Research Square

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A Randomized Controlled Trial Exploring Remimazolam Besylate–Based Anesthesia in Enhanced Recovery After Liver Transplantation

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Abstract

Background: Previous studies have demonstrated that remimazolam offers more stable hemodynamics and faster postoperative recovery than propofol. However, its efficacy in reducing postreperfusion syndrome (PRS) and facilitating Enhanced Recovery After Surgery (ERAS) after liver transplantation remains unclear.

Methods: This was a prospective, single-center, single-blind, double-arm, randomized controlled trial. Patients were randomized to receive remimazolam (induction 0.2–0.4 $mg.kg^{-1}$, maintenance 1–3 $mg.kg^{-1}.h^{-1}$) or propofol (induction 1–2 $mg.kg^{-1}$, maintenance 4–12 $mg.kg^{-1}.h^{-1}$). Primary outcome: PRS. Secondary outcomes: postoperative mechanical ventilation duration, ICU length of stay, hypotension during anesthesia induction, and postoperative delirium.

Results: In this ITT analysis (N=120, 60 per group), The incidence of PRS was 16.7% (10/60) in the remimazolam group vs. 25.0% (15/60) in the propofol group (P = 0.264). Post-hoc analysis of these events showed that the statistical power did not meet expectations, indicating that conclusions regarding the primary outcome measure remain inconclusive. Among prespecified secondary outcomes, remimazolam was associated with a lower incidence of hypotension during anesthesia induction (30.0% vs. 50.0%; P=0.025). In exploratory analyses, remimazolam showed signals of reduced adrenaline requirement within 5 min after reperfusion (P=0.034), and an exploratory subgroup interaction for portal vein occlusion time was observed (P=0.016). No other secondary outcomes differed significantly.

Conclusions:

Remimazolam did not significantly reduce the PRS incidence compared with propofol in this RCT. This trial was underpowered, rendering the primary conclusion inconclusive. Among the prespecified secondary endpoints, remimazolam was associated with a significantly lower incidence of hypotension during anesthesia induction, suggesting potential hemodynamic benefits during anesthetic induction. In exploratory analyses, remimazolam showed signals of reduced adrenaline requirements within 5 min after portal vein unclamping. No significant differences were observed in postoperative outcomes, including mechanical ventilation duration, ICU length of stay, or delirium. The exploratory subgroup interaction for portal vein occlusion time should be considered hypothesis-generating only. The observed event rates were lower than anticipated, which should be taken into account when interpreting the trial results. Given the limited statistical power and inconclusive primary outcome, the findings—particularly the signals observed in secondary and exploratory endpoints—require validation in adequately powered, confirmatory trials with larger sample sizes.

Trial registration: chictr.org.cn ChiCTR2500095774. Registered on January 13, 2025.

Background

Liver transplantation is an effective treatment for patients with acute liver failure and end-stage liver disease. As a country with a high burden of liver disease, China has seen a steady increase in the number of liver transplantations performed. Implementing the Enhanced Recovery After Surgery (ERAS) pathway is vital to accelerate postoperative recovery, reduce postoperative complications, and shorten hospital stays.

During liver transplantation, when the donor liver is reperfused, a significant drop in blood pressure is often observed. This phenomenon is known as postreperfusion syndrome (PRS), which may lead to severe cardiovascular system complications and metabolic disorders. Previous studies have shown that the incidence of PRS varies widely (ranging from 12% to 77%)[1–6]. An increasing number of studies have indicated that PRS is associated with significantly adverse postoperative outcomes, including prolonged postoperative mechanical ventilation, postoperative delirium, severe acute kidney failure, major cardiovascular events, and even increased in-hospital mortality[4, 7]. Therefore, we believe that reducing the incidence of PRS can improve patient outcomes, lower the occurrence of adverse events after liver transplantation, and promote the development of ERAS.

Liver transplant patients typically have impaired circulatory reserve, abnormal vascular tone regulation, and volume distribution imbalance before surgery, often accompanied by cirrhotic cardiomyopathy and cardiorespiratory complications, making them poorly tolerant to intraoperative hemodynamic fluctuations. Propofol is currently the most commonly used sedative drug for general anesthesia. However, propofol causes dose-dependent cardiovascular and respiratory depression. Its cardiovascular effects include hypotension—due to reduced cardiac contractility and peripheral vasodilation—and bradycardia from increased vagal tone. Respiratory effects mainly involve respiratory depression caused by suppression of the respiratory center[8]. Remimazolam is a newly approved, ultra-short-acting benzodiazepine for general anesthesia and sedation. It is rapidly metabolized by nonspecific tissue esterases into inactive, safe, and predictable metabolites—enabling reliable use even with prolonged infusion[9–12]. Multiple studies show that remimazolam is noninferior to propofol in anesthesia efficacy and safety—and is associated with lower rates of hypotension, bradycardia, and respiratory depression[13–17]. Therefore, we hypothesized that remimazolam may reduce the incidence of PRS, decrease postoperative adverse events, and improve patient outcomes.

This single-center, single-blind, randomized controlled trial was designed to investigate the effect of remimazolam on the PRS incidence during liver transplantation. We hypothesized that replacing propofol with remimazolam intraoperatively may reduce PRS incidence and support ERAS implementation by decreasing postoperative adverse events.

Methods

Trial design and ethics

This study followed the CONSORT 2025 guidelines for reporting. A total of 120 participants were enrolled between February 3, 2025, and February 28, 2026 (**Figure 1**). The study protocol is available as a

preprint on medRxiv (https://www.medrxiv.org/content/10.64898/2026.07.15.26358138v1). This trial was approved by the Ethics Committee of Qingdao University Affiliated Hospital (No.: QYFYEC2024-258). The study was conducted in accordance with the Declaration of Helsinki, and all participants provided written informed consent prior to enrollment.

This was a prospective, single-center, single-blind, double-arm, randomized controlled trial. We enrolled 120 patients scheduled for liver transplantation who met the inclusion criteria to evaluate remimazolam-based anesthesia in liver transplantation.

Participants

Inclusion and exclusion criteria

Patients aged 18–60 years who plan to undergo allogeneic liver transplantation under general anesthesia

Patients who underwent living donor liver transplantation, split liver transplantation, secondary liver transplantation, allergy to remimazolam, continuous renal replacement therapy before transplantation, acute liver failure, severe circulatory system instability (hypertension, coronary heart disease, severe arrhythmia), multiple organ transplantation, preoperative hepatic encephalopathy, or consciousness disorders were excluded from the study.

Outcomes

The primary outcome was PRS incidence. PRS was defined as a >30% decrease in mean arterial pressure compared with baseline within 5 min after reperfusion, lasting longer than 1 min.

The secondary outcomes included the duration of invasive mechanical ventilation after surgery, length of stay in the ICU, incidence of hypotension during anesthesia induction, and incidence of postoperative delirium. Postoperative delirium is defined as an acute, fluctuating disturbance in consciousness, attention, and cognitive function occurring after surgery, assessed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

In addition, the duration of surgery, blood loss, perioperative complications (type, severity, treatment details, date of occurrence, and outcome), postoperative laboratory test results, and in-hospital mortality were collected for intergroup comparison.

Anesthesia and intervention

All participants received standard anesthesia care according to the hospital's established anesthesia protocol for liver transplantation. Upon arrival in the operating room, routine monitoring included pulse oximetry, noninvasive and invasive arterial blood pressure (via radial artery), electrocardiography, and bispectral index (BIS). After anesthesia induction, a central venous catheter (CVC) and sheath were inserted via the internal jugular vein, and central venous pressure (CVP) was monitored. Routine

monitoring included nasopharyngeal temperature and urine output; when clinically indicated, a pulmonary artery catheter (Swan-Ganz catheter) was used to measure pulmonary artery pressures.

In the propofol group, anesthesia induction consisted of propofol (1–2 mg·kg⁻¹), sufentanil (0.1–0.3 μg·kg⁻¹), and either cisatracurium besylate (0.15–0.2 mg·kg⁻¹) or rocuronium (0.6–1 mg·kg⁻¹). Endotracheal intubation was performed thereafter. In the remimazolam group, remimazolam (0.2–0.4 mg·kg⁻¹) replaced propofol for anesthesia induction; all other drugs and procedures were identical to those in the propofol group. During surgery, propofol (4–12 mg·kg⁻¹·h⁻¹) was used for sedation maintenance in the propofol group, and remimazolam (1–3 mg·kg⁻¹·h⁻¹) in the remimazolam group. Both groups received cisatracurium besylate for neuromuscular blockade. Intraoperative analgesia was maintained with intermittent intravenous boluses of sufentanil (5–10 μg per bolus), administered at the discretion of the attending anesthesiologist based on hemodynamic responses—specifically, HR or MAP increasing by more than 20% above baseline—or clinical signs of inadequate analgesia. The total intraoperative sufentanil dose was recorded. Mechanical ventilation was standardized across groups with a tidal volume of 6–8 mL·kg⁻¹, PEEP of 3–5 cmH_2O, plateau pressure <30 cmH_2O, respiratory rate of 10–16 breaths·min⁻¹, and fractional inspired oxygen (FiO_2) of 50%–70%.

Intraoperative fluid management was guided by the attending anesthesiologist's clinical judgment, with 5% albumin solution administered to maintain hemodynamic stability. Fluid boluses (250–500 mL of 5% albumin) were administered in response to hypotension (MAP < 65 mmHg) or tachycardia (HR > 100 beats·min⁻¹), provided these were not attributable to inadequate anesthesia. Central venous pressure (CVP) and pulse pressure variation (PPV), when available, served as adjunctive hemodynamic parameters. Total fluid volumes (crystalloids, colloids, and blood products) were recorded for each patient. Meropenem was administered intravenously 30 minutes before surgery to prevent surgical site infection. If necessary, blood transfusion was performed to maintain the patient's hemoglobin level at 7-10 $g.dl^{-1}$ during the operation. Blood products, such as prothrombin complex or fibrinogen, were infused intraoperatively to maintain appropriate coagulation function. Basiliximab was administered to induce immunosuppression immediately after surgical incision, and intravenous corticosteroids were typically given before portal vein reperfusion to initiate immunosuppression. Vasoactive drugs delivered via infusion pump included norepinephrine and dopamine; adrenaline, atropine, and ephedrine were administered intravenously as needed based on the patient's hemodynamic status. Although multiple vasoactive drugs were permitted per institutional protocol, our primary focus was adrenaline administration within 5 minutes after portal vein unclamping, as it reflects immediate rescue therapy for PRS. Use of all other vasoactive drugs was recorded and compared between groups. For PRS-specific management, a reactive (not prophylactic) bolus of adrenaline (10 μg) was administered when mean arterial pressure (MAP) decreased by ≥30% from baseline. Additional boluses were repeated as required according to hemodynamic response. Prophylactic adrenaline administration before portal vein unclamping was avoided in both groups. Invasive arterial blood pressure was recorded before portal vein unclamping, immediately after unclamping, and at 10, 20, 30, 40, 50, and 60 seconds, then at 2, 3, and 5 minutes after unclamping.

Patients were transferred to the ICU after surgery for postoperative monitoring and management. Upon ICU admission, critical care physicians assessed vital signs and initiated fluid resuscitation, hemodynamic optimization, and internal environment stabilization. Sedative medications were administered only if clinically indicated—specifically, following assessment of the patient's level of consciousness, agitation, and comfort after sedation cessation—rather than based solely on time since awakening. During ICU stay, registered nurses provided continuous monitoring and documented all vital signs hourly. The Richmond Agitation–Sedation Scale (RASS) and Confusion Assessment Method for the ICU (CAM-ICU) were performed hourly to evaluate mental status. When patients met predefined ICU discharge criteria, they were transferred to the general ward for continued recovery until fulfillment of hospital discharge criteria.

Sample size calculation

Sample size and power calculations were based on a superiority design for the primary outcome. The sample size was determined according to the incidence of post-reperfusion syndrome (PRS). Drawing on data from a previous retrospective analysis[6], the PRS incidence during propofol-based anesthesia was approximately 43%, whereas during remimazolam-based anesthesia it was 15% (derived from our preliminary experiment).

Assuming a two-sided significance level (α) of 0.05 and 90% statistical power, the calculated sample size was 50 participants per group. Accounting for a 20% attrition rate, the final planned sample size was 60 participants per group.

Randomization and blinding

Randomization used sealed envelopes. An independent statistician generated a 1:1 allocation sequence via computer randomization. The study coordinator opened the envelope immediately before surgery. Because remimazolam and propofol differ visibly, anesthesiologists and assistants were unblinded to group assignment—but unaware of the study's primary objectives. Patients, outcome assessors, data collectors (trained and uninvolved in perioperative care), and the statistician conducting primary analyses were all blinded. No communication occurred between anesthesiologists and investigators during data collection or analysis.

Unblinding: For each patient, after completion of the 30-day postoperative follow-up period, all data underwent quality review and were entered into the database. Upon database lock, the first unblinding (i.e., disclosure of group assignments) was performed.

Statistical methods

In August 2025, after enrolling 80 patients, our statistician reanalyzed the primary outcome rates: 28% in the propofol group (lower than the 43% assumed for sample size calculation, based on prior retrospective analysis[6]) and 18% in the remimazolam group (consistent with our pilot study), yielding a 10% between-group difference. To maintain the originally targeted statistical power assuming a 28%

absolute risk difference, an additional 662 patients would have been required. Given the enrollment pace and the lower-than-anticipated treatment effect, the steering committee decided to conclude recruitment as planned—enabling timely dissemination of results.

Quantitative data were assessed for normality using the Shapiro–Wilk test. Normally distributed continuous variables were analyzed using the independent samples *t*-test and are reported as mean ±SD. Non-normally distributed variables were compared using the Mann–Whitney *U*-test and summarized as median (IQR [range]). Categorical variables were described using numbers (proportions) and analyzed using the chi-square test or Fisher's exact test. Repeated-measures ANOVA was used to evaluate between-group and within-group differences. The Mauchly's sphericity test was performed. If the sphericity assumption was violated, modified statistical tests, such as Greenhouse-Geisser and Huynh-Feldt, were used. If there was a significant interaction between time and group, post-hoc Bonferroni corrections were used to correct type I errors. Missing data were excluded from the analysis.

Based on the pre-determined and clinical concerns, we conducted the following subgroup exploratory analyses: (1) age> 45 years vs. ≤45 years; (2) sex; (3) Child-Pugh Score; (4) MELD score; (5) portal vein occlusion time; (6) graft cold ischemia time; (7) graft recipient weight ratio (GRWR). Subgroup analyses based on clinical covariates were performed using univariate logistic regression models to explore the consistency of the treatment effect between propofol and remimazolam across different subgroups. Subgroup analyses were used solely for exploratory description. Although statistical tests for interaction between intervention and subgroup variables were conducted, given the likely low incidence of the primary outcome in this study, the confidence in these interaction estimates may be limited.

All statistical analyses were performed using SPSS version 31.0.2.0 (IBM, Armonk, NY, USA, www.ibm.com/products/spss-statistics), with two-tailed P-values < 0.05 considered statistically significant. All figures in the text were created using GraphPad Prism, version 10.6.0 (890)(GraphPad Software, San Diego, California USA, www.graphpad.com).

Results

A total of 315 patients were assessed for eligibility between February 3, 2025, and February 28, 2026. Before randomization, 195 patients were excluded from the study. A total of 120 patients were randomly allocated: 60 to the remimazolam group and 60 to the propofol group. Sixty patients per group were included in the intention-to-treat analysis, and no patients withdrew from the study for any reason. Detailed participant information is presented in **Figure 1**.

The baseline characteristics, underlying liver disease, preoperative laboratory results, and donor-related information were well balanced between the remimazolam and propofol groups (**Table 1**). Surgical parameters including operative time, intraoperative fluid management, and blood product transfusion volumes were comparable between the two groups, indicating good cohort matching in this study (**Table 2**).

The incidence of postreperfusion syndrome and the use of vasoactive drugs

The overall PRS incidence was 20.83% (25/120). The incidence did not differ significantly between groups (remimazolam 16.67% vs. propofol 25.00%; P = 0.264). However, the study was severely underpowered to detect this difference (post hoc power 23.2%), rendering the primary outcome inconclusive.

Repeated-measures ANOVA on MAP values at 11 predefined time points showed a significant time effect within both groups (F = 10.89, P < 0.001), but no significant time × group interaction (F = 0.54, P = 0.859), indicating comparable MAP trajectories between the two anesthetic regimens. Bonferroni-corrected pairwise comparisons found no intergroup MAP differences at any individual time point (**Figure 2**).

We also compared the use of vasoactive drugs within 5 minutes after portal vein unclamping between the two groups. In post-hoc exploratory analyses, there were no significant differences in the use of norepinephrine, dopamine, ephedrine, or atropine. For adrenaline, we recategorized the data as a binary variable (received vs. not received) due to the predominance of zero values in both groups. Adrenaline was administered to 25/60 (42%) patients in the propofol group and 19/60 (32%) in the remimazolam group. Among the full cohort, the median(IQR [range]) dose was 0 (0–20 [0–90]) μg in the propofol group and 0 (0–10 [0–30]) μg in the remimazolam group (P = 0.034). Visual comparisons of vasoactive drug usage are presented in **Figure 3**. Given the exploratory nature of these analyses and the lack of adjustment for multiple comparisons, this adrenaline-related finding should be interpreted with caution.

Incidence of hypotension during the induction period

Our study collected and analyzed baseline MAP before anesthesia induction, as well as the highest and lowest MAP values within 10 minutes after induction. The incidence of hypotension after anesthesia induction was statistically evaluated. The incidence of hypotension during induction was 50.0% (30/60) in the propofol group and 30.0% (18/60) in the remimazolam group, with a statistically significant difference between the two groups (χ^2=5.00, df=1, p=0.025).

Additionally, the mean±SD of $\Delta MAP_{max\text{-}baseline}$ (change in maximum MAP during the first 10 min after induction compared to baseline MAP) was 3.5±9 in the remimazolam group and 1.5±11.75 in the propofol group, with no statistically significant difference between the two groups (P = 0.230). In contrast, the mean±SD of $\Delta MAP_{min\text{-}baseline}$ (change in minimum MAP during the first 10 minutes after induction compared to baseline MAP) was 17.0±15.25 in the remimazolam group and 22.0±16.75 in the propofol group, with statistically significant difference between the groups (p = 0.011, **Table 3**).

Postoperative outcomes

We collected postoperative patient data for analysis, as detailed in **Table 3**.

The postoperative mechanical ventilation duration was 21 (16–24 [10–74]) hours in the remimazolam group and 22 (17–32 [10–76]) hours in the propofol group, with no statistically significant difference between the two groups (*P* = 0.158). The median ICU length of stay was 67 (43-90 [29-215]) h in the remimazolam group and 64 (43-82 [25-562]) h in the propofol group, with no statistically significant difference between the groups (P = 0.767). The incidence of postoperative delirium (POD) was 50.0% (30/60) in the remimazolam group and 38.3% (23/60) in the propofol group, with no statistically significant difference between the groups (P = 0.198).

The maximum laboratory values within 7 days after surgery are summarized in **Table 3**. No statistically significant differences were observed between the remimazolam group and propofol group in the maximum values of creatinine, AST, ALT, total bilirubin, hs-cTnI, BNP, and NT-proBNP within seven days after surgery (all P > 0.050). There was also no statistically significant difference in the incidence of postoperative complications between the two groups.

Exploratory Subgroup analysis

We conducted an exploratory subgroup analysis to explore the potential effect modifiers between propofol and remimazolam treatment effects(**Figure 4**).

subgroup analysis revealed no significant intergroup differences in the primary outcome across the overall population (OR = 0.60, 95% CI: 0.24–1.47, P = 0.264). A statistically significant interaction was observed for portal vein occlusion time (interaction, P = 0.016). Specifically, among patients with portal vein occlusion time ≤35 min, the incidence of the primary outcome was significantly lower in the remimazolam group than in the propofol group (7.5% vs. 28.6%, OR = 0.20, 95% CI: 0.05–0.81, P = 0.024); however, no significant difference was found in patients with an occlusion time >35 min (35.0% vs. 20.0%, OR = 2.15, 95% CI: 0.56–8.25, P = 0.263). Cold ischemia time (interaction, P = 0.075) and MELD score (interaction, P = 0.066) also showed near-significant interactions. Among patients with a cold ischemia time ≤6 h, the event rate was significantly lower in the remimazolam group (19.0% vs. 57.1%, OR = 0.18, 95% CI: 0.04–0.81, P = 0.025); however, no clear difference was observed in patients with longer ischemia times. In patients with MELD scores ≤18, a trend toward reduced events with remimazolam was also noted (10.6% vs. 26.1%, OR = 0.34, 95% CI: 0.11–1.05, P = 0.061). No significant interactions were found for age, sex, Child-Pugh score, or GRWR (all interaction P values > 0.05), and no significant intergroup differences were observed within these subgroups.

Discussion

In this randomized controlled trial of remimazolam versus propofol for liver transplantation, remimazolam did not significantly reduce PRS incidence (16.7% vs. 25.0%). However, the study was severely underpowered (23.2% power), so this null result is inconclusive—not evidence of equivalence or non-superiority. Remimazolam was linked to less hypotension during induction—a prespecified secondary endpoint. In post-hoc analyses, the remimazolam group showed reduced adrenaline use within 5 minutes of portal vein unclamping; however, this exploratory finding is hypothesis-generating,

not conclusive. No differences emerged between groups in postoperative ventilation time, ICU stay, or delirium. While these results hint at early hemodynamic benefits, they require confirmation in larger, prospective trials.

PRS is associated with adverse clinical outcomes, including early graft dysfunction, primary nonfunction, acute kidney injury, and hemodynamic instability leading to mortality—thereby compromising both short- and long-term patient survival[2, 18–21]. Measures to reduce the occurrence of PRS include the use of vasoactive drugs, NRP or NMP during the preservation of the donor liver[22–24], and techniques such as portal venous bloodletting. Although substances such as alpha-lipoic acid and ascorbic acid have been studied to protect liver function and reduce the occurrence of PRS, few clinical studies have clearly proven their effectiveness[25, 26]. Remimazolam, an ultra-short-acting benzodiazepine drug, activates GABAa receptors and is metabolized by non-specific esterase (mainly carboxylesterase 1, CES1), with the metabolite (CNS7054) being inactive[27]. Preclinical studies have shown that it protects the liver from ischemia/reperfusion injury by inhibiting the MAPK/ERK pathway and reducing the release of proapoptotic and inflammatory mediators (TNF-α and IL-6)[28].

In this trial, remimazolam did not significantly reduce the incidence of PRS compared with propofol. This null finding reflects inadequate statistical power and therefore precludes definitive interpretation of the primary endpoint. Moreover, PRS pathogenesis involves multiple interdependent determinants, including donor graft quality, cold ischemic duration, recipient preoperative MELD score, and surgical variables. [29–31], Moreover, center-specific PRS management protocols may influence our primary outcome. Prior to portal vein reperfusion, norepinephrine infusion is titrated upward to mitigate profound hypotension. When standard vasoactive drugs support fails to stabilize hemodynamics, intravenous adrenaline is administered as a rescue intervention to maintain MAP above the threshold required to prevent PRS. This proactive hemodynamic strategy may have contributed to a lower-than-expected PRS incidence in the propofol group compared with historical reports, thereby compromising statistical power.

Exploratory analyses showed reduced adrenaline use within 5 minutes of portal vein unclamping in the remimazolam group—suggesting milder hemodynamic suppression than propofol during acute reperfusion. This finding is hypothesis-generating and requires validation in a larger trial. Subgroup analyses revealed that remimazolam's effect on PRS incidence was context-dependent: it significantly lowered PRS rates in patients with portal vein clamping time ≤ 35 min (P for interaction = 0.016) and showed a near-significant protective effect in those with cold ischemia time ≤ 6 h (P for interaction = 0.075) and MELD score ≤ 18. A shorter clamping time generally reflects less surgical complexity, reduced visceral congestion, and milder reperfusion metabolic disturbance[7, 32]; under these favorable conditions, remimazolam's weaker vasodilation and minimal negative inotropy may translate into a clinically observable reduction in PRS risk. Beyond 35 minutes of clamping, this protective effect disappears, likely because the hemodynamic impact of surgical manipulation and major fluid shifts (non-anesthetic factors) outweighs the modest benefit of sedative choice[33]. Similarly, when cold ischemia exceeded 6 hours, the incidence of PRS was nearly identical between groups, possibly because prolonged ischemia inflicts irreversible damage that exceeds remimazolam's regulatory capacity[28, 34,

35]. Notably, both subgroup interactions (P = 0.016 and P = 0.075) were nominal, unadjusted for multiple testing, therefore, they remain strictly exploratory and hypothesis-generating. Future studies should be designed to validate these preliminary observations and to define the optimal clinical context for remimazolam use in liver transplantation.

Previous studies have reported that remimazolam shortens awakening time and reduces delirium risk[36, 37]. In contrast, we did not observe these advantages in our liver transplant patients; indeed, the incidence of postoperative delirium was numerically higher in the remimazolam group (50.0% vs. 38.3%), although this difference was not statistically significant (P = 0.198). This discrepancy may be attributable to several factors. First, the trial was sized for the primary endpoint of PRS rather than for detecting differences in postoperative neurological outcomes, and the underpowering limits the conclusiveness of these secondary findings. Second, in patients with hepatic dysfunction, reduced plasma levels of non-specific esterases (including carboxylesterase 1, CES1) and albumin may slow remimazolam clearance, potentially offsetting its pharmacokinetic advantage of rapid offset[38, 39]. However, this remains speculative, as we did not measure serial drug concentrations or enzymatic activity. Third, this study did not routinely use flumazenil, and whether pharmacological antagonism can reduce emergence delirium remains to be further investigated.

The lack of significant differences in ICU length of stay, duration of mechanical ventilation, and total hospitalization likely reflects the multifactorial nature of these outcomes, which are influenced by donor graft quality, surgical complexity, and recipient baseline status—factors that overwhelm any modest effect of sedative choice alone. Future studies with adequate power, pharmacokinetic monitoring protocols are needed to evaluate whether remimazolam confers advantages in postoperative recovery in this specific population.

This study had several limitations. First and most importantly, the trial was severely underpowered (post hoc power 23.2%) for the primary outcome, as the sample size calculation was based on an overestimated effect size. This limits the conclusiveness of the negative PRS finding and precludes definitive interpretation of all secondary and exploratory analyses. Second, this was a single-center study with a relatively small sample size, which may limit the generalizability of our findings to other centers with different patient populations and perioperative protocols. Third, the dosing regimen of remimazolam was derived from case reports and the drug label, which provides limited guidance for patients with severe hepatic dysfunction. Although the label suggests no dose adjustment for mild-to-moderate hepatic impairment, the appropriate dose for end-stage liver disease patients remains unclear, and we did not employ pharmacokinetic monitoring to guide dosing. Fourth, we did not measure plasma carboxylesterase 1 (CES1) activity or remimazolam concentrations, limiting our ability to correlate drug exposure with clinical outcomes. These pharmacokinetic considerations warrant further investigation in future studies.

Conclusion

Remimazolam did not significantly reduce the PRS incidence compared with propofol in this RCT. This trial was underpowered, rendering the primary conclusion inconclusive. Among the prespecified secondary endpoints, remimazolam was associated with a significantly lower incidence of hypotension during anesthesia induction, suggesting potential hemodynamic benefits during anesthetic induction. In exploratory analyses, remimazolam showed signals of reduced adrenaline requirements within 5 min after portal vein unclamping. No significant differences were observed in postoperative outcomes, including mechanical ventilation duration, ICU length of stay, or delirium. The exploratory subgroup interaction for portal vein occlusion time should be considered hypothesis-generating only. The observed event rates were lower than anticipated, which should be taken into account when interpreting the trial results. Given the limited statistical power and inconclusive primary outcome, the findings—particularly the signals observed in secondary and exploratory endpoints—require validation in adequately powered, confirmatory trials with larger sample sizes.

Declarations

Ethical approval and consent to participate

This randomized controlled trial was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (Project Number: QYFYEC2024-258). Each participant signed a written version of the informed consent form before the intervention and agreed to have their anonymized trial data analyzed and published.

Consent for publication

Not applicable.

Data availability statement

The original data were stored in the ResMan (www.medresman.org). The anonymized individual participant data that support the findings of this study are not publicly available because of privacy or ethical restrictions but can be requested from the corresponding author.

Conflicts of interest disclosure

All authors declare no competing interests.

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Authorship Contribution Statement

X. L. Ge: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original manuscript. **Y. Wang**: Data curation, Investigation, Validation. **B. Y. Kong**: Software, Visualization, Investigation. **H.**

Dong: Investigation, Data curation. **A. J. Liu**: Validation, Data curation, and investigation. **X. J. Hao**: Resources (pharmaceutical interventions and medication safety) and methodology (pharmacological data interpretation and drug–drug interaction assessment). **F. Wang**: Resources (patient enrollment, clinical assessments, and organ transplantation-related evaluations) and validation (clinical data verification). **L. Lyu**: Supervision, Project administration, funding acquisition, writing – review and editing, and final manuscript approval. All authors have read and approved the final manuscript and agree to be accountable for all aspects of this study.

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Tables

Table1. Characteristics of the subjects and donors	Remimazolam (n=60)	Propofol (n=60)	p Value
Age;y	48.40±8.16	48.58±7.47	0.510
Sex;male	45 (75%)	45 (75%)	1.000
BMI;kg.m^{-2}	23.80±4.43	24.35±3.63	0.463
CHILD Score	8 (7-10 [5-13])	8 (7-9 [5-12])	0.819
MELD Score	12.9 (10.7-17.4 [9.4-28.1])	13.7 (11.2-17.0 [9.4-32.0])	0.168
Graft recipient weight ratio(GRWR);%	2.24±0.54	2.20±0.53	0.711
Smoker	18(30%)	14(23%)	0.409
Drinker	21(35%)	15(25%)	0.232
ASA classification			
	42(70%)	38(63%)	0.439
	18(30%)	22(37%)	0.439
Primary diagnosis			
Chronic hepatitis	40(67%)	41(68%)	0.845
Hepatic cancer	21(35%)	25(42%)	0.453
Alcoholic cirrhosis	9(15%)	8(13%)	0.793
Metabolic disease	9(15%)	9(15%)	1.000
Cholestatic disease	1(2%)	2(3%)	1.000
Other	11(18%)	12(20%)	0.817
Comorbidities			
Anaphylactic history	4(7%)	5(8%)	0.770
Kidney disease	0	1(2%)	1.000
Preoperation laboratory data			
Creatinine;μmol/L	54 (44-76 [28-173])	60 (51-77 [25-375])	0.112
AST;U/L	47 (34-65 [17-132])	42 (32-57 [22-396])	0.364
ALT;U/L	38 (23-46 [10-89])	30 (21-37 [11-132])	0.065
TBil,Total bilirubin;μmol/L	48 (22-104 [8-597])	42 (24-114 [4-856])	0.937
DBil,Direct bilirubin;μmol/L	20 (9-85 [2-471])	21 (11-56 [2-338])	0.798

Albumin;g/L	34 (29-39 [22-45])	33 (30-37 [25-51])	0.821
APTT;s	41 (35-50 [24-97])	43 (35-53 [23-142])	0.546
PT;s	17 (15-22 [12-38])	18 (15-22 [11-63])	0.567
INR	1.4 (1.2-1.9 [0.9-3.9])	1.6 (1.3-1.9 [1.0-8.2])	0.329
Hemoglobin;g/L	103 (81-122 [31-188])	87 (72-120 [54-167])	0.072
Platelets;10^9/L	65 (41-125 [25-251])	54 (35-96 [21-212])	0.139
Fibrinogen;g/L	1.7 (1.0-2.3 [0.6-4.4])	1.6 (1.0-2.3 [0.5-4.8])	0.633
hs-cTnI;ng/mL	0.04 (0.02-0.08 [0.02-0.53])	0.03 (0.02-0.04 [0.02-0.15])	0.233
BNP;ng/L	64 (22-173[10-762])	67 (27-118[10-962])	0.954
NT-ProBNP;ng/L	69 (24-110[6-509])	126 (55-212[15-340])	0.120
History of liver-related surgery	18(30%)	17(28%)	0.841
Donor Information			
DCD,donation after cardiac death	60(100%)	60(100%)	1.000
Cold ischemia time;min	310 (310-355 [190-430])	310 (250-370 [130-430])	0.394
Weight of the donor liver;g	1495 (1275-1763 [890-2330])	1535 (1258-1653 [985-2490])	0.453
Cause of death			
Trauma	15(25%)	22(37%)	0.167
Cerebrovascular accident	38(63%)	33(55%)	0.353
Other	7(12%)	5(8%)	0.543

Table 1. Preoperative characteristics of liver transplant patients included in the study, randomly allocated to propofol- or remimazolam-based anesthesia. Values are expressed as mean±SD, median(IQR [range]), or number(proportion).

Table2. Intraoperative characteristics	Remimazolam (n=60)	Propofol (n=60)	p Value
Anesthesia time;min	535 (496-584 [415-815])	555 (500-599 [425-760])	0.162
Surgery time;min	458 (418-510 [345-735])	470 (420-519 [325-665])	0.592
Portal occlusion time;min	34 (31-38 [26-60])	34 (29-40 [24-62])	0.943
Blood loss;ml	400 (300-600 [200-2000])	500 (400-800 [300-2200])	0.149
Life signs (before anesthesia induction)			
SpO2;%	99 (98-100 [91-100])	99 (98-100 [89-100])	0.810
MAP;mmHg	87±15.5	90±17.75	0.161
HR;bpm	77±17	78±23	0.886
Intraoperative fluid management;ml			
Crystalloid solution	3500 (3000-4000[1500-5500])	3000 (2500-3688 [1500-6000])	0.128
Sodium Bicarbonate	500 (500-750 [250-1000])	500 (500-750 [250-1250])	0.867
Intraoperative blood product management			
Autologous blood;ml	300 (0-720 [0-1200])	250 (0-400 [0-1960])	0.216
RBC,Red Blood Cell;U	3.5 (0-6.0 [0-16.5])	4.0 (2.0-7.0 [0-15.5])	0.131
Cold plasma concentrate;U	0 (0-9.5 [0-30])	0 (0-10 [0-20])	0.322
Plasma;ml	550 (370-800 [0-1260])	540 (400-640 [200-1910])	0.946
Platelets;Therapeutic dose	1 (0-1 [0-2])	1 (0-1 [0-10])	0.522
Fibrinogen;g	2.0 (1.5-2.5 [0-5.5])	2.0 (1.5-2.5 [0-6.5])	0.955
Prothrombin complex;U	1000 (0-1200 [0-2000])	1000 (0-1000 [0-1800])	0.496
Albumin;g	160 (140-200 [100-290])	160 (140-180 [100-240])	0.285
Drug use during surgery			
Tranexamic acid;g	2.5 (0.8-2.5 [0-5.5])	2.5 (0-2.5 [0-4.5])	0.295

Immunoglobulin;IU	10000 (2000-10000 [2000-10000])	10000 (2000-10000 [2000-12000])	0.871
Methylprednisolone;mg	520 (480-600 [160-800])	540 (500-600 [440-780])	0.344

Table 2. Intraoperative characteristics in the remimazolam and propofol groups. Skewed continuous data are expressed as median(IQR [range]); normally distributed data are shown as mean±SD.

Table3. Primary and secondary outcomes	Remimazolam (n=60)	Propofol (n=60)	p Value
Primary outcomes			
PRS,postreperfusion syndrome	10(17%)	15(25%)	0.264
Secondary outcomes			
postoperative mechanical ventilation duration;h	21 (16-24 [10-74])	22 (17-32 [10-76])	0.158
ICU length of stay;h	67 (43-90 [29-215])	64 (43-82 [25-562])	0.767
POD,Postoperative delirium	30(50%)	23(38%)	0.198
hypotension during anesthesia induction	18(30%)	30(50%)	0.025
MAP;mmHg			
Baseline MAP	87±12.6	90±12.5	0.161
$\Delta MAP_{max\text{-}baseline}$	3.5±9	1.5±11.75	0.230
$\Delta MAP_{min\text{-}baseline}$	17.0±15.25	22.0±16.75	0.011
Dose of vasoactive drugs within five minutes after unclamping			
Noradrenaline;μg	180 (76-335 [1-770])	235 (121-400 [21-700])	0.175
Dopamine;mg	0.6 (0.1-1.4 [0-4.0])	0.5 (0.1-1.0 [0-4.4])	0.465
Adrenaline;n(%)	19(32%)	25(42%)	0.256
Adrenaline;μg	0 (0-10 [0-30])	0 (0-20 [0-90])	0.034
Ephedrine; n(%)	0(0%)	1(2%)	1.000
Ephedrine;mg	0	0 (0 [0-6])	0.317
Atropine; n(%)	6(10%)	4(7%)	0.509
Atropine;mg	0 (0 [0-1])	0 (0 [0-2])	0.525
Hospital Length of Stay;day	32 (23-47 [12-140])	33 (23-52 [15-132])	0.726
Maximum laboratory test values within seven days after surgery			
Creatinine;μmol/L	113 (88-188 [65-383])	103 (84-189 [54-593])	0.113
AST;U/L	501 (319-950 [147-6374])	600 (341-842 [222-1138])	0.333

ALT;U/L	359 (225-629 [112-3113])	358 (304-457 [133-709])	0.061
TBil,Total bilirubin;μmol/L	70 (46-108 [14-288])	82 (35-122 [10-253])	0.344
hs-cTnI;ng/mL	0.15 (0.06-0.43 [0.04-2.12])	0.43 (0.12-1.03 [0.07-4.83])	0.333
BNP;ng/L	231 (96-406 [21-2249])	239 (139-630 [48.3-2879])	0.959
NT-ProBNP;ng/L	767 (291-1512 [51-17484])	888 (312-2624 [113-15724])	0.384
Postoperative complications;%			
Intracerebral hemorrhage	1(2%)	0	1.000
Myocardial infarction	0	1(2%)	1.000
Renal failure	4(7%)	3(5%)	1.000
Continuous renal replacement therapy (CRRT)	5(8%)	3(5%)	0.718
Heart failure	11(18%)	8(13%)	0.453
Reintubation	3(5%)	2(3%)	1.000
ICU readmission	4(7%)	1(2%)	0.364
Unplanned reoperation	4(7%)	2(3%)	0.679
Hospital Mortality	1(2%)	1(2%)	1.000

Table 3. Postoperative outcomes and indicators, Values are expressed as mean±SD, median(IQR [range]), or number(proportion).

Figures

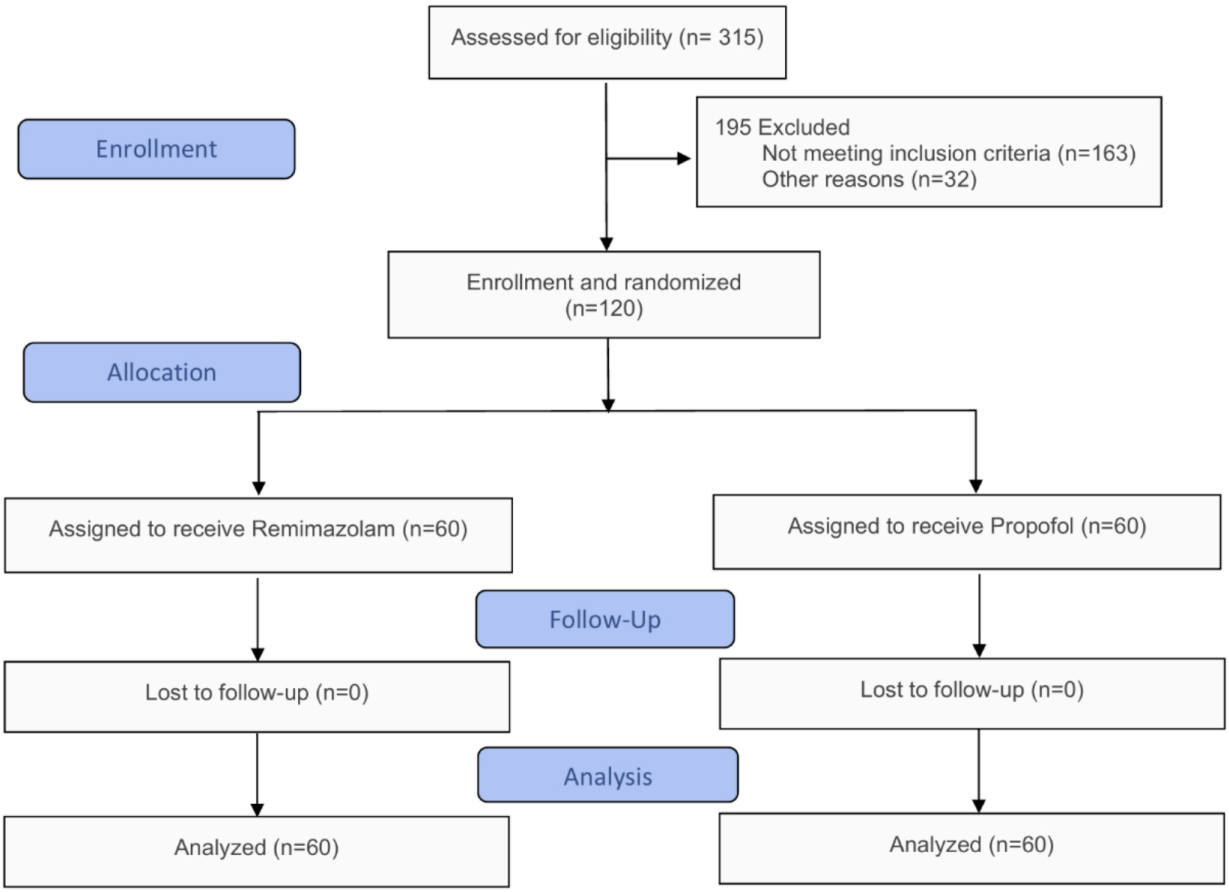
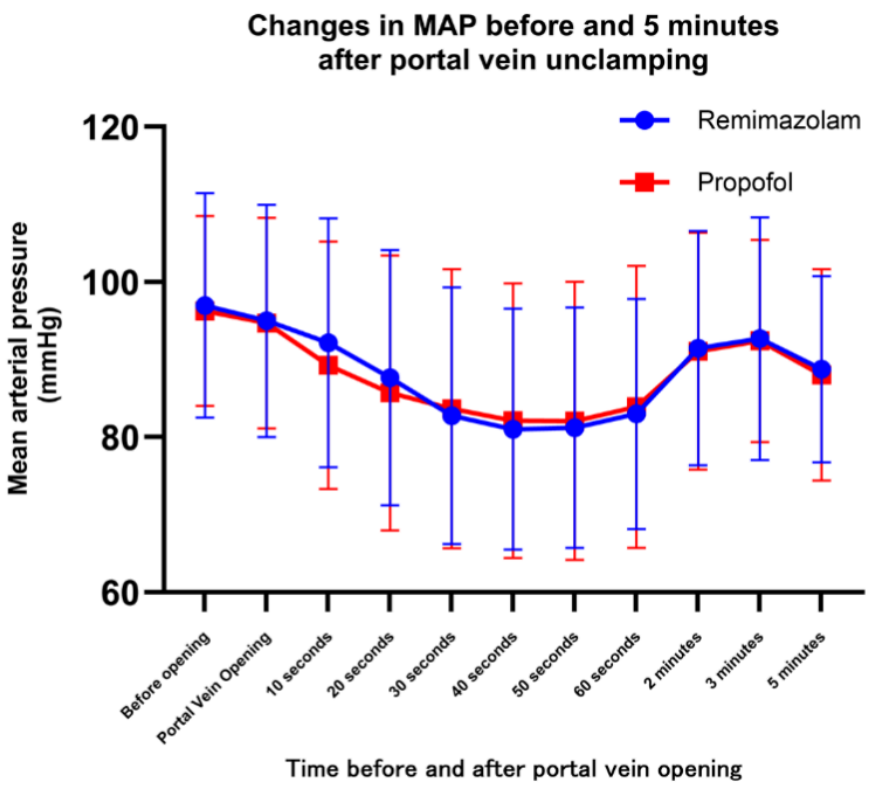


Figure 1

CONSORT flow diagram of participant enrollment, randomization, follow-up, and analysis.



Time	Group	MAP,Mean±σ	F	p
Before Opening	Propofol	96.28±12.28	0.087	0.769
	Remimazolam	97.01±14.51		
Portal Vein Opening	Propofol	94.64±13.54	0.022	0.884
	Remimazolam	95.03±15.03		
10 seconds	Propofol	89.27±15.88	0.979	0.324
	Remimazolam	92.16±16.10		
20 seconds	Propofol	85.71±17.71	0.412	0.522
	Remimazolam	87.71±16.49		
30 seconds	Propofol	83.68±17.94	0.075	0.785
	Remimazolam	82.82±16.53		
40 seconds	Propofol	82.13±17.73	0.120	0.729
	Remimazolam	81.07±15.55		
50 seconds	Propofol	82.10±17.85	0.086	0.770
	Remimazolam	81.20±15.45		
60 seconds	Propofol	83.97±18.13	0.102	0.750
	Remimazolam	83.00±14.84		
2 minutes	Propofol	91.07±15.29	0.019	0.890
	Remimazolam	91.45±15.08		
3 minutes	Propofol	92.43±13.06	0.009	0.924
	Remimazolam	92.68±15.57		
5 minutes	Propofol	88.06±13.64	0.093	0.760
	Remimazolam	88.77±11.20		

Figure 2

Changes in MAP before and 5 minutes after portal vein unclamping

Changes in MAP (mean ± SD) before and after portal vein opening in patients receiving remimazolam versus propofol. Intergroup comparisons at each time point yielded no statistically significant differences (all *p* > 0.05).

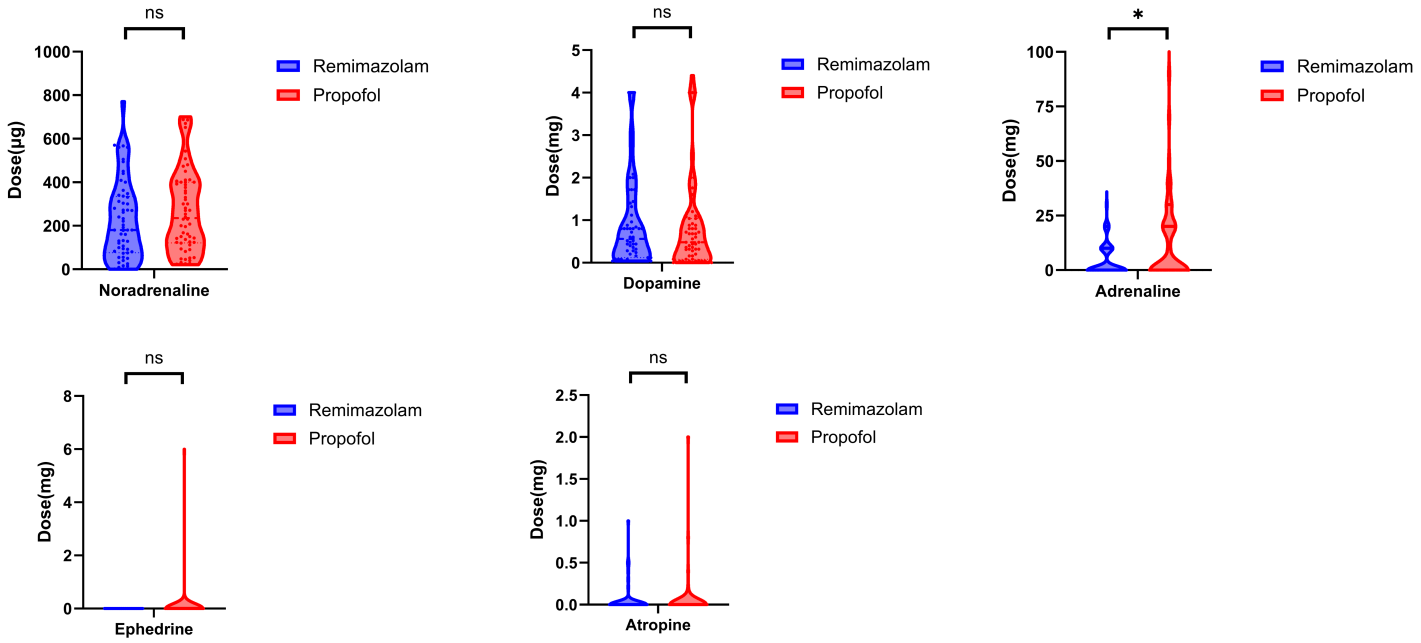


Figure 3

Violin plots of cumulative vasoactive drugs dose within 5 minutes after portal vein unclamping

Adrenaline showed a significant difference (*p* < 0.05); no significant statistical differences were observed with other drugs. The width of the violin plots reflects density, and the embedded box plots indicate median and interquartile range.

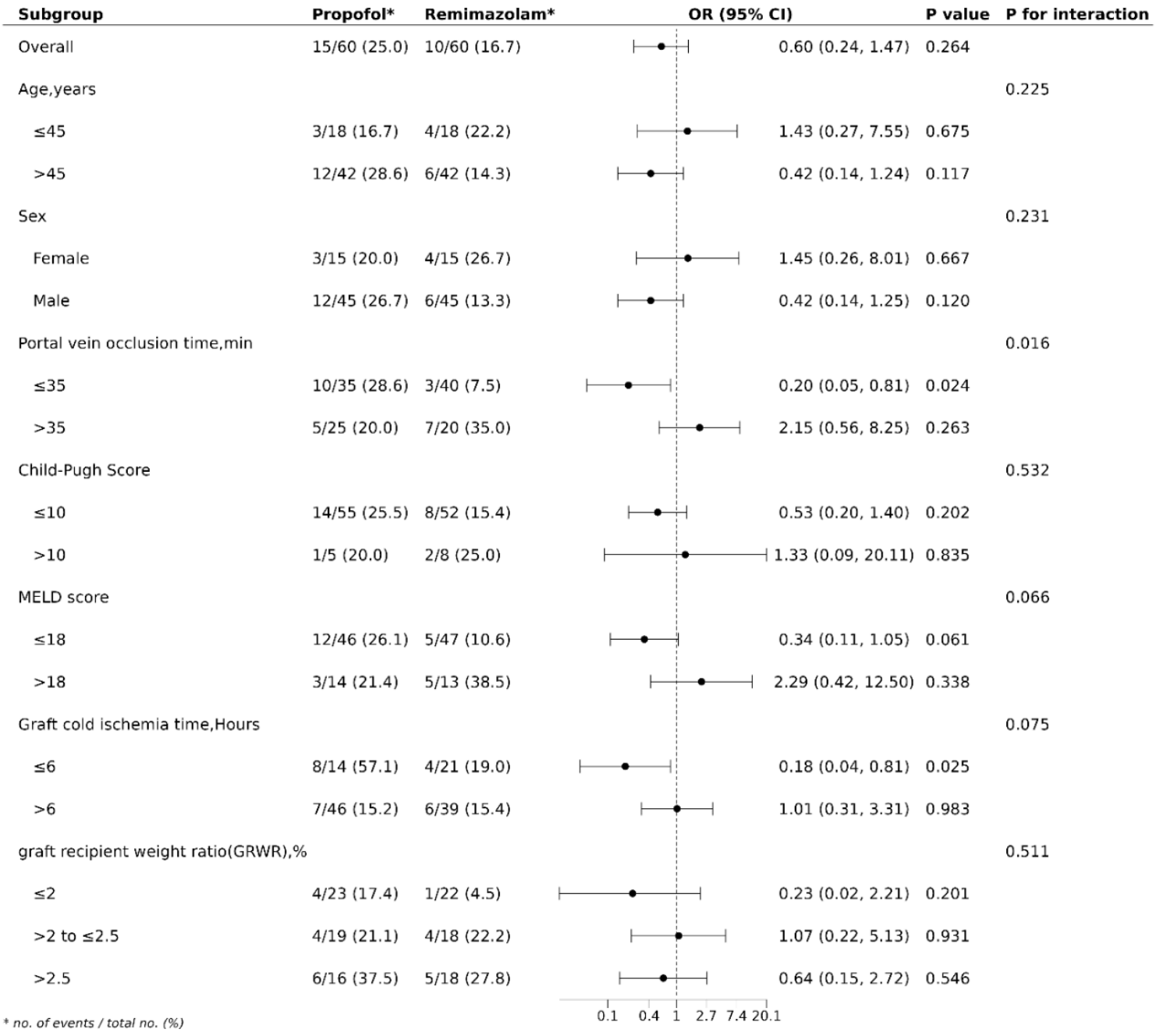


Figure 4

Forest plot of exploratory subgroup analysis

This figure shows outcome events (* n of events / total n (%)) comparing remimazolam with propofol. The overall OR was 0.60 (95% CI 0.24–1.47), *P*=0.264. A significant interaction was observed for portal vein occlusion time (≤35 vs. >35 min, *P* for interaction=0.016); in the ≤35 min subgroup, remimazolam was associated with a lower risk (OR 0.20, 95% CI 0.05–0.81). No other subgroup interactions were detected.