the prophylactic effect of remimazolam on POD is dose- and dosing strategy-dependent, and the dose should be individually adjusted according to population characteristics and dosing regimens to maximize its neuroprotective benefits in clinical applications.

Cardiac arrhythmias can lead to cognitive dysfunction[36] and perioperative arrhythmias, to large intraoperative hemodynamic fluctuations.[37] Results from a prospective cohort study have shown that blood pressure fluctuations during surgery are associated with early POD.[38,39] In patients with arrhythmia undergoing cardiac radiofrequency ablation, remimazolam reduces the incidence of hypotensive events and the need for vasopressor medication.[40] Therefore, in the anesthetic management of patients with cardiac arrhythmias, remimazolam may be the optimal choice for reducing POD incidence by stabilizing the hemodynamics and reducing the risk of hypotension.

This study has some limitations. The retrospective design may entail unmeasured confounding factors; therefore, even after adjusting for known confounders, the effect size of remimazolam might still be influenced by residual confounding. The dose–response relationship observed in the study is suggestive; however, confirmation will require further prospective validation.

## Conclusion

Based on current evidence, administering an appropriate dose of remimazolam (total dose ≥10.29 mg; maintenance infusion rate ≥0.51 mg $kg^{-1}$ $h^{-1}$) during general anesthesia in patients with hyperlipidemia reduces POD incidence and severity and improves long-term cognitive function, as confirmed using a target trial emulation. Further multicenter prospective trials are warranted to validate these findings and optimize dosing strategies for metabolically high-risk surgical populations.

## Abbreviations

ASA, American Society of Anesthesiologists; aRD, Adjusted risk difference; BMI, Body mass index; CI, Confidence intervals; HDL-C, High-density lipoprotein-cholesterol; LDL-C, Low-density lipoprotein-cholesterol; OR, Odds ratios; PACU, Post-anesthesia care unit; POD, Postoperative delirium; TC, Total cholesterol; TG, Triglyceride; 3D-CAM, 3-Minute Diagnostic Interview for Confusion Assessment Method.

## Data Sharing Statement

The datasets generated during and/or analyzed during the current study are not publicly available due to the privacy policy but are available from the corresponding authors on reasonable requests.

## Acknowledgments

Assistance with the article: We would like to thank Editage (www.editage.co.kr) for English language editing. We also express our gratitude to all patients who participated in this study and thereby made this work possible.

## Funding

This work was supported by the Hengrui Special Research Grant Program of Sichuan Medical Association (2024HR88) and The Affiliated Hospital of Southwest Medical University Medical Research Project (2025LCYXZX34).

## Disclosure

The authors declare that they have no conflicts of interest.

The abstract of this paper was presented as written communication at the 30th Annual Meeting of the Chinese Society of Anesthesiology, featuring interim findings. The abstract was published in the "Abstract Collection" of the 30th Annual Meeting of the Chinese Society of Anesthesiology. This paper has been uploaded to Social Science Research Network as a preprint: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=5391652

## References

1. Li T, Li J, Yuan L, et al. Effect of regional vs general anesthesia on incidence of postoperative delirium in older patients undergoing hip fracture surgery: the RAGA randomized trial. *JAMA*. 2022;327(1):50–58. doi:10.1001/jama.2021.22647
2. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth*. 2020;125(4):492–504. doi:10.1016/j.bja.2020.06.063
3. Bramley P, McArthur K, Blayney A, McCullagh I. Risk factors for postoperative delirium: an umbrella review of systematic reviews. *Int J Surg*. 2021;93:106063. doi:10.1016/j.ijsu.2021.106063
4. Goldberg TE, Chen C, Wang Y, et al. Association of delirium with long-term cognitive decline: a meta-analysis. *JAMA Neurol*. 2020;77(11):1373–1381. doi:10.1001/jamaneurol.2020.2273
5. Feinkohl I, Janke J, Slooter AJC, Winterer G, Spies C, Pischon T. Metabolic syndrome and the risk of postoperative delirium and postoperative cognitive dysfunction: a multi-centre cohort study. *Br J Anaesth*. 2023;131(2):338–347. doi:10.1016/j.bja.2023.04.031
6. de Dios C, Abadin X, Roca-Agujetas V, et al. Inflammasome activation under high cholesterol load triggers a protective microglial phenotype while promoting neuronal pyroptosis. *Transl Neurodegener*. 2023;12(1):10. doi:10.1186/s40035-023-00343-3
7. Cheng D, Zhang M, Zheng Y, et al. α-Ketoglutarate prevents hyperlipidemia-induced fatty liver mitochondrial dysfunction and oxidative stress by activating the AMPK-pgc-1α/Nrf2 pathway. *Redox Biol*. 2024;74:103230. doi:10.1016/j.redox.2024.103230
8. Kitayama J, Faraci FM, Lentz SR, Heistad DD. Cerebral vascular dysfunction during hypercholesterolemia. *Stroke*. 2007;38(7):2136–2141. doi:10.1161/strokeaha.107.481879
9. Zhao Y, Zhong K, Zheng Y, et al. Postoperative delirium risk in patients with hyperlipidemia: a prospective cohort study. *J Clin Anesth*. 2024;98:111573. doi:10.1016/j.jclinane.2024.111573
10. Heybati K, Deng J, Xie G, et al. Propofol, triglycerides, and acute pancreatitis: a multicenter epidemiologic analysis. *Ann Am Thorac Soc*. 2025;22(2):235–246. doi:10.1513/AnnalsATS.202407-781OC
11. Deljou A, Soleimani J, Martin DP, Schroeder DR, Sprung J, Weingarten TN. Anesthetic management and deep sedation after emergence from general anesthesia: a retrospective cohort study. *Anesth Analg*. 2023;136(6):1154–1163. doi:10.1213/ane.0000000000006470
12. Kim SH, Fechner J. Remimazolam - current knowledge on a new intravenous benzodiazepine anesthetic agent. *Korean J Anesthesiol*. 2022;75(4):307–315. doi:10.4097/kja.22297
13. Zhou L, Shi H, Xiao M, et al. Remimazolam attenuates lipopolysaccharide-induced neuroinflammation and cognitive dysfunction. *Behav Brain Res*. 2025;476:115268. doi:10.1016/j.bbr.2024.115268
14. Shi M, Chen J, Liu T, et al. Protective effects of remimazolam on cerebral ischemia/reperfusion injury in rats by inhibiting of NLRP3 inflammasome-dependent pyroptosis. *Drug Des Devel Ther*. 2022;16:413–423. doi:10.2147/dddt.S344240
15. Fujimoto D, Obata N, Mizobuchi S. Effectiveness of remimazolam in preventing postoperative delirium in elderly patients with proximal femoral fractures. *J Anesth*. 2024;38(4):475–482. doi:10.1007/s00540-024-03339-z
16. Arias JA, Wegner GRM, Wegner BFM, Silva LS, Bezerra FJL, Filardi RGM. Association of remimazolam with delirium and cognitive function: a systematic review and meta-analysis of randomised controlled trials. *Eur J Anaesthesiol*. 2025;42(4):285–297. doi:10.1097/eja.0000000000002107
17. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007;370(9596):1453–1457. doi:10.1016/s0140-6736(07)61602-x
18. Li JJ, Zhao SP, Zhao D, et al. 2023 Chinese guideline for lipid management. *Front Pharmacol*. 2023;14:1190934. doi:10.3389/fphar.2023.1190934
19. Wang SS, Lay S, Yu HN, Shen SR. Dietary Guidelines for Chinese Residents (2016): comments and comparisons. *J Zhejiang Univ Sci B*. 2016;17(9):649–656. doi:10.1631/jzus.B1600341
20. Yang L, Sun DF, Han J, Liu R, Wang LJ, Zhang ZZ. Effects of intraoperative hemodynamics on incidence of postoperative delirium in elderly patients: a retrospective study. *Med Sci Monit*. 2016;22:1093–1100. doi:10.12659/msm.895520
21. Duan W, Zhou CM, Yang JJ, et al. A long duration of intraoperative hypotension is associated with postoperative delirium occurrence following thoracic and orthopedic surgery in elderly. *J Clin Anesth*. 2023;88:111125. doi:10.1016/j.jclinane.2023.111125

22. Forbes SS, Eskicioglu C, Nathens AB, et al. Evidence-based guidelines for prevention of perioperative hypothermia. *J Am Coll Surg*. 2009;209(4):492–503.e1. doi:10.1016/j.jamcollsurg.2009.07.002
23. Cascella M, Bimonte S, Di Napoli R. Delayed emergence from anesthesia: what we know and how we act. *Local Reg Anesth*. 2020;13:195–206. doi:10.2147/lra.S230728
24. Wang J, Lu S, Huang Y, et al. A nurse-administered 3-Minute diagnostic interview for CAM-defined Delirium (3D-CAM Chinese version) in hospitalized elderly patients: a validation study. *Int J Nurs Stud*. 2020;110:103701. doi:10.1016/j.ijnurstu.2020.103701
25. Vasunilashorn SM, Devinney MJ, Acker L, et al. A new severity scoring scale for the 3-minute confusion assessment method (3D-CAM). *J Am Geriatr Soc*. 2020;68(8):1874–1876. doi:10.1111/jgs.16538
26. Seo EH, Lee DY, Kim SG, et al. Validity of the telephone interview for cognitive status (TICS) and modified TICS (TICSm) for mild cognitive imparment (MCI) and dementia screening. *Arch Gerontol Geriatr*. 2011;52(1):e26–30. doi:10.1016/j.archger.2010.04.008
27. Haneuse S, Rotnitzky A. Estimation of the effect of interventions that modify the received treatment. *Stat Med*. 2013;32(30):5260–5277. doi:10.1002/sim.5907
28. Díaz I, Williams N, Hoffman KL, Schenck EJ. Nonparametric causal effects based on longitudinal modified treatment policies. *J Am Stat Assoc*. 2023;118(542):846–857. doi:10.1080/01621459.2021.1955691
29. Young JG, Herńan MA, Robins JM. Identification, estimation and approximation of risk under interventions that depend on the natural value of treatment using observational data. *Epidemiol Methods*. 2014;3(1):1–19. doi:10.1515/em-2012-0001
30. Muñoz ID, van der Laan M. Population intervention causal effects based on stochastic interventions. *Biometrics*. 2012;68(2):541–549. doi:10.1111/j.1541-0420.2011.01685.x
31. van der Laan MJ, Polley EC, Hubbard AE. Super learner. *Stat Appl Genet Mol Biol*. 2007;6:25. doi:10.2202/1544-6115.1309
32. Lin Y, Peng X, Lin X, et al. Potential value of serum lipid in the identication of postoperative delirium undergoing knee/hip arthroplasty: the perioperative neurocognitive disorder and biomarker lifestyle study. *Front Psychiatry*. 2022;13:870317. doi:10.3389/fpsyt.2022.870317
33. Cai W, Shen F, Zhu L, et al. Remimazolam tosylate or propofol and delirium in frail elderly patients after hip surgery: a randomised controlled clinical trial. *Eur J Anaesthesiol*. 2025;42(12):1064–1073. doi:10.1097/eja.0000000000002226
34. Raposeiras-Roubin S, Rosselló X, Oliva B, et al. Triglycerides and residual atherosclerotic risk. *J Am Coll Cardiol*. 2021;77(24):3031–3041. doi:10.1016/j.jacc.2021.04.059
35. Schüttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers: part I. *Pharmacokinetics Clin Pharmacodynamics Anesthesiol*. 2020;132(4):636–651. doi:10.1097/aln.0000000000003103
36. Diener HC, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial fibrillation and cognitive function: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73(5):612–619. doi:10.1016/j.jacc.2018.10.077
37. Melduni RM, Koshino Y, Shen WK. Management of arrhythmias in the perioperative setting. *Clin Geriatr Med*. 2012;28(4):729–743. doi:10.1016/j.cger.2012.08.006
38. Hirsch J, DePalma G, Tsai TT, Sands LP, Leung JM. Impact of intraoperative hypotension and blood pressure fluctuations on early postoperative delirium after non-cardiac surgery. *Br J Anaesth*. 2015;115(3):418–426. doi:10.1093/bja/aeu458
39. Radinovic K, Markovic Denic L, Milan Z, Cirkovic A, Baralic M, Bumbasirevic V. Impact of intraoperative blood pressure, blood pressure fluctuation, and pulse pressure on postoperative delirium in elderly patients with Hip fracture: a prospective cohort study. *Injury*. 2019;50(9):1558–1564. doi:10.1016/j.injury.2019.06.026
40. Yim S, Choi CI, Park I, Koo BW, Oh AY, Song IA. Remimazolam to prevent hemodynamic instability during catheter ablation under general anesthesia: a randomized controlled trial. *Can J Anaesth*. 2024;71(8):1067–1077. doi:10.1007/s12630-024-02735-z