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Original Article

Remimazolam-based spontaneous breathing sedation for endoscopic retrograde cholangiopancreatography: a propensity score-matched retrospective cohort study

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Abstract: Objective: To compare the efficacy and safety of remimazolam-based and propofol-based sedation protocols for ERCP using a propensity score-matched (PSM) retrospective cohort. Methods: Consecutive patients undergoing ERCP with spontaneous breathing sedation from January 2023 to December 2025 were retrospectively enrolled. Patients receiving remimazolam-based sedation were compared with the propofol-based sedation. PSM (1:1 nearest-neighbor, caliper = 0.02) was used to adjust for baseline covariates. The primary outcomes were recovery time and incidence of intraoperative hypoxemia (SpO_2 < 90%). Secondary outcomes included PACU stay, patient satisfaction, hypotension, bradycardia, injection pain, body movement requiring rescue, and procedure success rate. Kaplan-Meier curves with log-rank tests were used for survival analysis. Multivariable Cox regression stratified by matched pairs was performed to identify risk factors for hypoxemia. Results: After propensity score matching, 99 matched pairs (n = 198) were successfully generated, with all standardized mean differences being < 0.1. The remimazolam group demonstrated a significantly shorter recovery time (3.46 ± 1.15 vs. 7.55 ± 2.93 min, P < 0.001) and PACU stay (25.07 ± 6.02 vs. 34.71 ± 8.23 min, P < 0.001), and significantly higher patient satisfaction (9.31 ± 0.68 vs. 8.14 ± 1.21, P < 0.001). The incidence of hypoxemia was significantly lower in the remimazolam group (19.2% vs. 41.4%, P < 0.001), as were hypotension (6.1% vs. 21.2%, P = 0.005) and injection pain (4.0% vs. 34.3%, P < 0.001). Kaplan-Meier analysis showed superior hypoxemia-free survival in the remimazolam group (log-rank χ^2 = 9.832, P = 0.002). Multivariable Cox regression demonstrated a protective trend for remimazolam against hypoxemia (HR = 0.462, 95% CI: 0.212-1.008, P = 0.052). Subgroup analyses consistently favored remimazolam across most strata. Conclusions: Remimazolam-based spontaneous breathing sedation for ERCP was associated with faster recovery, shorter PACU stay, and significantly lower incidences of hypoxemia, hypotension, and injection pain compared with propofol. These findings support remimazolam as a safer and more efficient sedative agent for ERCP, particularly in patients at high risk of respiratory and hemodynamic compromise.

Keywords: Remimazolam, propofol, endoscopic retrograde cholangiopancreatography, sedation, propensity score matching, hypoxemia

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is a key procedure for diagnosing and treating diseases of the biliary and pancreatic systems, and is widely used for conditions such as common bile duct stones, obstructive jaundice, acute cholangitis, and pancreatic-biliary tumors [1]. Unlike ordinary digestive endoscopy, ERCP has a longer procedure time, frequent insertion and removal of endoscopic instruments, and intense stimulation to the patient during procedures such as duodenal papilla catheterization and incision. Patients are often placed in the prone or left lateral position, and the depth of sedation/anesthesia requirements are relatively high [2]. Therefore, during the ERCP procedure, it is often necessary to implement a certain level of sedation or anesthesia while ensuring the comfort and safety of the patient, in order to suppress the adverse reactions related to the procedure and maintain hemodynamic stability and spontaneous breathing [3].

Currently, there are various sedation protocols used in ERCP. Among them, propofol is widely used in endoscopic procedures due to its rapid

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onset, quick recovery, and good controllability of sedation depth [4]. However, propofol has a narrow therapeutic window, and it has significant inhibitory effects on the respiratory center and cardiovascular system, especially with a high incidence of respiratory depression, manifested as slowed respiratory rate, reduced tidal volume, and even transient apnea. This is particularly prominent in non-intubated sedation with preserved spontaneous breathing [5]. Previous studies have reported that the incidence of propofol-related hypoxemia in ERCP sedation can reach 20% to 40%, and in severe cases, it may require suspending the procedure, jaw retraction, face mask positive pressure ventilation, or even tracheal intubation, which can interrupt the procedure and compromise patient safety [6, 7]. Additionally, propofol injection pain is also a common clinical problem, with an incidence of approximately 30% to 70%, which not only increases patient discomfort but also destabilizes the induction phase [8]. Therefore, in this high-stimulation and long-duration procedure scenario of ERCP, it is of great clinical significance to find a new sedative drug that has controllable sedation depth, mild effects on the respiratory and circulatory systems, and less injection pain.

Remimazolam is a novel ultra-short-acting benzodiazepine sedative. It exerts sedative, hypnotic and anti-anxiety effects by selectively acting on the gamma-aminobutyric acid A-type (GABAA) receptor [9]. Compared with midazolam, remimazolam takes effect faster and patients recover more rapidly; compared with propofol, it causes significantly less respiratory and circulatory depression, and its metabolism is independent of hepatic and renal function. It is mainly metabolized by tissue esterase into inactive metabolites, making it suitable for elderly patients and those with hepatic or renal impairment [10, 11]. In recent years, several studies have preliminarily explored the efficacy and safety of remimazolam in gastrointestinal endoscopy [12], bronchoscopy [13], and anesthesia induction [14]. The results showed that remimazolam has significant advantages in maintaining spontaneous breathing, reducing the incidence of hypoxemia, and alleviating injection pain. However, the current clinical evidence regarding the application of remimazolam in ERCP, a special endoscopic procedure, is still limited. In particular, there is a lack of large-sample, retrospective cohort studies using strict statistical methods to control confounding factors.

Based on this, this study adopted a retrospective cohort study design. Propensity score matching (PSM) was used to control for confounding biases between groups, and it systematically compared the efficacy and safety of the spontaneous breathing sedation protocols based on remimazolam and based on propofol in ERCP. The primary outcome measures were recovery time and the incidence of hypoxemia, with the aim of providing clinical evidence for the optimization selection of ERCP sedation protocols.

Materials and methods

Research design and ethical review

This was a single-center retrospective cohort study. The research plan was approved by the Ethical Committee of Shulan (Hangzhou) Hospital (Ethical Approval Number: 2025122201). Due to the retrospective nature of the study, the ethical committee waived the need for patient informed consent. All research procedures were conducted in accordance with the principles of the Helsinki Declaration (2013 revision).

Research subjects

Consecutive patients who underwent ERCP at Shulan (Hangzhou) Hospital from January 2023 to December 2025 and received a sedation protocol that preserved spontaneous breathing were continuously included.

Inclusion criteria: (1) Age ≥ 18 years; (2) American Society of Anesthesiologists (ASA) classification I-III; (3) Scheduled for ERCP treatment; (4) Receiving a sedation protocol that preserved spontaneous breathing based on remimazolam or propofol.

Exclusion criteria: (1) Patients who have undergone tracheal intubation or mechanical ventilation before the surgery; (2) Patients with severe heart or lung diseases (ASA classification ≥ IV); (3) Patients with a history of allergy to benzodiazepines or propofol; (4) Pregnant or lactating women; (5) Patients with severe liver dysfunction (Child-Pugh C grade); (6) Patients with incomplete clinical data.

Sedation protocol

All patients were fasted for 8 hours and without fluids for 4 hours before the ERCP procedure. After entering the room, an upper limb venous access was established, and routine monitoring of heart rate (HR), pulse oxygen saturation (SpO_2), non-invasive blood pressure (NIBP, recorded every 5 minutes), and electrocardiogram (ECG) was performed. All patients maintained spontaneous breathing and did not undergo tracheal intubation. Oxygen was administered via nasal cannula or face mask (flow rate 2-4 L/min).

According to the anesthesia maintenance medication plan, the patients were divided into two groups:

Remi group: The induction was performed by intravenous injection of remimazolam at 0.15-0.25 mg/kg, followed by continuous infusion at 0.5-1.0 mg/(kg·h) to maintain anesthesia. The infusion rate was adjusted according to the Ramsay sedation score (target 3-4 points). The anesthesiologist could administer alfentanil (5-10 μg/kg) or dexmedetomidine (0.5 μg/kg) as an adjunctive analgesic.

Propofol group (Prop group): Induction was achieved by intravenous injection of 1.0-2.0 mg/kg of propofol, followed by continuous infusion at a rate of 4-6 mg/(kg·h). The dose was adjusted based on Ramsay sedation score of 3-4.

If significant body movement affected the procedure in either group of patients, corresponding sedative drugs (remimazolam 2.5-5.0 mg or propofol 20-50 mg) were administered. If severe hypoxemia (SpO_2 < 85% lasting > 30 seconds) occurred and airway intervention measures such as jaw traction and face mask positive pressure oxygenation are ineffective, the procedure may need to be suspended and the rescue airway management process should be initiated.

Data collection

Two independent researchers extracted data from the hospital electronic medical record system, anesthesia record sheets, and endoscopy report systems, and recorded the data using a standardized case report form (CRF). The collected variables included:

Baseline data: age, gender, body mass index (BMI), ASA classification, smoking history, drinking history, comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, coronary heart disease).

Operational-related variables: type of ERCP procedure (diagnostic/treatment), total procedure duration (from entering the scope to withdrawing the scope).

Anesthetic agents and perioperative variables: anesthesia protocol group, recovery time (from the end of the procedure to the patient's response to being called), PACU stay time.

Adverse events: hypoxemia (SpO_2 < 90% for ≥ 15 seconds continuously), severe hypoxia requiring jaw/face mask ventilation, hypotension (systolic blood pressure < 90 mmHg or > 30% decrease from baseline), bradycardia (heart rate < 50 beats/minute), injection pain (patient complaint or facial pain expression during induction), intraoperative movement requiring rescue sedative boluses, procedure failure/interruption.

Patient-reported outcomes: patient satisfaction score 24 hours after surgery (0-10 point numerical rating scale, 0 = very dissatisfied, 10 = very satisfied).

The definitions of all adverse events were based on the standards of previous ERCP sedation studies.

Propensity score matching

To minimize the selection bias caused by the baseline imbalance between the two groups in the retrospective study, this study used the PSM to perform 1:1 matching of the patients in the two groups.

Variable selection: The covariates included in the matching model were age, gender, BMI, ASA classification (grade I/II vs. grade III), procedure type (diagnostic vs. therapeutic), procedure duration (< 60 min vs. ≥ 60 min), and comorbidities (hypertension, diabetes, COPD). All these variables were considered as confounding factors that might affect the choice of sedation regimen based on clinical judgment.

Matching method: The propensity score for each patient receiving remimazolam treatment

was calculated using a multivariate Logistic regression model. The 1:1 nearest-neighbor matching method was used for matching, with a caliper value (caliper) set as 0.02 times the standard deviation of the propensity score, without replacement.

Matching effect evaluation: The balance between the groups before and after matching was evaluated using the standardized mean difference (Standardized Mean Difference, SMD), and a SMD < 0.1 was considered as good group balance.

Outcome indicators

Primary outcomes: (1) Wake-up time: defined as the time interval (in minutes) from the end of the procedure to the patient's response by opening their eyes upon being called; (2) Incidence of intraoperative hypoxemia: defined as the proportion of patients with SpO_2 < 90% for ≥ 15 seconds.

Secondary outcome: (1) PACU stay time (in minutes); (2) Patient satisfaction score at 24 hours after surgery (0-10 points); (3) Incidence of severe hypoxia requiring jaw/chest mask ventilation; (4) Incidence of hypotension (SBP < 90 mmHg or a decrease of > 30% from baseline); (5) Incidence of bradycardia (HR < 50 beats per minute); (6) Incidence of injection pain; (7) Incidence of requiring additional sedative drugs due to intraoperative movement; (8) Completion rate of ERCP procedure.

Statistical analysis

Data analysis was performed using SPSS 26.0 statistical software (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro-Wilk test. Variables that met the normal distribution criteria were expressed as mean ± standard deviation (SD), and comparisons between groups were conducted using independent sample t-tests (before matching) or paired t-tests (after matching). Variables with non-normal distribution were expressed as median (interquartile range) [M (IQR)], and comparisons between groups were performed using the Mann-Whitney U test (before matching) or Wilcoxon signed-rank test (after matching). Categorical variables were expressed as the number of cases (percentage) [n (%)]. Before matching, group comparisons were conducted using the χ^2 test or Fisher's exact test, and after matching, McNemar test was used. Propensity score matching was performed using a 1:1 nearest neighbor matching method, with a caliper of 0.02, and a standardized mean difference (SMD) < 0.1 was considered as good balance. The cumulative survival curve of intraoperative no hypoxemia was plotted using the Kaplan-Meier method, and group differences were tested using the Log-rank test. The Cox proportional hazards regression model (with paired ID as a stratification variable) was used to evaluate the independent risk factors for hypoxemia, and the core variables included in the model were grouping, age, procedure duration, and ASA grade III. Results were expressed as hazard ratio (HR) and 95% confidence interval (CI). Subgroup analysis was stratified by age, ASA classification, procedure duration, hypertension, diabetes, and COPD. The differences in the incidence of hypoxemia between the two groups within each subgroup were compared, and results were expressed as odds ratio (OR) and 95% CI. The C-index (concordance index) was calculated to evaluate the discriminative ability of the Cox model. Given the explanatory rather than predictive nature of our analysis, Brier scores and calibration curves were not computed. All tests were two-sided, and a *P* value < 0.05 was considered statistically significant.

Results

Study population and matching results

This study included a total of 350 patients who underwent ERCP and received sedation with spontaneous breathing. Among them, 204 patients were in the remimazolam group, and 146 patients were in the propofol group. After propensity score matching (PSM), 99 pairs (a total of 198 cases) were successfully matched. The matching rate was 48.5% (99 of 204 remimazolam patients). After matching, there were no significant differences in baseline characteristics, including age, sex, BMI, ASA classification, procedure type, procedure duration, and comorbid conditions (hypertension, diabetes, COPD), between the two groups (all *P* values > 0.05), indicating a good matching effect and comparability of the two groups (**Tables 1**, **2**; **Figures 1**-**3**).

Table 1. Baseline characteristics of patients before propensity score matching

Variable	Remi (n = 204)	Prop (n = 146)	t/χ^2	*P* value
Age (years)	58.55 ± 12.11	50.65 ± 13.46	5.743	< 0.001
Sex			0.016	0.899
Male	106 (52.0%)	74 (50.7%)		
Female	98 (48.0%)	72 (49.3%)		
BMI (kg/m^2)	24.31 ± 3.66	23.69 ± 3.54	1.573	0.117
ASA				
1	32 (15.7%)	34 (23.3%)	6.251	0.044
2	124 (60.8%)	91 (62.3%)		
3	48 (23.5%)	21 (14.4%)		
Procedure type			20.864	< 0.001
Therapeutic	21 (10.3%)	44 (30.1%)		
Diagnostic	183 (89.7%)	102 (69.9%)		
Procedure duration (min)	48.48 ± 13.87	41.99 ± 14.77	4.200	< 0.001
Hypertension			0.897	0.343
No	155 (76.0%)	118 (80.8%)		
Yes	49 (24.0%)	28 (19.2%)		
Diabetes			0.000	1.000
No	178 (87.3%)	128 (87.7%)		
Yes	26 (12.7%)	18 (12.3%)		
COPD			0.030	0.862
No	198 (97.1%)	143 (97.9%)		
Yes	6 (2.9%)	3 (2.1%)		

Data are presented as mean ± SD or n (%). *P* values were calculated using independent-samples t-test for continuous variables and chi-square test for categorical variables. Notes: BMI, body mass index; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

Perioperative outcome comparison

Primary outcome: The recovery time in the remimazolam group was significantly shorter than that in the propofol group (3.46 ± 1.15 min vs. 7.55 ± 2.93 min, P < 0.001).

The incidence of intraoperative hypoxemia (SpO_2 < 90%) in the remimazolam group was 19.2% (19/99), significantly lower than 41.4% (41/99) in the propofol group (P < 0.001). The Kaplan-Meier survival curve analysis showed that the cumulative probability of remaining free from hypoxemia during the procedure in the remimazolam group was significantly higher than that in the propofol group (Log-rank P < 0.001) (**Figure 4**).

Secondary outcome: The postoperative recovery unit (PACU) stay time in the remimazolam group was significantly shorter than that in the propofol group (25.07 ± 6.02 min vs. 34.71 ± 8.23 min, P < 0.001), and the patient satisfaction score was significantly higher than that in the propofol group (9.31 ± 0.68 vs. 8.14 ± 1.21, P < 0.001).

In terms of adverse events, the incidence of hypotension (6.1% vs. 21.2%, P = 0.005) and injection pain (4.0% vs. 34.3%, P < 0.001) in the remimazolam group was significantly lower than that in the propofol group. There were no statistically significant differences in severe hypoxia (7.1% vs. 15.2%, P = 0.136), bradycardia (7.1% vs. 5.1%, P = 0.773), intraoperative movement (17.2% vs. 12.1%, P = 0.424), and procedure completion rate (100.0% vs. 97.0%, P = 0.248) between the two groups (**Table 3**; **Figure 5**).

Multivariate cox regression analysis of risk factors for hypoxemia

To further evaluate whether the protective effect of remimazolam on hypoxemia is independent of confounding factors, we included age, procedure duration, and ASA classification in the multivariate Cox regression model for

Table 2. Baseline characteristics of patients after propensity score matching

Variable	Remi (n = 99)	Prop (n = 99)	t/χ^2	*P* value
Age (years)	55.85 ± 11.94	55.10 ± 12.88	0.531	0.596
Sex			0.180	0.671
Male	45 (45.5%)	49 (49.5%)		
Female	54 (54.5%)	50 (50.5%)		
BMI (kg/m^2)	23.97 ± 3.64	23.87 ± 3.50	0.193	0.848
ASA			0.791	0.673
1	24 (24.2%)	19 (19.2%)		
2	57 (57.6%)	62 (62.6%)		
3	18 (18.2%)	18 (18.2%)		
Procedure type			2.118	0.146
Therapeutic	81 (81.8%)	88 (88.9%)		
Diagnostic	18 (18.2%)	11 (11.1%)		
Procedure duration (min)	45.82 ± 13.93	46.81 ± 13.75	-0.569	0.570
Hypertension			0.000	1.000
No	22 (22.2%)	23 (23.2%)		
Yes	77 (77.8%)	76 (76.8%)		
Diabetes			0.062	0.803
No	10 (10.1%)	10 (10.1%)		
Yes	89 (89.9%)	89 (89.9%)		
COPD			0.000	1.000
No	1 (1.0%)	2 (2.0%)		
Yes	98 (99.0%)	97 (98.0%)		

Data are presented as mean ± SD or n (%). *P* values were calculated using paired t-test for continuous variables and McNemar's test for categorical variables. SMDs were all < 0.1, indicating adequate balance. Notes: BMI, body mass index; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference.

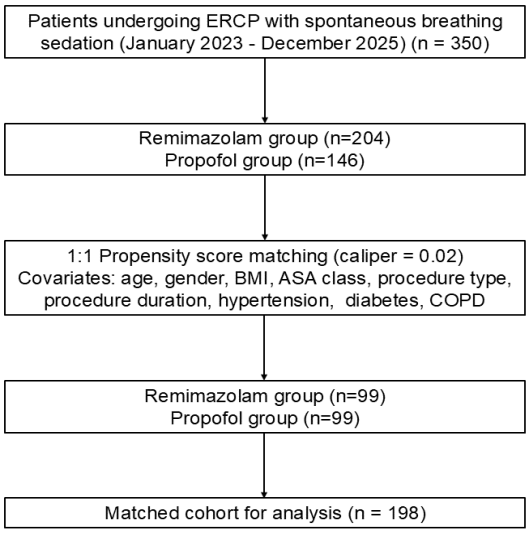


Figure 1. CONSORT flow diagram of patient selection. Note: CONSORT, Consolidated Standards of Reporting Trials.

correction. The results showed that the remimazolam regimen was associated with a marginally reduced risk of hypoxemia (HR = 0.462, 95% CI: 0.212-1.008, P = 0.052), with marginal statistical significance. Age (HR = 1.042, 95% CI: 0.938-1.158, P = 0.442), procedure duration (HR = 0.955, 95% CI: 0.877-1.040, P = 0.287), and ASA grade III (HR = 5.374, 95% CI: 0.599-48.226, P = 0.133) were not independent risk factors for hypoxemia (**Table 4**).

Subgroup analysis

The subgroup analysis revealed that the protective effect of remimazolam against hypoxemia was consistent across all subgroups. In the subgroups of patients aged ≥ 65 years (OR = 0.127, 95% CI: 0.036-0.450), hypertension (OR = 0.249, 95% CI: 0.083-0.743), diabetes (OR = 0.166, 95% CI: 0.028-0.974), and non-COPD (OR = 0.352, 95% CI: 0.199-0.623), remimazolam demonstrated significant hypoxia protection (**Table 5**; **Figure 6**).

Discussion

This study, through a retrospective cohort design, used PSM to control for confounding

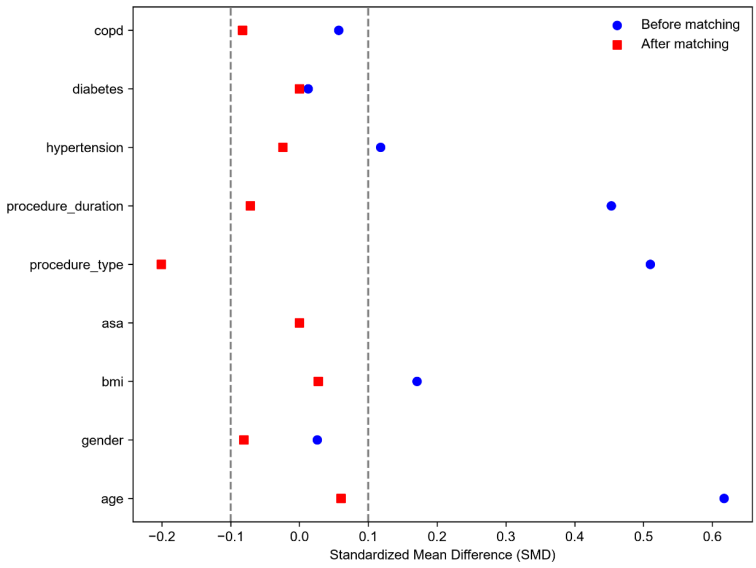


Figure 2. Love plot showing standardized mean differences for covariates before and after propensity score matching. Blue circles represent SMDs before matching; red squares represent SMDs after matching. The dashed vertical lines indicate the threshold of 0.1 for acceptable balance. After matching, all covariates had SMDs < 0.1, indicating successful balance between groups. Note: SMD, standardized mean difference.

biases and systematically compared the efficacy and safety of the spontaneous breathing sedation protocols based on remimazolam and propofol in ERCP. The results showed that compared with the propofol protocol, the remimazolam protocol significantly shortened the patient's recovery time (3.46 min vs. 7.55 min, $P < 0.001$) and the PACU stay time (25.07 min vs. 34.71 min, $P < 0.001$), significantly reduced the incidence of hypoxemia (19.2% vs. 41.4%, $P < 0.001$), hypotension (6.1% vs. 21.2%, $P = 0.005$), and injection pain (4.0% vs. 34.3%, $P < 0.001$), and were associated with significantly higher patient satisfaction scores (9.31 vs. 8.14, $P < 0.001$). Multivariate Cox regression analysis showed that the remimazolam protocol was associated with a reduced risk of hypoxemia (HR = 0.462, 95% CI: 0.212-1.008, $P = 0.052$), showing a marginal statistical significance. Subgroup analysis further confirmed that the protective effect of remimazolam remained consistent in most subgroups. These results suggest that the spontaneous breathing sedation protocol based on remimazolam in ERCP has good efficacy and safety, and may be considered a preferred option for ERCP sedation.

In this study, the recovery time of the remimazolam group (3.46 min) was significantly shorter than that of the propofol group (7.55 min), and the difference was highly statistically significant. This finding is consistent with the pharmacological properties of remimazolam. Remimazolam is an ultra-short-acting benzodiazepine sedative, whose mechanism of action is to selectively activate the γ-aminobutyric acid A-type (GABAA) receptor, resulting in sedation, hypnosis, and anti-anxiety effects [15]. Unlike propofol, which is mainly metabolized by the liver, remimazolam is mainly hydrolyzed by tissue esterase (especially carboxylesterase-1, CES-1) into an inactive carboxylic acid metabolite (CNS 7054), which is independent of hepatic or renal function and is pharmacologically inactive, so the elimination half-life is short (about 0.75-1.0 h), and patients can wake up quickly after discontinuation [16, 17]. Previous studies have also confirmed that the recovery time of remimazolam is significantly better than that of propofol in colonoscopy [18] and bronchoscopy [19]. In the scenario of ERCP, which has a relatively long procedure time and special patient positions, rapid awakening not only helps shorten the PACU stay time, accelerate the efficiency of the endoscopy center, but also reduces the risk of complications related to prolonged sedation.

Unlike routine gastrointestinal endoscopy, ERCP is typically performed in the prone or semi-prone position, where gravity predisposes the patient to tongue base collapse and limited mandibular protrusion, thereby increasing the risk of upper airway obstruction [20]. Furthermore, ERCP involves prolonged procedural time and repeated instrumentation of the duodenal papilla, imposing stronger and more sustained noxious stimuli that demand a stable depth of sedation [21]. In this unique and challenging setting, our study demonstrated a more pronounced benefit of remimazolam against hypoxemia (absolute risk reduction 22.2%, OR = 0.336), with an effect size that appears larger than that reported in previous meta-analyses for routine gastrointestinal endoscopy (OR ≈

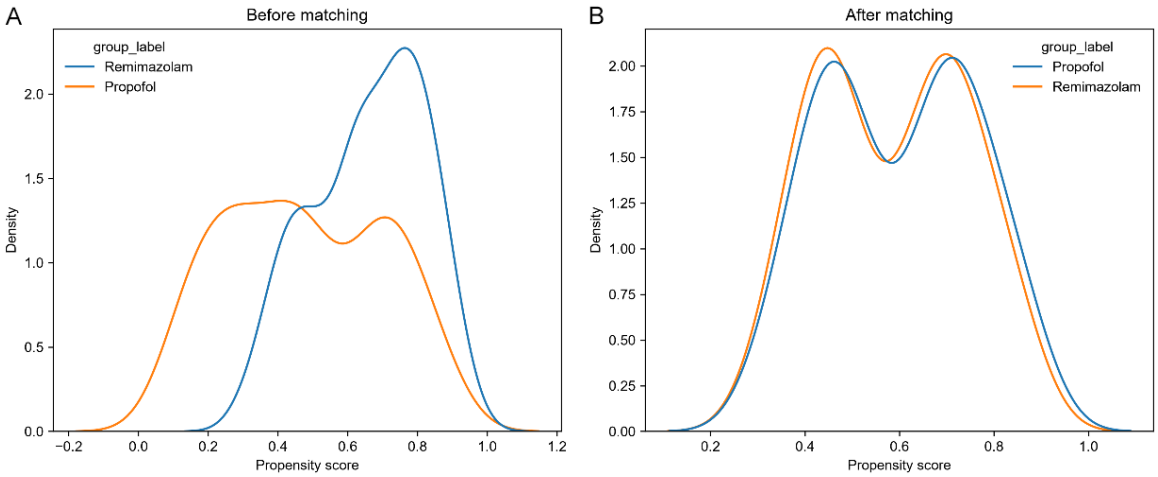


Figure 3. Propensity score density distribution before and after propensity score matching. A. Before matching: the two density curves showed substantial separation, indicating baseline differences. B. After matching: the curves overlapped almost completely, confirming successful balance. Remi, remimazolam group; Prop, propofol group.

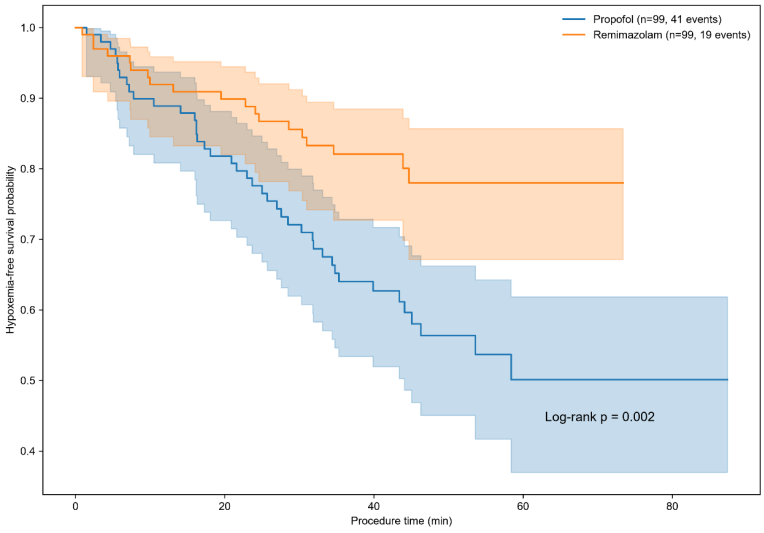


Figure 4. Kaplan-Meier curves for intraoperative hypoxemia-free survival. The remimazolam group (red line, n = 99, 19 events) demonstrated significantly higher hypoxemia-free survival probability compared with the propofol group (blue line, n = 99, 41 events). Log-rank test: χ^2 = 9.832, P = 0.002. Shaded areas indicate 95% confidence intervals.

0.40-0.50). This observation suggests that the airway-protective effect of remimazolam may be amplified under the prone position where airway collapsibility is increased. The proposed mechanism is that remimazolam, as a GABAA receptor agonist, exerts weaker depression on the brainstem respiratory centers and the hypoglossal nucleus compared with propofol, thus preserving upper airway dilator muscle tone and maintaining airway patency even in the prone position [22]. In contrast, propofol is known to increase upper airway collapsibility by suppressing hypoglossal nucleus activity [23]. This position-specific airway protection is difficult to fully capture in routine endoscopy (which is usually performed in the left lateral position) and represents the unique contribution of our ERCP-focused study, distinguishing it from previous investigations in general endoscopic sedation.

Hypoxemia is one of the most common and clinically significant adverse events in ERCP sedation. Previous studies have shown that the incidence of hypoxemia in propofol sedation for ERCP is approximately 20%-40% [24, 25], which is basically consistent with the 41.4% in the propofol group of this study. The incidence of hypoxemia in the remimazolam group was 19.2%, which was more than 50% lower than that of the propofol group, with an absolute risk reduction of 22.2%, with a number needed to treat (NNT) of approximately 5. The Kaplan-Meier survival curve also showed that the cumulative survival rate without hypoxemia during the procedure in the remimazolam group was significantly higher than that in the propofol group (Log-rank P = 0.002). The potential mechanisms underlying remimazolam's mild respiratory effects include:

Table 3. Comparison of perioperative outcomes between groups after propensity score matching

Outcome	Remi (n = 99)	Prop (n = 99)	t/χ^2	*P* value
Recovery time (min)	3.46 ± 1.15	7.55 ± 2.93	-12.682	< 0.001
PACU stay (min)	25.07 ± 6.02	34.71 ± 8.23	-9.366	< 0.001
Patient satisfaction (0-10)	9.31 ± 0.68	8.14 ± 1.21	8.123	< 0.001
Hypoxemia (SpO_2 < 90%)	19 (19.2%)	41 (41.4%)	11.025	< 0.001
Severe hypoxemia	7 (7.1%)	15 (15.2%)	2.227	0.136
Hypotension	6 (6.1%)	21 (21.2%)	7.840	0.005
Bradycardia	7 (7.1%)	5 (5.1%)	0.083	0.773
Injection pain	4 (4.0%)	34 (34.3%)	24.735	< 0.001
Body movement requiring rescue	17 (17.2%)	12 (12.1%)	0.640	0.424
Procedure success	99 (100.0%)	96 (97.0%)	1.333	0.248

Data are presented as mean ± SD or n (%). *P* values were calculated using paired t-test for continuous variables and McNemar's test for categorical variables. PACU, post-anesthesia care unit. Notes: PACU, post-anesthesia care unit.

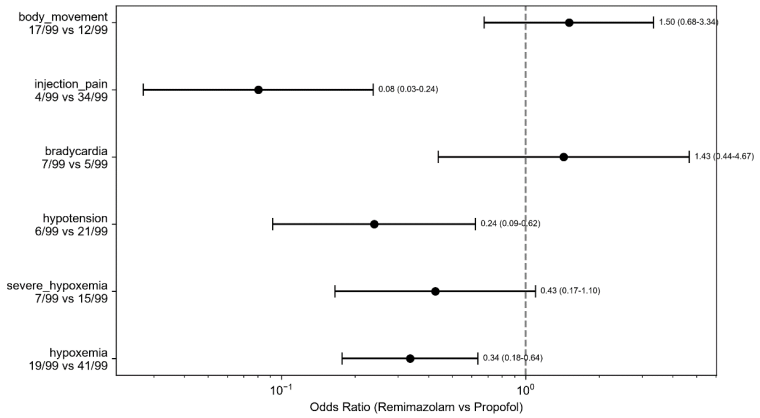


Figure 5. Forest plot of odds ratios for major adverse events after propensity score matching. OR with 95% CIs for adverse events in the remimazolam group compared with the propofol group. Event counts (remimazolam vs. propofol) are shown adjacent to each outcome: hypoxemia (19/99 vs. 41/99), severe hypoxemia (7/99 vs. 15/99), hypotension (6/99 vs. 21/99), bradycardia (7/99 vs. 5/99), injection pain (4/99 vs. 34/99), and body movement requiring rescue (17/99 vs. 12/99). The vertical dashed line at OR = 1 indicates no effect. Note: OR, odds ratio; CI, confidence interval.

Firstly, as a GABAA receptor agonist, remimazolam has a weaker inhibitory effect on the brainstem respiratory center than propofol, and patients can still maintain the ventilation response to hypoxia and hypercapnia in the sedated state [26]; Secondly, the depth of sedation induced by remimazolam is dose-dependent, but it is not likely to cause apnea within the conventional clinical dose range [27]; Thirdly, remimazolam does not inhibit the muscle tension of the upper airway, which is conducive to maintaining airway patency. This makes remimazolam have a unique advantage in non-intubation sedation that retains spontaneous breathing. For the ERCP scenario where the procedure duration is long and the patient is in a prone position, which is unfavorable for airway management, the respiratory safety advantage of remimazolam is particularly important.

It is worth noting that the multivariate Cox regression analysis shows that although the protective effect of remimazolam on hypoxemia has a marginal statistical significance (HR = 0.462, 95% CI: 0.212-1.008, P = 0.052), the effect size (HR < 1) is consistent with the results of the univariate analysis. The *P* value in the multivariate analysis did not reach statistical significance, which may be related to the limited sample size (99 pairs) and the number of hypoxemia events (60 cases) after matching, rather than the absence of an effect. This interpretation is also supported by the subgroup analysis - in the vast majority of subgroups, remimazolam shows a consistent hypoxia protection effect.

In this study, the incidence of hypotension in the remimazolam group (6.1%) was significantly lower than that in the propofol group (21.2%, P = 0.005), suggesting that remimazolam has a more mild inhibitory effect on the cardiovascular system. The main mechanism of propofol-induced hypotension includes reduced peripheral vascular resistance, inhibition of sympa-

Table 4. Multivariable Cox regression analysis for risk factors of hypoxemia

Variable	HR (95% CI)	Z	*P* value
Remimazolam (vs. Propofol)	0.462 (0.212-1.008)	-1.941	0.052
Age (per year increase)	1.042 (0.938-1.158)	0.768	0.442
Procedure duration (per min increase)	0.955 (0.877-1.040)	-1.065	0.287
ASA III (vs. ASA I/II)	5.374 (0.599-48.226)	1.502	0.133

Adjusted for age, procedure duration, and ASA III status. Stratified by matched pairs. Notes: HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists.

Table 5. Subgroup analysis for hypoxemia and dose-related outcomes

Subgroup	Remi n/N (%)	Prop n/N (%)	OR (95% CI)	*P* value
High airway risk	13/50 (26.0%)	23/47 (48.9%)	0.367	0.033
Low airway risk	6/49 (12.2%)	18/52 (34.6%)	0.264	0.016
High dose (≥ median)	10/56 (17.9%)	9/43 (20.9%)	-	0.899
Recovery time (high vs. low dose)	3.65 ± 1.28	3.23 ± 0.93	-	0.070
Body movement (high vs. low dose)	8/56 (14.3%)	9/43 (20.9%)	-	0.548

High airway risk was defined as BMI ≥ 28 kg/m^2, age ≥ 65 years, or ASA III. The median remimazolam maintenance dose (0.75 mg/kg/h) was used as the cutoff for high-dose versus low-dose stratification. Data are presented as n/N (%) or mean ± SD. Notes: OR, odds ratio; CI, confidence interval; ASA, American Society of Anesthesiologists.

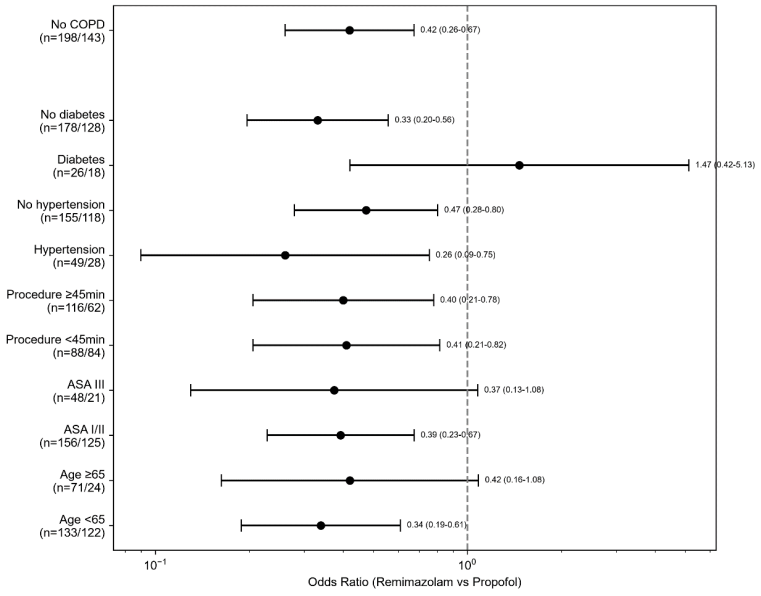


Figure 6. Subgroup analysis forest plot for the protective effect against hypoxemia. Subgroup analyses stratified by age, ASA status, procedure duration, hypertension, diabetes, and COPD. Sample sizes for each subgroup (remimazolam/propofol) are shown in parentheses: age < 65 (133/122), age ≥ 65 (71/24), ASA I/II (156/125), ASA III (48/21), procedure < 45 min (88/84), procedure ≥ 45min (116/62), hypertension (49/28), no hypertension (155/118), diabetes (26/18), no diabetes (178/128), and no COPD (198/143). Most subgroups showed ORs < 1, indicating a consistent protective effect of remimazolam. Data for the COPD subgroup were insufficient for reliable estimation. Note: OR, odds ratio; CI, confidence interval; COPD, chronic obstructive pulmonary disease.

thetic nerve activity, and weakened myocardial contractility [28, 29], while the effect of remimazolam on hemodynamics is relatively mild, which may be attributed to its minimal suppression of sympathetic tone [30]. For ERCP patients aged 65 or older, ASA grade III, and with cardiovascular diseases, remimazolam has clear clinical benefits in maintaining hemodynamic stability.

Injection pain is one of the most common adverse reactions during propofol induction, with an incidence of up to 30%, mainly caused by the direct stimulation of vascular endothelium and activation of the kinin release enzyme - kinin system by propofol [31-33]. The incidence of injection pain in the propofol group in this study was 34.3%, consistent with the literature reports; while the incidence of injection pain in the remimazolam group was only 4.0% (P < 0.001), almost completely avoiding it. This advantage not only significantly improves the comfort and satisfaction of patients during the anesthesia induction period (this study also con-

firmed that the satisfaction score of the remimazolam group was significantly higher), but also avoids the adverse effects of body movement caused by injection pain on the procedure.

Subgroup analysis showed that the protective effect of remimazolam on hypoxemia is consistent in most subgroups, especially in patients younger than 65 years old, ASA grade I/II, procedure duration < 45 minutes, hypertension, and non-diabetic patients; in patients aged ≥ 65 years and ASA grade III, the OR value did not reach the traditional significance level, but the direction is consistent and the effect size is similar (≥ 65 years: OR = 0.420, 95% CI: 0.163-1.085; ASA III grade: OR = 0.374, 95% CI: 0.130-1.079), suggesting that the protective effect of remimazolam is not significantly heterogeneous among different subgroups. The COPD subgroup, due to the small sample size (only 3 COPD patients after matching), the data is insufficient for reliable estimation, reflecting the inherent limitations of rare subgroup analysis in retrospective studies.

Our findings are consistent with previous studies on the application of remimazolam in digestive endoscopy sedation. In a randomized controlled trial, Chudziński et al. [34] reported that remimazolam had non-inferior sedation success rate in colonoscopy compared to propofol, and the incidence of respiratory depression was lower. The meta-analysis by Sneyd et al. [35] included multiple randomized controlled studies comparing remimazolam with propofol, and also confirmed that remimazolam had better respiratory safety in maintaining spontaneous breathing during sedation. However, most of these studies focused on routine gastroscopy, and research on ERCP, a highly stimulating, long-duration, and position-specific procedure scenario, was still limited.

Based on the results of this study, remimazolam has the following clinical application value in ERCP with spontaneous breathing maintenance: (1) rapid awakening, which is conducive to the efficient turnover of the endoscopy center; (2) significantly reduced incidence of hypoxemia, hypotension, and injection pain, with prominent safety advantages; (3) particularly suitable for high-risk patients such as the elderly, those with concurrent heart and lung diseases, those with longer expected procedure time, or those who need to maintain spontaneous breathing. With the increasing demand for ERCP diagnosis and treatment and the intensification of population aging, remimazolam is expected to become the preferred drug for ERCP sedation.

This study has the following limitations: First, this study was a single-center retrospective design. Although propensity score matching controlled for observable confounding factors, the matching was limited to the collected covariates and there may still be residual confounding caused by unmeasured confounding factors (such as operator experience, endoscopist preference, intraoperative emergencies, etc.), which is an inherent limitation of all retrospective studies. Second, the sample size after matching was 99 pairs (a total of 198 cases), although it was sufficient for statistical analysis, the sample size of some subgroups (such as COPD) was still insufficient, resulting in less precise effect estimation. Third, some patients in the remimazolam group received concomitant alfentanil or dexmedetomidine at the anesthesiologist's discretion. Due to the retrospective design, the electronic anesthesia records did not systematically document the specific indications or dosing regimens of these adjuvants in a structured format, precluding reliable subgroup analyses. We therefore cannot completely rule out their potential influence on the observed outcomes. Nevertheless, the substantial effect sizes-54% reduction in hypoxemia, 71% in hypotension, and 94% in injection pain-are unlikely to be entirely attributable to adjuvant use. Moreover, both groups were managed with consistent Ramsay sedation targets (score 3-4), and the use of adjuvants reflected real-world clinical practice rather than systematic bias. We acknowledge this as an inherent limitation and emphasize that future prospective studies with standardized combination regimens are warranted to clarify the independent effect of remimazolam monotherapy. Fourth, this study did not assess the fine indicators of postoperative cognitive function recovery (such as the Montreal Cognitive Assessment Scale score), and the impact of remimazolam on postoperative cognitive function warrants further investigation. Fifth, all patients in this study were of Chinese ethnicity, and whether the research conclusion is applicable to other ethnic groups needs to be verified. Future stud-

ies should conduct multicenter, prospective, large-sample randomized controlled trials to further verify the conclusions of this study.

Conclusion

Remimazolam-based sedation with preserved spontaneous breathing demonstrated favorable efficacy and safety in ERCP. Compared with the propofol protocol, the remimazolam protocol can significantly shorten the patient's recovery time and PACU stay time, significantly reduce the incidence of hypoxemia, hypotension and injection pain, and improve patient satisfaction. Both propensity score matching and multivariate regression analysis support the protective trend of remimazolam against hypoxemia. Remimazolam can be used as the preferred option for spontaneous breathing sedation in ERCP, especially for high-risk patients who are elderly or have comorbidities of heart and lung diseases.

Disclosure of conflict of interest

None.

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