Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Determining the Median Effective Dose of Remimazolam for Anesthesia Induction in Patients Undergoing Endoscopic Retrograde Cholangiopancreatography: An Age-Stratified Study

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Background: Endoscopic Retrograde Cholangiopancreatography (ERCP) requires precise anesthesia control. Remimazolam is ideal for induction due to its rapid onset and minimal cardiorespiratory impact, but its optimal dose across ages is unclear. This study determined the median effective dose (ED_{50}) of remimazolam for ERCP induction and assessed the influence of age.

Methods: In this prospective study, 110 patients aged 50–89 years (ASA I–III, BMI 18–30 kg/m^2) scheduled for ERCP were stratified into four age groups: R1 (50–59), R2 (60–69), R3 (70–79), and R4 (80–89). The Dixon up-and-down method was used, with the initial dose for R1 set at 0.1 mg/kg remimazolam and sequentially reduced by 0.01 mg/kg for the first patient in each older group. Patients received 0.1 μg/kg sufentanil prior to the intravenous administration of a predetermined dose of remimazolam. Anesthesia success was defined as a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score of 0 at 3 minutes after intravenous remimazolam administration, which served as the endpoint for determining the effective induction dose.

Results: To determine the effective dose for inducing anesthesia, the ED_{50} of remimazolam were calculated for groups R1 to R4 as follows: 0.122, 0.108, 0.093, and 0.078 mg/kg, respectively. Similarly, the dosage required to achieve ED_{95} for the same groups was determined to be 0.132, 0.122, 0.113, and 0.090 mg/kg.Bivariate and multivariable linear regression analyses confirmed a significant inverse correlation between age and remimazolam dose requirement ($r = -0.829$, $p < 0.001$), with age remaining an independent predictor after adjusting for confounders.

Conclusion: This study confirms a significant and independent inverse correlation between age and the required induction dose of remimazolam for ERCP. The ED_{50} decreases progressively with advancing age. We recommend a tailored reduction in the remimazolam induction dose for geriatric patients to enhance safety.

Keywords: remimazolam, endoscopic retrograde cholangiopancreatography, median effective dose, age-stratified

Introduction

In recent years, ERCP has emerged as an essential, minimally invasive interventional procedure for diagnosing and treating biliary and pancreatic disorders.[1] Annually, over one million individuals worldwide undergo ERCP.[2] Nevertheless, the procedure's complexity, duration, and invasive nature can induce anxiety, discomfort, and pain in patients. Consequently, deep sedation and general anesthesia are increasingly used in ERCP for diagnosis and treatment.[3] The optimal anesthesia for ERCP should ensure that patients remain pain-free and comfortable, while maintaining respiratory and circulatory stability and facilitating rapid recovery. However, commonly employed anesthesia techniques, such as local anesthesia or traditional sedation combined with analgesia and anesthesia, present challenges, including

Received: 1 May 2025
Accepted: 29 October 2025
Published: 4 November 2025

poor patient cooperation, delayed drug onset, and an increased risk of respiratory depression.[4] Therefore, there is an urgent need to develop more optimized anesthesia protocols.

As a novel benzodiazepine, remimazolam is characterized by a rapid onset, brief duration of action, swift metabolism, and minimal respiratory and circulatory suppression. These pharmacological attributes suggest its promising application in short-duration, minor surgical procedures, such as painless gastrointestinal endoscopy.[5–8] Its pharmacokinetic and pharmacodynamic properties render it a potentially ideal agent for anesthesia induction in ERCP. However, significant variability exists in the response to anesthetic agents among patients of different age groups. As age increases, there is a decline in the hepatic metabolic capacity, a decrease in plasma protein binding rate, and an increase in central nervous system sensitivity, all of which necessitate adjustments in drug dosage.[9–11] Currently, there is a lack of age-stratified studies on the median effective dose of remimazolam for ERCP anesthesia induction, which hinders the precision of its clinical application.

This study seeks to investigate the ED_{50} of remimazolam for anesthesia induction during ERCP using an age-stratified method. This approach aims to establish a foundation for personalized medication strategies tailored to patients of varying ages. The findings of this research are anticipated to optimize anesthesia management for ERCP, enhance patient safety and comfort, and provide empirical support for the development of anesthesia protocols for specific populations, including elderly patients.

Methods

Ethics Approval

This study received ethical approval from the Ethics Committee of the First Affiliated Hospital of the University of Science and Technology of China (USTC) (Approval No. 2022 KY 044; Approval Date: April 6, 2022). In accordance with the Declaration of Helsinki, all participants provided written informed consent prior to their involvement in the trial. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR) prior to participant enrollment (Registration No. ChiCTR2200060357; Principal Investigator: Xu Min; Enrollment Date: May 29, 2022). The research was conducted at the First Affiliated Hospital of USTC from October 2022 to December 2023. The manuscript adheres to the relevant guidelines of the Consolidated Standards of Reporting Trials (CONSORT).

Participants

This prospective study recruited a total of 165 patients aged 50 to 89 years, with ASA levels I to III and a BMI ranging from 18 kg/m^2 to 30 kg/m^2, who underwent ERCP surgery under general anesthesia. Eligible patients should be able to understand the study, voluntarily sign the informed consent, and be willing to comply with the trial protocol requirements. Exclusion criteria included: (1) individuals who are allergic to or contraindicated for benzodiazepines, opioids, propofol, flumazenil, naloxone, and other related medications; (2) Patients with severe cardiac dysfunction (eg, New York Heart Association Class III–IV), severe respiratory insufficiency (eg, chronic obstructive pulmonary disease GOLD grade 3–4, or baseline room air $SpO_2 < 92\%$), severe renal impairment (eg, estimated glomerular filtration rate < 30 $mL/min/1.73m^2$), or other uncontrolled chronic conditions (eg, unstable hypertension or diabetes) that, in the investigator's judgment, would pose a significant risk for tolerating anesthesia; (3) individuals with mental illness; (4) with a history of alcoholism, opioid allergy, or drug abuse; (5) with uncontrolled severe hypertension; (6) emergency surgery patients; (7) pregnant or lactating women; (8) surgeries lasting longer than one hour; and (9) any other condition that, in the opinion of the investigator, may pose a risk to the patient or interfere with the study objectives and procedures.

Patients were categorized into four groups based on age: R1 group (50–59 years old; 27 cases), R2 group (60–69 years old; 29 cases), R3 group (70–79 years old; 30 cases), and R4 group (80–89 years old; 24 cases) (Figure 1). The first patient in the R1 group received an induction dose of remimazolam at 0.1 mg/kg. For groups R2 to R4, the initial dose for the first patient in each subsequent group was reduced by one dose gradient (0.01 mg/kg) as age increased. This study employed the Dixon up-and-down method for dose escalation/escalation design, enrolling patients in each cohort until

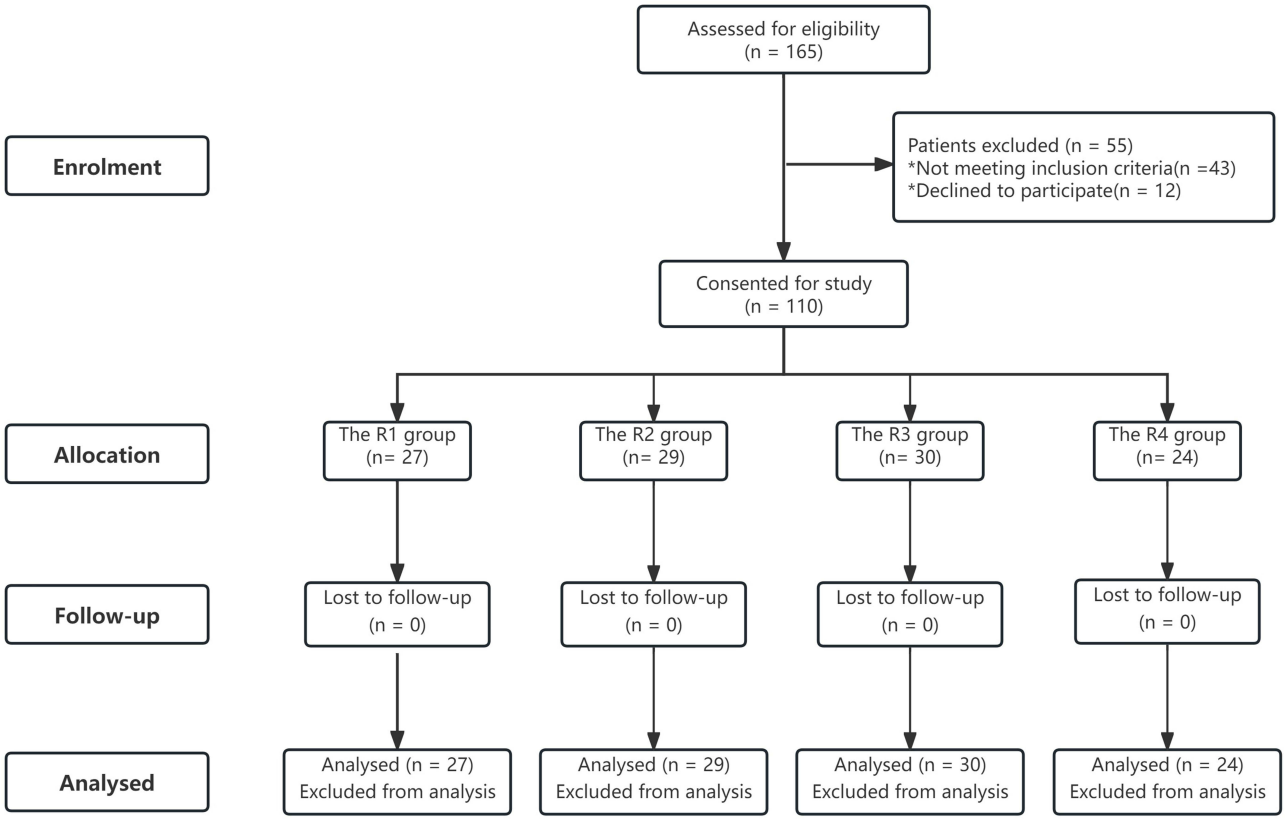

Figure 1 Flow diagram of patient recruitment.

seven crossovers were observed. This method is extensively used in determining the ED_{50} of anesthetic drugs;[12] consequently, an a priori sample size calculation was not performed.

Anesthesia Protocol

The patient fasted for 8 hours and abstained from drinking for 4 hours before the surgery. Upon entering the operating room, heart rate (HR), electrocardiogram (ECG), oxygen saturation (SpO_2), and bispectral index (BIS) values were continuously monitored. Radial artery puncture and catheterization were performed for invasive arterial pressure monitoring under local anesthesia. The patient received 10 mL of dyclonine hydrochloride mucilage (0.1% dyclonine hydrochloride) and supplemental oxygen (3–4 L/min) for 3 minutes. After establishing intravenous access, an anesthesiologist, blinded to the group assignment, administered sufentanil at a dosage of 0.1 μg/kg, followed by a preset dose of remimazolam injected one minute later. After 180 seconds of intravenous remimazolam injection, an ERCP examination was conducted when the MOAA/S score reached 0. If the examination proceeded smoothly, anesthesia was deemed successful, and the next patient would receive a lower dose of remimazolam (the dose was reduced by 0.01mg/kg). If the MOAA/S score remained ≥1 after 3 minutes, or if the MOAA/S score reached 0 but the ERCP examination was unsuccessful (due to movement, coughing, etc)., anesthesia was classified as a failure. Under these circumstances, emergency anesthesia using propofol at 1 mg/kg was administered, with the process repeated every 3 minutes until the MOAA/S score reached 0 and the ERCP was concluded, followed by an increased remimazolam dosage (increased by 0.01 mg/kg) for the subsequent patient. A single negative outcome and a single positive outcome were sequentially documented as a single cross. The experiment concluded after the completion of seven crosses. A different anesthesiologist documented the test outcomes and notified the nurse, who was not involved in the study, to prepare the experimental drug for the next patient. For maintenance purposes, normal saline was used as the solution, while remimazolam was employed for mixing. A 20 mL syringe was used to mix the recommended remimazolam dosage, resulting in a total volume of 20 mL.

https://doi.org/10.2147/DDDT.S537897

During diagnosis and treatment, ephedrine should be administered for symptomatic relief if the systolic blood pressure (SBP) falls below 30% of the baseline value. In cases where the HR is ≤ 50 beats per minute, the intravenous administration of 0.5 mg atropine is indicated. If the SpO_2 drops to ≤93%, it is essential to maintain the patient's jaw position and increase the oxygen flow. Should the SpO_2 decrease to ≤ 80%, the endoscopic procedure must be halted, and supplemental oxygen should be administered via a mask. Remimazolam should be discontinued immediately after surgery, and the patient should be transferred to the post-anesthesia care unit (PACU). Once the Aldrete score reaches ≥9, the patient may return to the ward, accompanied by family members.

Data Collection

The primary objective of this research was to determine the ED_{50} and ED_{95} of remimazolam in conjunction with 0.1 μg/kg sufentanil for patient induction. Furthermore, as a secondary outcome, HR, mean arterial pressure (MAP), peripheral SpO_2, and BIS were measured at various time points: prior to the initiation of anesthesia induction (T0), and at 10 seconds (T1), 20 seconds (T2), 40 seconds (T3), 60 seconds (T4), 90 seconds (T5), 120 seconds (T6), and 180 seconds (T7) following induction. Concurrently, adverse events and corresponding treatment measures were documented throughout the study.

Statistical Analysis

The data analysis was performed using SPSS version 27. Descriptive statistics are presented as means with standard deviations (SD) or medians with interquartile ranges, depending on whether the data distribution is normal or skewed. Categorical data are expressed as percentages. For categorical data analysis, the Chi-square test or Fisher's exact test was employed, while the Mann–Whitney *U*-test was used for nonparametric statistics. A one-way analysis of variance (ANOVA) was used to compare multiple groups. A two-way ANOVA was conducted to analyze data collected at various time points across the groups. The effective doses (ED_{50} and ED_{95}) of remimazolam, along with their corresponding CIs, were determined using probit regression analysis. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant. Sequential graphs and dose-response curves were generated using GraphPad Prism version 8.

A trio of multivariable linear regression models was formulated to evaluate the independent correlation between age and remimazolam dosage. The model I remained unchanged, while Model II underwent modifications for the gender and BMI. Model III received additional adjustments for the levels of albumin (ALB), alanine aminotransferase (ALT), serum creatinine (Scr), and blood urea nitrogen (BUN). Variables were chosen for the models when they showed possible impact factors, as evidenced by a univariate analysis p-value below 0.05. Furthermore, indices closely linked to remimazolam metabolism and the clinical functions of the liver and kidneys are integrated.[13,14] A collinearity diagnosis was conducted to prevent the inclusion of highly correlated variables in the model. To explore the linear relationship between age and remimazolam dosage, smooth curve fitting was applied after adjusting for potential confounding variables.

Results

General Data

Figure 1 shows that out of 165 patients screened for recruitment, 55 were excluded and 110 were assigned to groups R1 (n=27), R2 (n=29), R3 (n=30), and R4 (n=24). All 110 enrolled patients completed the study and were included in the primary outcome analysis. Table 1 displays the baseline characteristics of the 110 patients. Apart from age (p <0.001) and ALB (p <0.001), the four groups have similar demographic characteristics.

In the investigation of effective dosing, the ED_{50} of remimazolam for anesthesia induction was quantified using the probit regression model. The results indicated ED_{50} values of 0.122 mg/kg (95% CI: 0.115, 0.127), 0.108 mg/kg (95% CI: 0.101, 0.115), 0.093 mg/kg (95% CI: 0.084, 0.103), and 0.078 mg/kg (95% CI: 0.070, 0.085) for groups R1 through R4, respectively. Correspondingly, the dose required to achieve ED_{95} was determined to be 0.132 mg/kg (95% CI: 0.127, 0.161), 0.122 mg/kg (95% CI: 0.115, 0.164), 0.113 mg/kg (95% CI: 0.103, 0.172), and 0.090 mg/kg (95% CI: 0.084,

Table 1 Demographic Characteristics

Variable	R1 Group (n=27)	R2 Group (n=29)	R3 Group (n=30)	R4 Group (n=24)	*p value*
Male, (male/female)	15/12	14/15	14/16	12/12	0.919**
Age, (years), median(IQR)	54[52;55]	61[61;63]	74[71;77]	83[81;84]	<0.001*
BMI, (kg/m^2)	23.7±2.9	23.8±3.1	22.3±3.2	21.8±3.4	0.052#
ASA (II/III)	17/10	13/16	12/18	12/12	0.349**
Types of special diseases, n (%)					
Obstructive jaundice	5	6	12	10	0.118**
Choledocholithiasis	13	17	14	12	0.767**
Co-morbidities (n)					
Hypertension	7	12	10	8	0.662**
Diabetes	4	4	6	2	0.687**
CHD	0	2	3	1	0.399**
INR, median (IQR)	1.04[0.95,1.08]	0.99[0.94,1.05]	1.05[0.99,1.09]	1.03[0.97,1.09]	0.074*
Liver function					
Albumin, median (IQR), g/L	40.0[36.7,43.7]	42.5[41.3,45.1]	38.4[33.5,39.4]	37.2[34.3,39.9]	<0.001*
Bilirubin, median (IQR), μmol/L	19.8[13.4,51.1]	18.7[12.5,42.2]	23.0[13.8,93.6]	29.7[14.8,108.7]	0.352*
ALT, median (IQR), U/L	48[29,114]	57[28,143]	42[24,74]	58[19,182]	0.856*
AST, median (IQR), U/L	41[20,87]	31[24,89]	32[25,56]	71[27,132]	0.295*
Kidney function					
Scr, median (IQR), μmol/L	61[51,69]	59[48,76]	59[52,75]	69[51,76]	0.630*
BUN, median (IQR), mmol/L	5.20[4.44,5.71]	5.11[4.03,6.66]	5.26[4.45,6.15]	5.33[3.82,6.70]	0.969*

Note: *p-values from Kruskal–Wallis test. **p-values from χ^2 test or Fisher's exact test. #p-values from One-way ANOVA.
Abbreviations: IQR, interquartile range; BMI, body mass index; ASA, American society of anesthesiologists; CHD, coronary heart disease; INR, international normalized ratio; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine, BUN, blood urea nitrogen.

0.128) for the same groups, as presented in Table 2. Importantly, both ED_{50} and ED_{95} values demonstrated a statistically significant reduction with increasing age from group R1 to group R4 ($p < 0.05$). The results of the Dixon up-and-down method for each group are illustrated in Figure 2, and the dose-response curves for remimazolam induction across the groups are shown in Figure 3.

Bivariate linear correlation analysis in Table 3 showed a significant negative correlation between the requirement for remimazolam and age (r = −0.829, 95% CI: −0.875 to −0.753, $p < 0.001$). A rise in BMI correlated with a reduced need for remimazolam (r = −0.198, 95% CI: −0.021 to −0.375, $p = 0.04$). On the other hand, a notable positive correlation was found between the need for remimazolam dosage and ALB levels, with statistical significance (r = 0.249, 95% CI: 0.066–0.407, $p = 0.009$). There were no notable links detected between other indicators of organ function and the required dosage of remimazolam. Furthermore, to clarify the direct correlation between age and the need for remimazolam dosage, a smooth curve fitting method was used, factoring in variables such as gender, BMI, ALB, ALT, Scr, and BUN, which were found to be statistically significant (Figure 4).

Model I was established as a basic model, incorporating only the age factor to initially assess its impact on the required dosage of remimazolam. Based on the results of univariate linear regression analysis, BMI and gender were identified as significant factors ($p < 0.05$) and were therefore included in Model II. Building on these findings, Model III was further adjusted for levels of ALB, ALT, Scr, and BUN. The diagnostic tests for collinearity showed no variables with strong interconnections that required removal from the multivariable linear regression model. The research revealed

Table 2 ED_{50} and ED_{95} of Remimazolam for Anesthesia Induction

Variable	R1 Group (n=27)	R2 Group (n=29)	R3 Group (n=30)	R4 Group (n=24)
ED_{50},mg/kg	0.122[0.115,0.127]	0.108[0.101,0.115]	0.093[0.084,0.103]	0.078[0.070,0.085]
ED_{95},mg/kg	0.132[0.127,0.161]	0.122[0.115,0.164]	0.113[0.103,0.172]	0.090[0.084,0.128]

Note: The ED_{50} and ED_{95} with their 95% confidence intervals.
Abbreviation: ED50, median effective dose.

https://doi.org/10.2147/DDDT.S537897

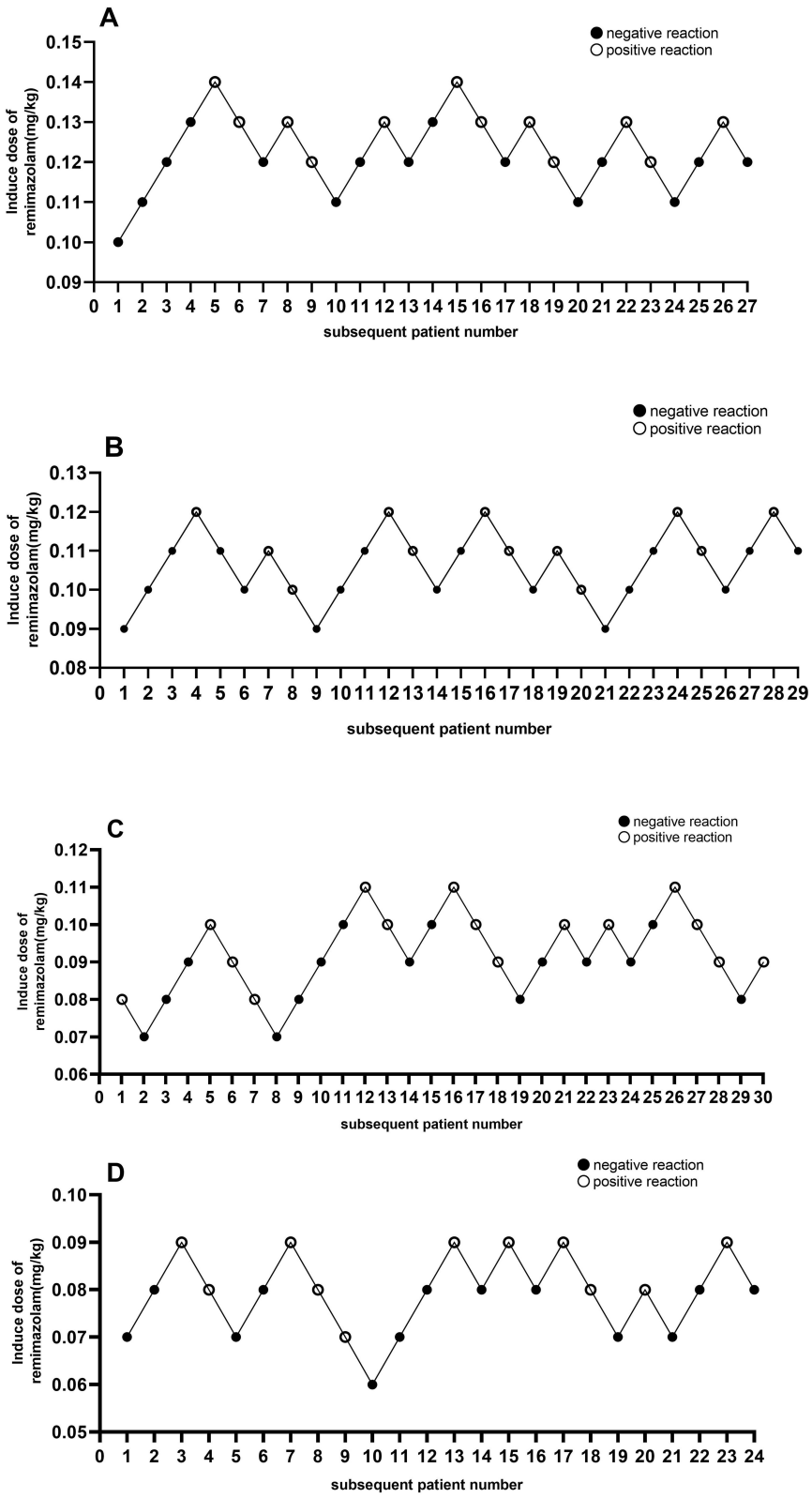

Figure 2 The up-and-down sequence of Remimazolam dose for anesthesia Induction. (**A**) R1 group; (**B**) R2 group; (**C**) R3 group; (**D**) R4 group; "●"represent negative reaction, patient anesthesia failed, "◯" represent positive reaction, patient successfully anesthesia.

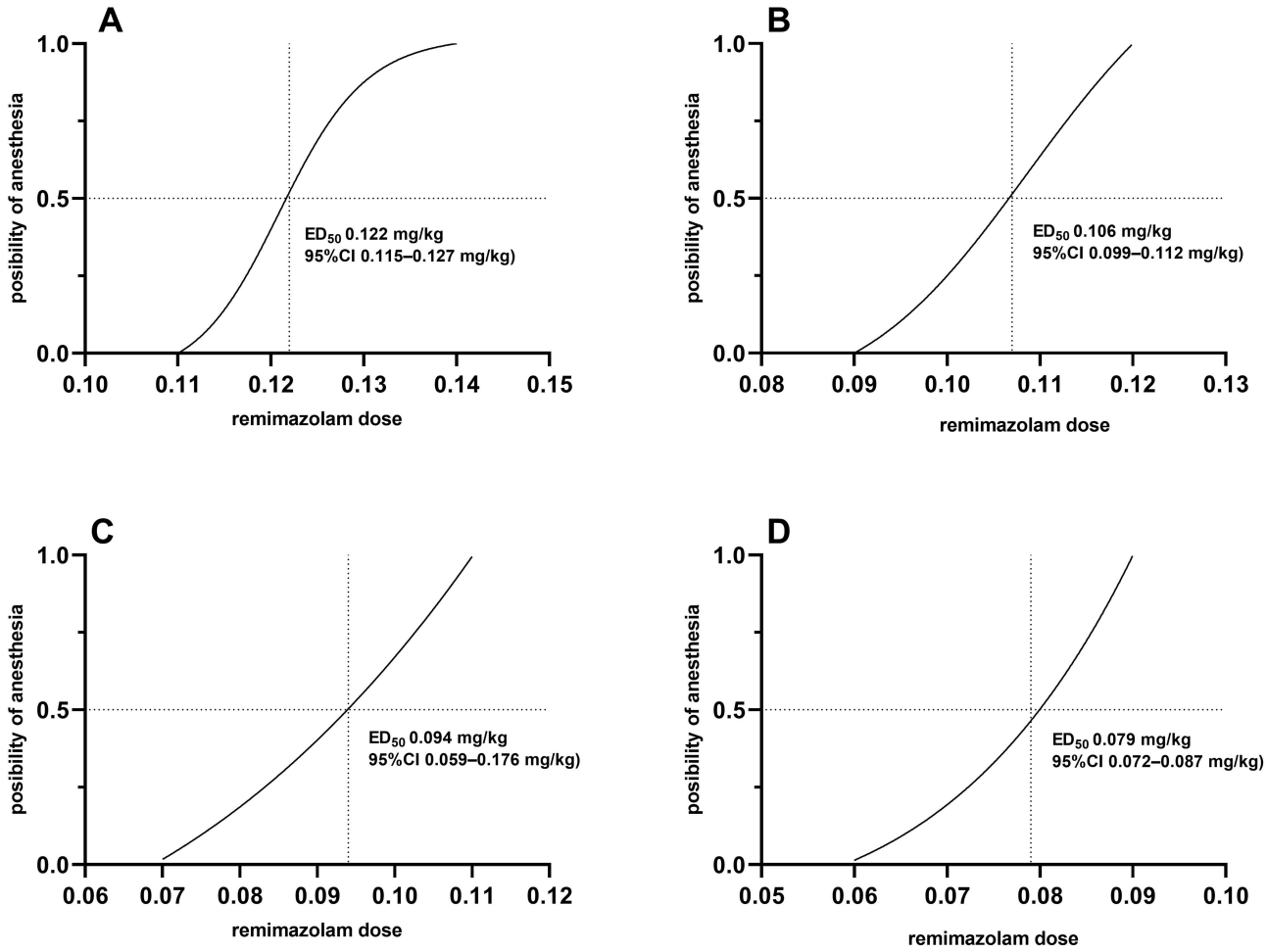

Figure 3 The dose-response curve from the probit analysis of remimazolam dosage and probability of success anesthesia. X-axis: Remimazolam dose (mg/kg); Y-axis: Probability of successful anesthesia (probit-transformed cumulative percentage). The dashed vertical line indicates ED_{50} with 95% CI (shaded area). (**A**) R1 group; (**B**) R2 group; (**C**) R3 group; (**D**) R4 group.
Abbreviations: ED_{50}, median effective dose; CI, confidence interval.

a notable correlation between advancing age and a reduced need for remimazolam ($p < 0.001$) in Model I. This relationship persisted and remained significant even after accounting for BMI and gender in Model II ($p < 0.001$), and after additional adjustments for ALB, ALT, Scr, and BUN levels in Model III ($p < 0.001$).

No serious adverse events occurred during induction with remimazolam combined with sufentanil across all age groups. Some patients experienced transient decreases in blood pressure or heart rate, which were promptly corrected with ephedrine or atropine. The incidence of hypoxemia ($SpO_2 \leq 93\%$) was low, with the following cases per group: R1: 2 case (7.4%), R2: 1 cases (3.4%), R3: 3 cases (10.0%), R4: 2 cases (8.3%). All cases were managed by jaw-thrust maneuver or increased oxygen flow without the need to interrupt the endoscopic procedure. No instances of severe respiratory depression or circulatory collapse requiring endotracheal intubation or ICU transfer occurred.

Discussion

This study is the first to employ an age-stratified design to systematically investigate the ED_{50} of remimazolam for anesthesia induction during ERCP and its relationship with patient age. The results demonstrate a significant age-dependent decline in ED_{50} across groups (R1 to R4: 0.122, 0.108, 0.093, and 0.078 mg/kg, respectively), with age identified as an independent predictor of dosage requirements ($r = -0.829$, $p < 0.001$). By addressing the homogeneity limitations of previous dose-finding studies, this research provides evidence-based guidance for reducing anesthetic doses in elderly patients, thereby advancing precision in clinical anesthesia management.

https://doi.org/10.2147/DDDT.S537897

Table 3 Correlation Coefficients Between Age and Remimazolam Requirement

	Remimazolam Requirement, mg/kg		
	r	**95% CI**	***p* value**
Age, (years), median(IQR)	−0.829	−0.875~-0.753	< 0.001
BMI, (kg/m^2)	−0.198	−0.021~-0.375	0.040*
INR	−0.098	−0.276~0.103	0.319
Albumin, median (IQR), g/L	0.249	0.066~0.407	0.009
Bilirubin, median (IQR), μmol/L	−0.041	−0.225~0.139	0.667
ALT, median (IQR), U/L	0.182	−0.024~0.375	0.057
AST, median (IQR), U/L	0.063	−0.140~0.267	0.516
Scr, median (IQR), μmol/L	−0.114	−0.301~0.069	0.235
BUN, median (IQR), mmol/L	−0.13	0.204~0.0178	0.895

Note: *p value in Pearson's (r) and p value in Spearman's (rs) correlation coefficients.
Abbreviations: IQR, interquartile range; BMI, body mass index; INR, international normalized ratio; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Scr, serum creatinine, BUN, blood urea nitrogen.

Notably, previous studies have also reported age-dependent reductions in remimazolam dosage requirements. For instance, Oh et al[15] demonstrated a lower ED_{95} for loss of consciousness in elderly patients compared to younger adults, while Song et al[13] observed a significantly reduced ED_{50} in patients aged over 65 years. Similarly, Chae et al[16] suggested stratified induction doses across different age decades, corroborating the necessity of age-adjusted dosing.

Remimazolam, an ultrashort-acting benzodiazepine, exerts its effects by enhancing γ-aminobutyric acid (GABA) receptor activity in the central nervous system (CNS).[17] Unlike propofol or midazolam, remimazolam undergoes rapid hydrolysis by tissue esterases to an inactive metabolite (CNS 7054), bypassing hepatic or renal metabolism.[18] This pharmacokinetic profile confers unique advantages for elderly populations. However, our findings revealed a substantial reduction in ED_{50} among older patients (11.5%–16.1% per decade of age), despite the absence of age-related metabolic impairment. This suggests that heightened CNS sensitivity to remimazolam, rather than altered metabolism, drives the observed dose reduction. Similar age-dependent patterns have been reported for propofol, with declining neuronal density, altered neurotransmitter receptor expression, and changes in blood-brain barrier permeability proposed as mechanisms.[19,20]

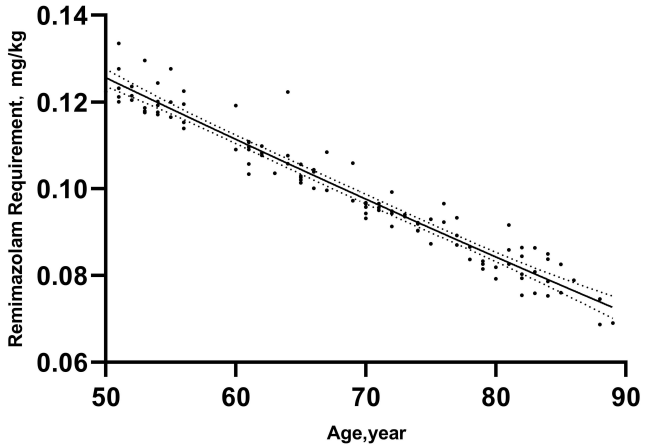

Figure 4 Adjusted dose-response linear between age and remimazolam requirement. Adjusted for gender, BMI, ALB, ALT, Scr, BUN.
Abbreviations: BMI, body mass index; ALB,albumin; ALT,alanine aminotransferase; Scr, serum creatinine; BUN,blood urea nitrogen.

Prior studies on remimazolam induction in elderly patients reported reduced dosage requirements but failed to fully disentangle the confounding metabolic factors.[15] For instance, propofol studies identified correlations between dosage and serum ALB or glomerular filtration rate (GFR), implying that clearance variability might obscure age-related effects.[21] To isolate the independent influence of age on remimazolam dosing, our multivariate models adjusted for hepatic (ALT, ALB) and renal (Scr, BUN) markers. Age remained a robust independent predictor of dosage, aligning with physiologically based pharmacokinetic (PBPK) frameworks that integrate organ perfusion and enzyme activity to differentiate CNS sensitivity from metabolic contributions.[22] The bivariate correlation analysis revealed a notable positive link between the need for remimazolam and ALB concentrations ($r = 0.249$, $p = 0.009$), and a reverse relationship with BMI ($r = -0.198$, $p = 0.04$). Remimazolam's pharmacokinetic analysis relies on a tripartite model, characterized by a reduced apparent volume of distribution and an increased clearance rate.[23] Nonetheless, the interaction between body mass and pharmacokinetic factors is complex.[24] Observational data support the idea that BMI is a statistically significant covariate in predicting the likelihood of unconsciousness in patients treated with remimazolam during general anesthesia.[25] Consequently, adjusting the remimazolam dosage based on BMI could mitigate the impact of body weight on drug metabolism, making this approach more logical than fixed-dose treatments. ALB serves as the principal drug-binding protein in plasma, interacting with various drugs through multiple binding sites, thereby forming a "reservoir" that influences the free concentration, distribution, and clearance of drugs.[26] Benzodiazepines, such as midazolam, exhibit high rates of ALB binding, with 94% of the drug bound to protein.[27] This characteristic can result in significant increases in free drug concentrations during states of hypoalbuminemia. In contrast, remimazolam possesses distinct pharmacokinetic properties. Its metabolism is predominantly reliant on esterase activity, which facilitates the rapid clearance of unbound drug, thereby reducing its susceptibility to fluctuations in ALB levels compared to midazolam. However, recent findings by Song et al[13] indicate that ALB concentrations significantly influence the induction efficacy of remimazolam.

Although ERCP is performed across a wide age range, epidemiological data and clinical practice indicate that the majority of procedures are concentrated in patients aged 50 to 89 years, who are more frequently affected by biliary and pancreatic diseases requiring interventional management.[28,29] Focusing on this age range not only ensures an adequate sample size but also enhances the clinical relevance and applicability of our findings. Furthermore, as age advances, patients often exhibit diminished physiological reserves and reduced tolerance to anesthesia, necessitating more individualized dosing strategies to mitigate perioperative risks.[29–31] In this study, we stratified patients in 10-year increments, starting with an initial dose of 0.1 mg/kg. For each subsequent age group, the first patient received a 0.01 mg/kg dose reduction to determine the ED_{50} and ED_{95} of remimazolam in patients over 50 years old. Prior research efforts[15–17] have investigated the induction dosage of remimazolam across various age cohorts. Compared with previous studies, our findings are consistent with the dose trend reported by Oh et al[15] indicating increased sensitivity to remimazolam and a significantly reduced induction dose required in elderly patients. However, the ED_{95} values we observed were lower than reported by Oh et al. Furthermore, while Zhang et al[17] noted in their systematic review that remimazolam demonstrates good hemodynamic stability and rapid recovery across different age groups, they did not provide specific age-stratified dosing recommendations. Our study addresses this gap by employing precise stratification in 10-year increments, systematically quantifying for the first time the inverse relationship between remimazolam induction dose and age in patients over 50 years old, providing evidence for personalized dosing in advanced age populations.

The study by Song et al[13] (n=120), using a continuous infusion of remimazolam at 0.05 mg/kg/min, observed that the ED_{50} for inducing loss of consciousness was 0.26 mg/kg and 0.19 mg/kg in patients aged 18–64 years and those ≥65 years, respectively. Chae et al[16] (n=120), employing probit regression to analyze the dose-response relationship across six bolus dose groups (0.02–0.27 mg/kg), suggested that the optimal induction doses of remimazolam were 0.25–0.33 mg/kg for patients aged <40 years, 0.19–0.25 mg/kg for those aged 60–80 years, and 0.14–0.19 mg/kg for patients >80 years. In contrast, our ED_{50} and ED_{95} values for comparable age segments are substantially lower. This discrepancy can likely be attributed to several key methodological differences. First, we administered 0.1 μg/kg of sufentanil before remimazolam. Opioids exhibit pharmacodynamic synergy, significantly reducing remimazolam induction requirements. Substantial evidence[32,33] indicates that opioids indirectly inhibit GABA interneurons in the ventral tegmental area, disinhibiting dopaminergic pathways while potentiating the GABA effects of benzodiazepines, thereby enhancing the depth of

anesthesia. In painless endoscopic procedures which typically target deep sedation, coadministration of alfentanil reduces remimazolam requirements by 20–30%.[34] Although the target depth differs, the synergistic principle between opioids and remimazolam is consistent. Second, the age-remimazolam dose relationship is nonlinear: (1) Elderly patients demonstrate increased CNS sensitivity to sedatives, potentially due to altered neuronal receptor density and blood-brain barrier permeability.[31] This sensitivity may increase abruptly after the age of 65, causing a sharp reduction in anesthetic requirements. (2) Hepatic blood flow decreases by 0.3–1.5% per decade, with accelerated hepatocyte loss after the age of 60.[35] This nonlinear decline further reduces remimazolam clearance in elderly patients, necessitating dose adjustments beyond linear model predictions. (3) Elderly patients, particularly those with frailty or chronic diseases, often have reduced plasma ALB,[36] which decreases drug-binding sites and increases free drug concentrations, thereby enhancing the drug's effects. Clinical study[37] shows that the relationship between remimazolam's effect-site concentration (Ce) and BIS values follows a sigmoid curve, with a leftward shift in elderly patients, indicating that lower concentrations achieve an equivalent depth of sedation. This shift becomes more pronounced with advancing age, suggesting an inverse nonlinear correlation between age and dose requirements. Our findings confirm this phenomenon, showing an accelerated dose reduction between groups R3 and R4. Therefore, age-stratified investigations allow for the precise characterization of nonlinear age-dose relationships, avoiding the underestimation of dose variations that may occur with broader age categories. Third, our combined use of MOAA/S scores and BIS monitoring improves the accuracy of anesthetic depth assessment, reducing both false negatives and false positives, and enabling a more precise calculation of the ED_{50} for remimazolam. This can prevent a single evaluation index from increasing the assessment bias, which could result in the overestimation or underestimation of the remimazolam dose requirement.

This study effectively determined the ED_{50} of remimazolam in different age groups using Dixon's up-and-down method. However, it is important to note that this method has limitations for estimating parameters at the distribution tail, such as the ED_{95}, as evidenced by the relatively wide confidence intervals we calculated for the ED_{95} (eg, 0.103–0.172 mg/kg in group R3). This reflects the inherent challenge of precisely estimating high-percentile effective doses with a limited sample size. Therefore, when clinicians refer to the ED_{95} values from this study for medication guidance, they should be aware of this uncertainty and cautiously perform individualized dose adjustments based on the specific circumstances of the patient. Future studies with larger sample sizes or employing different experimental designs (eg, randomized assigned dose groups) will help to more precisely determine the ED_{95} of remimazolam.

The primary strength of this study lies in its refined age-stratified design and multivariate model adjustment, which systematically quantifies, for the first time, the significant negative linear correlation between remimazolam dosage requirements and age. Although the study enrolled patients across a broad age range of 50–89 years, the oldest group (R4, 80–89 years) was predominantly composed of individuals aged 81–84 years, with only a small proportion aged 85 years or older. This underrepresentation of the oldest-old subgroup may limit the generalizability of our findings to individuals aged 85 years and above. Additionally, although patients with severe hepatic or renal dysfunction were excluded, the cohort was not specifically designed to recruit or stratify elderly individuals with chronic comorbidities such as diabetes or neurodegenerative diseases, who may exhibit altered drug sensitivity and thus introduce potential bias in the results. Furthermore, sufentanil was administered at a fixed dose as an adjunct without individual titration or systematic dose-response analysis, potentially leading to an underestimation of its modulatory effect on remimazolam's potency. Finally, Although our study adjusted for age, BMI, and organ function markers, we did not collect data on functional capacity (eg, metabolic equivalents, METs) or frailty indices, which are known to influence anesthetic sensitivity and perioperative outcomes. Future studies should incorporate these metrics to further refine remimazolam dosing in elderly patients.

Furthermore, it is noteworthy that although chronic comorbidities (eg, diabetes) were not used as stratification or exclusion criteria, some patients in the cohort might indeed have had such conditions. Metabolic diseases like diabetes can influence drug response through various mechanisms, including alterations in blood-brain barrier permeability, effects on hepatic and renal function, or pathological changes in the peripheral and central nervous systems, potentially increasing sensitivity to sedative drugs. Although we adjusted for liver and kidney function-related indicators (ALB, ALT, Scr, BUN) in our multivariate models, information on patient comorbidities was not systematically collected, which represents a limitation of this study. Future research should further explore the impact of comorbidities on the dose-response relationship of remimazolam to enable more precise personalized medication.

Future studies should be expanded to include extremely elderly populations (≥90 years) and those with comorbidities, while exploring multifactorial predictive models (eg, age + ALB + comorbidity burden) to optimize individualized dosing. Given remimazolam's short-acting properties, further investigation is warranted to validate its dosing patterns in non-ERCP settings, such as day-case surgeries and ICU sedation. Integrating target-controlled infusion (TCI) technology may enable dynamic "dose-effect-age" matching, ultimately enhancing anesthesia safety in geriatric patients.

This study quantified the age-dependent reduction in the ED_{50} of remimazolam for anesthesia induction during ERCP. The ED_{50} decreased progressively from 0.122 mg/kg (95% CI: 0.115–0.127) in patients aged 50–59 years to 0.078 mg/kg (95% CI: 0.070–0.085) in those aged 80–89 years. Multivariable linear regression confirmed age as an independent predictor of remimazolam requirements, even after adjusting for BMI, ALB, and hepatic/renal function markers. These results emphasize the necessity of age-stratified dosing to mitigate overdosing risks in elderly populations, particularly given their heightened central nervous system sensitivity. Future studies should be expanded to include extremely elderly populations (≥90 years) and those with comorbidities to further refine personalized dosing strategies.

Data Sharing Statement

The authors state that all data in the manuscript are accessible if requested (contact e-mail address seumexumin@163.com). The authors verify that all data intended for sharing is de-identified.

Funding

This study was supported by the "Rui" Special Fund for Scientific Research from Hubei Chen Xiaoping Science and Technology Development Foundation (CXPJJH12000005-07-116); Anhui Provincial Health Care Commission Health Research Project (AHWJ2024BAc30062). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosure

The authors declare no conflicts of interest in this work.

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