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Effects of Propofol–remifentanil on Apoptotic Molecules, Plasma CXCL10, and CXCL13 in Pancreatic Cancer Patients

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ABSTRACT

This study aimed to investigate whether propofol-remifentanil anesthesia offers superior perioperative outcomes compared to propofol-fentanyl in pancreatic cancer surgery patients, with a focus on its effects on apoptotic molecules, plasma CXCL10/CXCL13 levels, and postoperative recovery.

A total of 150 pancreatic cancer patients were divided into 2 cohorts receiving either propofol-fentanyl (control group, n=75) or propofol-remifentanil (study group, n=75) anesthesia. We measured perioperative hemodynamics (cardiac index [CI], mean arterial pressure [MAP], heart rate [HR]), T-cell subsets, postoperative recovery indices (eye-opening time, extubation time, spontaneous respiration recovery time), sedation and analgesia levels (via Ramsay sedation score [RSS] and visual analog scale [VAS]), plasma CXCL10/CXCL13 levels, and apoptosis-related proteins (*Survivin*, *Bax*, *Caspase-4*, *Bcl-2*) using enzyme-linked immunosorbent assays (ELISAs). Adverse reactions were also recorded.

The study group exhibited significant advantages in hemodynamic stability and immune preservation. Despite similar baseline cardiovascular parameters, the remifentanil group maintained better CI, MAP, and HR stability during and after surgery. Flow cytometry analysis revealed better preservation of T-cell immunity ($CD4^+$, $CD3^+$, $CD4^+/CD8^+$ T cells) at 24 hours post-surgery. The intervention group also demonstrated accelerated postoperative recovery with significantly reduced emergence times (eye-opening, extubation, spontaneous respiration). Notably, the study group had more favorable inflammatory profiles (lower CXCL10/CXCL13 levels) and enhanced apoptotic responses (modulated *Bax*, *Caspase-4*, *Survivin*, and *Bcl-2* expression). Clinical outcomes were superior in the study group, with significantly fewer adverse events (2 vs. 9 patients).

Propofol-remifentanil anesthesia provides effective sedation and analgesia in pancreatic cancer surgery, modulates key biological pathways related to apoptosis and inflammation, and improves postoperative recovery. These findings suggest that the choice of anesthesia regimen may have significant implications for perioperative outcomes and potentially long-term prognosis in pancreatic cancer patients. Future research should further explore the underlying mechanisms and long-term clinical benefits of this anesthesia strategy.

Keywords: Apoptosis; CXCL10 Chemokine; CXCL13 Chemokine; Pancreatic neoplasms; Propofol; Remifentanil

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INTRODUCTION

Pancreatic cancer is a malignant tumor originating from pancreatic tissue that is characterized by high invasiveness and early metastasis.[1] Owing to its nonspecific early symptoms, approximately 60% of patients exhibit metastatic disease upon their initial diagnosis, often reaching advanced stages with poor treatment outcomes, resulting in its designation as one of the most lethal malignancies.[2] Currently, effective treatment options for pancreatic cancer are limited. At present, surgical excision coupled with chemotherapy continues to constitute the sole potentially curative therapeutic strategy, albeit with significant postoperative mortality risks.[3] The perioperative period constitutes a critical time window for cancer cell dissemination because of surgical manipulation, immunosuppression, and physiological alterations, which may contribute to tumor recurrence.[4] As an integral component of perioperative care, anesthetic management has drawn increasing research attention. The current literature suggests that anesthetic compounds may modify key biological processes, including cellular multiplication, maturation, migration, and neovascularization, indicating their potential role in influencing malignancy development and patient survival through unidentified biological mechanisms.[5] Propofol, a widely used intravenous anesthetic for tumor resection surgeries, offers advantages, including smooth induction and rapid recovery.[6] In addition to its anesthetic properties, propofol has multiple nonanesthetic effects, particularly antitumor activity. Previous studies have confirmed that propofol can directly or indirectly affect malignant progression through the modulation of critical RNAs, signaling pathways, and immune function.[7]

Although propofol has advantages, including rapid onset, quick metabolism, and short recovery time, its anesthetic effect may be insufficient when it is used alone.[8] This is primarily attributed to the limited analgesic properties of propofol, particularly in extensive surgeries with prolonged durations or high analgesic demands, where it may inadequately suppress surgical stress responses and pain perception.[9] For example, in complex pancreatic cancer surgeries characterized by wide operative fields, extended duration, and significant tissue trauma, propofol monotherapy often fails to provide sufficient analgesia. This insufficiency may lead to intraoperative hemodynamic instability, elevated stress hormone levels, and potentially compromised postoperative recovery and long-term outcomes.[10] Consequently, in clinical practice, propofol is typically combined with adjunctive agents, particularly opioids, to enhance analgesic efficacy and maintain anesthetic stability. Owing to its unique pharmacological profile, remifentanil, a novel μ-opioid receptor agonist, has gained widespread clinical application.[11] It achieves peak effects within one minute and has an ultrashort duration of action (elimination half-life: 3–10 minutes), enabling precise dose titration according to surgical requirements.[12] Unlike conventional opioids, nonspecific esterases distributed throughout the blood and tissues catalyze the rapid hydrolytic degradation of remifentanil, independent of hepatic or renal function.[13] This metabolic pathway ensures safe use even in patients with organ dysfunction while preventing drug accumulation and facilitating prompt recovery after discontinuation. These superior pharmacokinetic properties establish remifentanil as an ideal intraoperative analgesic that is now widely adopted in clinical practice across numerous countries.[14]

Recent studies have demonstrated that anesthetic agents may indirectly influence tumor progression and patient prognosis by modulating immune function and the tumor microenvironment. In pancreatic cancer surgery, the propofol-remifentanil anesthesia may offer significant advantages. Propofol and remifentanil may exert potential effects on the biological behavior of tumor cells through mechanisms involving apoptosis regulation and inflammatory cytokine release.[15] The objective of our study was to analyze the impact of propofol-remifentanil on the levels of apoptotic molecules and plasma CXCL10 and CXCL13 in patients who underwent pancreatic cancer surgery. CXCL10 and CXCL13 are critical chemokines that participate in regulating immune cell migration and inflammatory responses, potentially acting as key determinants in tumor niche formation and neoplastic evolution. By investigating the effects of propofol-remifentanil at these molecular levels, this study not only provides a scientific basis for selecting anesthesia regimens for pancreatic cancer surgery but also offers novel insights into improving postoperative recovery and long-term prognosis. The findings are expected to provide valuable references for clinical anesthesia practices, further

optimize anesthesia management strategies for pancreatic cancer surgery, and ultimately augment clinical benefits while optimizing quality of life.

MATERIALS AND METHODS

A total of 150 patients who underwent surgical resection for pancreatic cancer between December 2021 and December 2023 were enrolled and divided into control and study groups. The control group (n=75) received propofol-fentanyl for anesthesia maintenance, whereas the study group (n=75) received propofol-remifentanil. The inclusion criteria were as follows: histologically or cytologically confirmed pancreatic cancer; localized tumors with or without local invasion but no distant metastasis meeting the resection criteria; radiographic assessment indicating complete tumor resectability (R0 resection) without major vascular invasion or with invasion within surgically manageable limits; no prior radiotherapy, chemotherapy, or other antitumor treatments; American Society of Anesthesiologists (ASA) classification of I–III; adequate cardiopulmonary, hepatic, and renal function to tolerate surgery; and the absence of severe coagulation disorders or immune system diseases. The exclusion criteria included radiographic or intraoperative evidence of extensive tumor invasion or distant metastasis; major vessels encased or invaded by the tumor preventing complete resection; severe cardiopulmonary insufficiency; hepatic or renal failure or other comorbidities contraindicating surgery; a history of pancreatic surgery or other major upper abdominal surgeries complicating the current procedure; uncontrolled infections or active inflammatory diseases; and pregnancy or lactation. The study protocol is outlined in Figure 1.

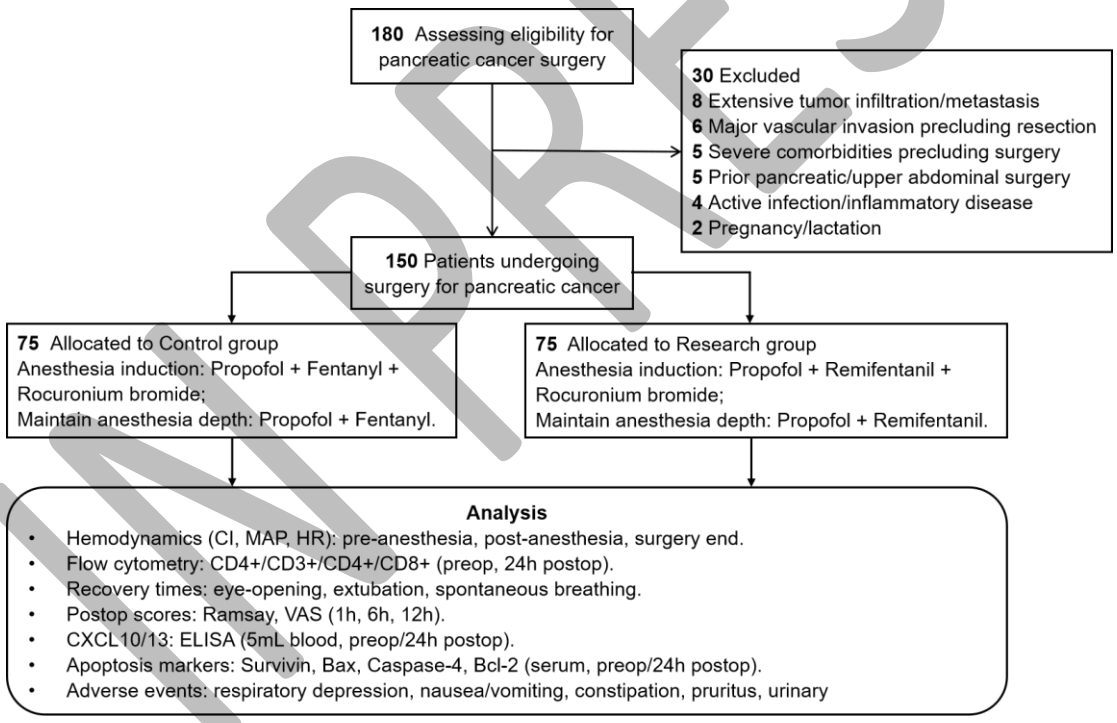

Figure 1. Flowchart of patient enrollment and study design

Blinding Description

This study is a retrospective cohort analysis. Data were extracted from the electronic medical records of patients who underwent pancreatic cancer surgery between December 2021 and December 2023. Patients were categorized into two cohorts based on the anesthesia regimen documented in their records: the propofol-fentanyl cohort (control group, n=75) and the propofol-remifentanil cohort (study group, n=75). To ensure objectivity during data analysis, all patient identifiers were removed, and data were coded before statistical processing. The analysts were blinded to the group assignments during the analysis phase.

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Sample Size Calculation

Sample size determination was conducted via an independent two-sample *t* test methodology using G*Power software. The parameters used were as follows: a medium effect size (Cohen's d = 0.5),[16] two-tailed significance level α=0.05, and desired statistical power of 0.80. The calculations yielded a required sample size of 64 participants per study arm (N_1=N_2=64), totaling 128 participants. To ensure adequate statistical power, we identified 150 eligible records, exceeding the minimum requirement and ensuring compliance with the study design specifications.

Anesthesia Protocol

Preoperative Preparation: Both groups underwent routine preoperative fasting and received intravenous midazolam (0.05 mg/kg) (Ni'erxin, Enhua Pharmaceutical, Jiangsu, China) prior to anesthesia induction.

Anesthesia Induction: In the control group, anesthesia was induced via intravenous administration of propofol (2 mg/kg) (Diprivan, AstraZeneca), fentanyl (3 μg/kg) (Renfu, Yichang Renfu Pharmaceutical, Hubei, China), and rocuronium (0.6 mg/kg) (Esmeron, Organon). In the study group, anesthesia was induced with intravenous propofol (2 mg/kg), remifentanil (1 μg/kg) (Ultiva, GlaxoSmithKline), and rocuronium (0.6 mg/kg).

Anesthesia Maintenance: In the control group, anesthesia was maintained intraoperatively with continuous intravenous infusion of propofol (4–6 mg/kg/h) and fentanyl (1–2 μg/kg/min), with infusion rates adjusted according to the surgical stimulus intensity and patient vital signs. In the study group, anesthesia was maintained with continuous intravenous infusion of propofol (4–6 mg/kg/h) and remifentanil (0.1–0.3 μg/kg/min), with infusion rates similarly adjusted on the basis of surgical stimulus intensity and patient vital signs.

Outcome Measures

Peripheral venous blood samples (5 mL) were collected from all patients preoperatively and 24 hours postoperatively. Blood was drawn into EDTA-containing tubes, gently inverted, and centrifuged at 3000 rpm for 10 minutes within 2 hours of collection. The plasma supernatant was aliquoted and immediately stored at -80 °C in the hospital's institutional biobank for future biomarker analysis. All patients had provided written informed consent for the storage and research use of biological specimens.

(1) General patient information, including sex, age, body mass index (BMI), history of diabetes mellitus, hepatitis, smoking, and alcohol use.

(2) Comparisons of the cardiac index (CI), mean arterial pressure (MAP), and heart rate (HR) between the two groups before anesthesia, after anesthesia induction, and at the end of surgery were performed.

(3) Peripheral venous blood $CD4^+$, $CD3^+$, and $CD4^+/CD8^+$ T cell levels in the 2 groups were detected via flow cytometry preoperatively and 24 hours postoperatively.

(4) The postoperative eye-opening time, extubation time, and spontaneous breathing recovery time were recorded for both groups.

(5) Ramsay sedation scores and visual analog scale (VAS) scores were recorded for both groups at 1 hour, 6 hours, and 12 hours postoperatively.

(6) Plasma CXCL10 and CXCL13 levels: Enzyme-linked immunosorbent assays (ELISAs) were used to measure the concentrations of CXCL10 and CXCL13 in the plasma.

(7) Apoptosis-related molecules: Peripheral blood was collected preoperatively and 24 hours postoperatively to detect the serum levels of apoptosis-related molecules, including *Survivin*, *Bax*, *Caspase-4*, and *Bcl-2*.

(8) Adverse reactions: The incidence of adverse events was meticulously recorded to evaluate the safety and tolerability of the anesthetic protocols. The definitions of complications were consistent with the standard clinical criteria. For instance, respiratory depression was defined as a decrease in respiratory rate to less than 10 breaths per minute or the need for assisted ventilation. Nausea and vomiting were defined as any occurrence of these symptoms requiring antiemetic intervention. Urinary retention was defined as the inability to void within 6 hours postoperatively, necessitating catheterization. The monitoring duration for adverse events extended from the time of anesthesia induction until 24 hours postoperatively. This period was chosen to capture both immediate and early postoperative adverse reactions. Additionally, we specifically monitored for opioid-induced hyperalgesia (OIH), defined as increased pain sensitivity or worsening pain despite adequate opioid analgesia.

Statistical Analysis

The data were analyzed via SPSS 25.0. During data collection for this study, we conducted a detailed review of all patients' electronic medical records to ensure the completeness and accuracy of the data. For missing data, we first attempted to obtain it by making supplementary inquiries into the medical records or contacting the attending physicians; if it could not be supplemented, the patient was excluded from the study. Normally distributed continuous variables are presented as the means±SDs and were compared via Student's *t* test, whereas nonnormally distributed data are reported as medians (IQRs) and were analyzed with Mann–Whitney U tests. Categorical variables are expressed as counts (%) and were assessed via the χ^2 test or Fisher's exact test. Given the multiple endpoints evaluated in this study, we applied the Bonferroni correction to adjust for multiple comparisons and reduce the risk of Type I error. A two-tailed value of $p<0.05$ was considered statistically significant.

RESULTS

Comparison of Baseline Data

Table 1 compares the baseline characteristics between the groups. No significant differences were observed in demographics, medical history, or tumor-related features (all $p>0.05$), confirming balanced preoperative profiles.

Comparison of Hemodynamic Parameters at Different Time Points

Before anesthesia, the CI, MAP, and HR of both groups were within the normal range and were not significantly different, indicating that the baseline statuses of the two groups were similar before anesthesia ($p>0.05$). Compared with the control group, the study group had a greater CI, a MAP closer to the normal range, and a more stable HR ($p<0.05$), suggesting that the study group displayed less impact on cardiac output function after anesthesia, better maintenance of blood pressure, and a lower heart rate. At the end of surgery, the CI, MAP, and HR of the study group were closer to the normal range, more stable, and recovered more quickly ($p<0.05$), indicating that the study group had better postoperative recovery of circulatory function, stronger blood pressure regulation ability, and better heart rate regulation ability. Therefore, the combination of propofol and remifentanil resulted in more stable hemodynamic parameters and faster recovery after anesthesia and at the end of surgery. See Table 2.

Table 1. Baseline data of patients.

Indicator	Control group (n=75)	Study Group (n=75)	χ^2/t	*p*
Male/female, n (%)	45 (60.00)/30 (40.00)	47 (62.67)/28 (37.33)	0.112	0.737
Age, years	60.13±5.66	59.25±6.22	0.906	0.366
BMI, kg/m²	22.34±3.02	22.18±2.87	0.354	0.724
History of diabetes, n (%)	17 (22.67)	22 (29.33)	0.866	0.352
History of smoking and drinking, n (%)	30 (40.00)	35 (46.67)	0.679	0.410
History of hepatitis, n (%)	6 (8.00)	7 (9.33)	0.084	0.772
Imaging tumor diameter, mm	30.41±11.51	29.21±10.63	0.663	0.508
Tumor location [pancreatic head, n (%)	46 (61.33)	40 (53.33)	0.981	0.322
Enlarged lymph nodes, n (%)	33 (44.00)	31 (41.33)	0.109	0.741
Pancreatic duct dilation, n (%)	52 (69.33)	57 (76.00)	0.839	0.360
Pancreatic atrophy, n (%)	20 (26.67)	29 (38.67)	2.455	0.117
Jaundice, n (%)	22 (29.33)	23 (30.67)	0.032	0.858

BMI: body mass index.

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Table 2. Comparison of hemodynamic parameters at different time points (mean±SD).

Indicator	Point-in-time	Control group (n=75)	Study Group (n=75)	t	*p*	Effect size
CI, L/min/m²	Preanesthesia	2.91±0.28	2.90±0.34	0.340	0.693	
	Post-induction	2.53±0.52	2.70±0.33	2.502	0.014	0.390
	At the end of surgery	2.59±0.46	2.81±0.33	3.407	0.000	0.550
MAP, mmHg	Preanesthesia	92.33±11.46	91.61±12.46	0.368	0.713	
	Post-induction	65.65±7.44	75.51±6.64	8.557	0.000	1.398
	At the end of surgery	77.65±8.71	86.65±9.87	5.920	0.000	0.967
HR, beats/min	Preanesthesia	75.33±6.54	75.52±6.20	0.179	0.858	
	Post-induction	60.36±5.32	66.81±5.46	7.333	0.000	1.197
	At the end of surgery	68.45±6.22	72.12±4.30	4.200	0.000	0.686

CI: cardiac index; HR: heart rate; MAP: mean arterial pressure.

Comparison of Immune Function Parameters before and after Surgery

There was no significant difference in immune function between the two groups before surgery (p>0.05), which eliminated the influence of the preoperative immune status on the results. Both groups presented decreases in immune parameters ($CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ T cells) at 24 hours after surgery, which was consistent with the immunosuppressive effects of surgical stress and anesthesia. However, the degree of immunosuppression was milder in the study group (p<0.05), suggesting that remifentanil may alleviate postoperative immunosuppression. This result may be related to its short-acting and precise pharmacokinetic properties, which may reduce the risk of postoperative infections and promote recovery. See Table 3 and Figure 2.

Comparison of Awakening Effects

Compared with those in the control group, patients in the study group had better postoperative recovery indicators, with shorter eye-opening times, earlier extubation times, and accelerated recovery of spontaneous breathing. All comparisons were statistically significant (all p<0.05), indicating that the rapid metabolic properties of remifentanil significantly improved postoperative recovery efficiency, which was beneficial for surgical turnover and accelerated recovery. See Table 4.

Table 3. Comparison of immune function parameters before and after surgery (mean±SD).

Indicator	Point-in-time	Control group (n=75)	Study Group (n=75)	χ^2/t	*p*	Effect size
$CD3^+$,%	Before surgery	62.33±5.14	62.79±5.71	0.508	0.613	
	24 h after surgery	50.66±4.35	56.33±4.77	7.599	0.000	1.242
$CD4^+$, %	Before surgery	36.44±3.45	35.88±3.19	1.014	0.312	
	24 h after surgery	27.63±2.67	32.33±3.21	9.765	0.000	1.592
$CD4^+/CD8^+$	Before surgery	1.47±0.45	1.48±0.42	0.003	0.998	
	24 h after surgery	1.21±0.32	1.32±0.21	2.278	<0.001	0.406

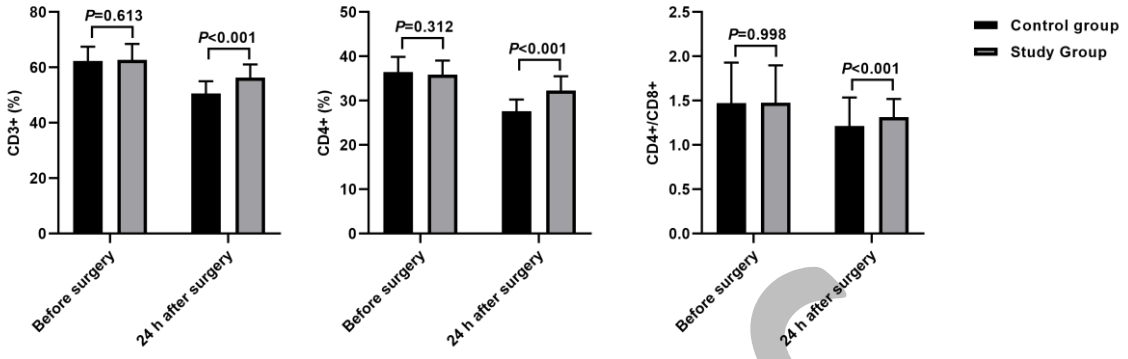

Figure 2. Comparison of immune function parameters before and after surgery.

Table 4. Comparison of awakening effects (mean±SD, min).

Indicator	Control group (n=75)	Study Group (n=75)	t	*p*	Effect size
Eye-opening time	15.68±2.49	11.22±2.15	11.692	<0.001	1.917
Extubation time	22.68±2.89	18.22±2.75	9.699	<0.001	1.581
Recovery time of spontaneous breathing	13.42±2.31	9.21±2.97	9.692	<0.001	1.582

Comparison of Ramsay Sedation Scores and VAS Scores

Compared with those at 1 hour after surgery, both groups had significantly higher VAS pain scores and significantly lower Ramsay sedation scores at 6 and 12 hours after surgery (all $p<0.05$). However, there were no statistically significant differences in the VAS score or Ramsay sedation score between the two groups at 1, 6, or 12 hours after surgery (all $p>0.05$). The results indicated that the anesthesia regimens of propofol combined with remifentanil or fentanyl had similar effects on pain control and sedation in the early postoperative period (within 12 hours). See Table 5. The trend toward increased postoperative pain and decreased sedation over time suggested that enhanced analgesia management was needed within 12 hours after surgery, regardless of the anesthetic drugs used.

Table 5. Comparison of Ramsay sedation scores and VAS scores [M (Q1, Q3), score].

Indicator	Point-in-time	Control group (n=75)	Study Group (n=75)	Z	*p*
Ramsay Sedation Scores	1 h after surgery	3 (3, 4)	3 (3, 4)	−0.838	0.402
	6 h after surgery	3 (2, 3)*	3 (2, 3)*	−1.312	0.190
	12 h after surgery	2 (2, 2)*	2 (2, 2)*	−0.535	0.593
VAS Scores	1 h after surgery	2 (1, 2)	2 (1, 2)	−0.656	0.512
	6 h after surgery	3 (2, 3)*	2 (2, 3)*	−0.979	0.328
	12 h after surgery	3 (3, 3)*	3 (3, 3)*	−0.976	0.329

Compared with 1 h after surgery in the same group, *$p<0.05$.

VAS: visual analog scale.

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Comparison of Plasma CXCL10 and CXCL13 Levels

Compared with the preoperative baseline levels, the levels of CXCL10 and CXCL13 in both groups were significantly lower at 24 hours after surgery (all $p<0.05$). Notably, the postoperative levels of CXCL10 and CXCL13 in the study group decreased more significantly than those in the control group did (all $p<0.05$). These findings suggest that remifentanil may have a stronger anti-inflammatory effect, effectively inhibiting postoperative inflammatory responses and promoting postoperative recovery and the long-term prognosis. See Table 6 and Figure 3.

Comparison of Plasma Apoptotic Molecular Levels

At 24 hours after surgery, the levels of *Bax* and *Caspase-4* in both groups were greater than the preoperative levels, and the postoperative levels of *Bax* and *Caspase-4* in the study group were greater than those in the control group ($p<0.05$). Moreover, the levels of *Survivin* and *Bcl-2* in both groups were lower than the preoperative levels at 24 hours after surgery, with the study group showing lower levels than the control group did ($p<0.05$). These findings suggest that remifentanil may enhance the apoptosis of pancreatic cancer cells through a dual regulatory mechanism involving the upregulation of proapoptotic factors and the downregulation of antiapoptotic factors. This discovery provides molecular-level evidence for the potential antitumor effect of remifentanil in pancreatic cancer surgery. See Table 7 and Figure 4.

Table 6. Comparison of plasma CXCL10 and CXCL13 levels (mean±SD, pg/mL).

Indicator	Point-in-time	Control group (n=75)	Study Group (n=75)	t	*p*	Effect size
CXCL10	Before surgery	673.45±86.27	668.73±81.88	0.343	0.732	
	24 h after surgery	516.81±78.63*	420.57±52.12*	8.834	0.000	1.443
CXCL13	Before surgery	668.66±74.22	672.32±69.38	0.311	0.756	
	24 h after surgery	512.88±69.54*	387.21±57.22*	12.086	0.000	1.974

Compared with the same group before operation, *$p<0.05$.

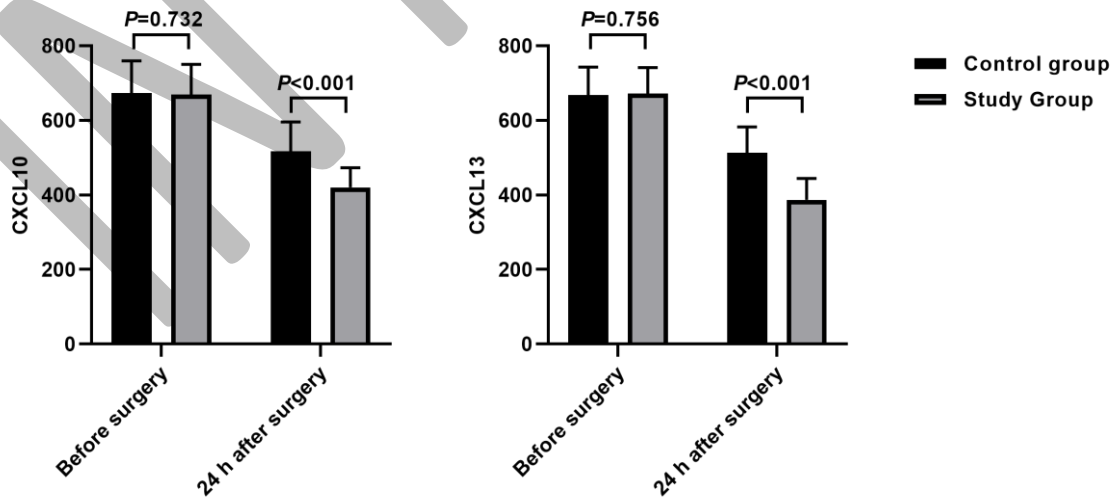

Figure 3. Comparison of plasma CXCL10 and CXCL13 levels.

Table 7. Comparison of plasma apoptotic molecular levels (mean±SD, ng/mL).

Indicator	Point-in-time	Control group (n=75)	Study Group (n=75)	t	*p*	Effect size
Bax	Before surgery	19.33±2.51	18.97±2.14	0.973	0.332	
	24 h after surgery	24.33±2.52*	29.16±3.43*	9.850	0.000	1.605
Caspase-4	Before surgery	4.51±1.28	4.48±1.02	0.211	0.834	
	24 h after surgery	5.83±1.14*	7.52±1.22*	8.802	0.000	1.431
Survivin	Before surgery	31.22±3.42	30.46±3.51	1.343	0.181	
	24 h after surgery	25.33±2.45*	20.16±2.11*	13.872	0.000	2.216
Bcl-2	Before surgery	16.55±2.17	16.24±2.33	0.843	0.400	
	24 h after surgery	11.45±1.67*	8.55±1.02*	12.781	0.000	2.096

Compared with the same group before operation, *p<0.05.

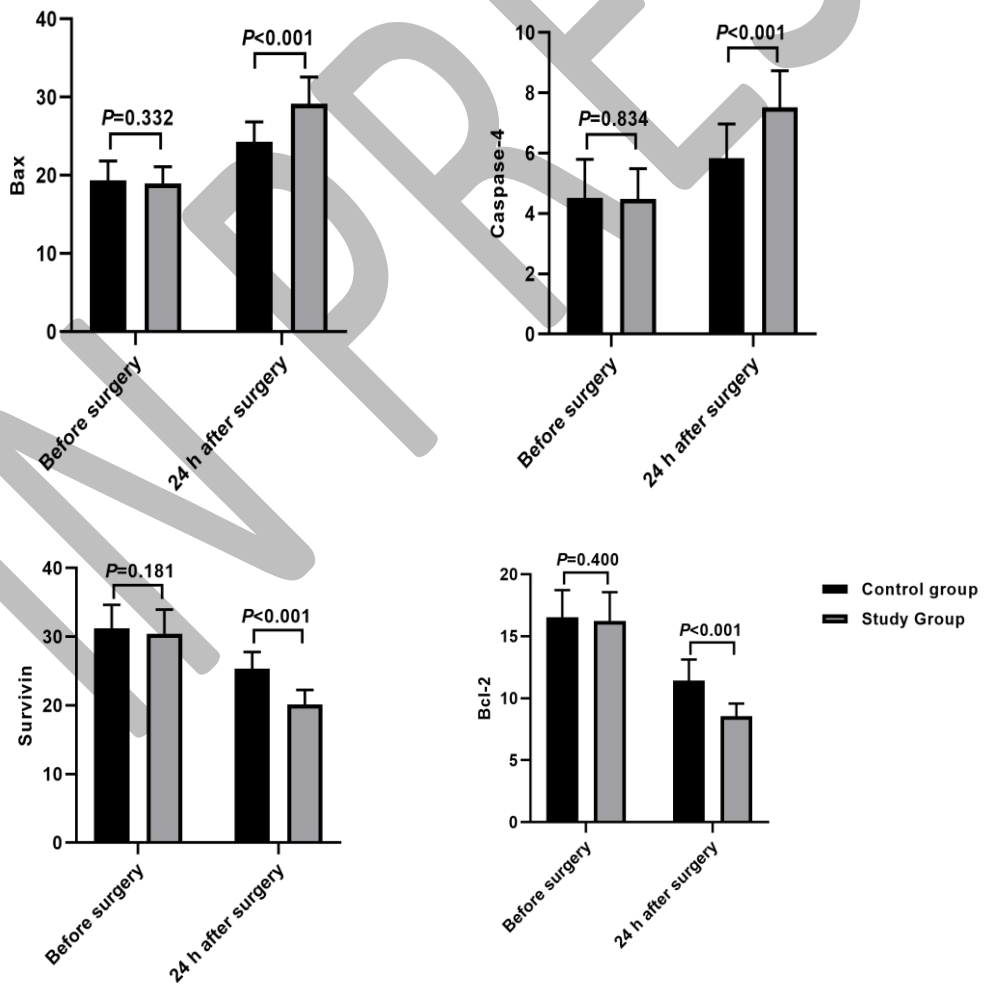

Figure 4. Comparison of plasma apoptotic molecular levels.

Comparison of Adverse Reaction Rates

No cases of OIH were observed in either group during the monitoring period. In this study, a total of 9 adverse reactions occurred in the control group, including 3 cases of respiratory depression, 5 cases of nausea and vomiting, and 1 case of urinary retention. In contrast, only 2 cases of nausea and vomiting occurred in the study group. Statistical analysis revealed a significant difference in the incidence of adverse reactions between the two groups, with the study group having a significantly lower incidence rate than the control group (χ^2=4.513, p=0.034). These findings confirm that the propofol-remifentanil anesthesia regimen offers a superior safety advantage, reducing complications and promoting postoperative recovery, thereby providing evidence-based support for the preference of remifentanil in pancreatic cancer surgery (Table 8).

Table 8. Comparison of adverse reaction rates, n (%)

Indicator	Control group (n=75)	Study Group (n=75)	χ^2	p	Effect Size
Respiratory depression	3 (4.00)	0 (0.00)			
Nausea and vomiting	5 (6.67)	2 (2.67)			
Urinary retention	1 (1.33)	0 (0.00)			
Total incidence	9 (12.00)	2 (2.67)	4.513	0.034	0.179

DISCUSSION

During pancreatic cancer surgery, anesthesia must ensure painlessness and loss of consciousness while maintaining hemodynamic stability, minimizing stress responses induced by surgical trauma, preserving immune function, and promoting rapid postoperative recovery.[17] However, traditional anesthetic combinations often have limitations in meeting these multifaceted demands. In recent years, with the development and application of novel anesthetic agents, the propofol-remifentanil regimen has garnered increasing attention. This study aimed to explore the effects of this regimen on the levels of apoptotic molecules and plasma CXCL10 and CXCL13 in patients undergoing pancreatic cancer surgery.

While previous studies have evaluated propofol-remifentanil anesthesia in cancer surgery, our study uniquely investigates its comprehensive effects on both hemodynamic stability and immune function, with a particular focus on the modulation of apoptotic molecules and inflammatory cytokines in pancreatic cancer patients. This multifaceted approach provides novel insights into the potential mechanisms through which anesthesia may influence tumor progression and patient outcomes. Specifically, our findings that propofol-remifentanil anesthesia enhances postoperative recovery and modulates key biological pathways related to apoptosis and inflammation represent significant advancements in understanding the role of anesthesia in cancer surgery.

During the perioperative period, circulatory indicators such as the CI, MAP, and HR are important parameters for assessing a patient's circulatory status. Maintaining a stable circulatory status is crucial for ensuring tissue perfusion and oxygen supply. In the study group, the hemodynamic indicators were more stable after anesthesia and at the end of surgery, with faster recovery and better anesthetic effects, which may be related to the pharmacological properties of remifentanil. Remifentanil is an ultrashort-acting μ-opioid receptor agonist, and its ester bond structure allows it to be rapidly hydrolyzed by nonspecific esterases in the blood and tissues, with a half-life of only 3–10 minutes.[18] This rapid metabolic characteristic prevents drug accumulation, thereby reducing continuous suppression of the cardiovascular system and maintaining a relatively stable CI, MAP, and HR. In contrast, fentanyl, although it is also a commonly used anesthetic analgesic, has a relatively long metabolic time in the body. As surgery nears completion and surgical stimulation decreases, the drug concentration may still remain at a certain level, exerting continuous suppressive effects on the cardiovascular system and leading to greater fluctuations in indicators such as the CI, MAP, and HR.[19] Hemodynamic stability is crucial

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for patients undergoing pancreatic cancer surgery. Pancreatic cancer patients may already have varying degrees of reduced cardiovascular functional reserve due to factors such as tumor consumption and vascular invasion.[20] Severe intraoperative hemodynamic fluctuations may increase the risk of cardiovascular complications such as myocardial ischemia and arrhythmias, affecting surgical safety and patient prognosis.[21] Furthermore, a good circulatory status helps ensure tissue perfusion and promotes postoperative recovery. The circulatory advantages of the study group at the end of surgery may have created more favorable physiological conditions for their rapid awakening and recovery after surgery, while maintaining internal environmental stability to reduce stress responses and promote overall rehabilitation.[22]

The host immune response constitutes a vital defense mechanism against surgical injury, and the levels of $CD4^+$, $CD3^+$, and $CD4^+/CD8^+$ T cells in peripheral blood are important indicators for assessing immune function.[23] In this study, the levels of $CD4^+$, $CD3^+$, and $CD4^+/CD8^+$ T cells in both groups decreased at 24 hours postoperatively, possibly because the stress response caused by surgical trauma led to the redistribution and functional suppression of immune cells. Surgical trauma in pancreatic cancer can activate the body's neuroendocrine system, releasing a large amount of stress hormones such as cortisol and catecholamines, which suppress immune system function through various pathways, resulting in changes in the number and ratio of T lymphocyte subsets.[24] However, the levels of $CD4^+$, $CD3^+$, and $CD4^+/CD8^+$ T cells in the study group at 24 hours postoperatively were greater than those in the control group, indicating that propofol-remifentanil anesthesia has a milder suppressive effect on immune function to some extent. The potent analgesic effect of remifentanil can effectively reduce the intensity of the stress response caused by surgical trauma and decrease the excessive release of stress hormones, thereby indirectly reducing the suppression of the immune system, which is sensitive to stress hormones. A study by Lu XY et al[25] demonstrated that, compared with fentanyl, remifentanil administration during radical hysterectomy for cervical cancer resulted in better preservation of T lymphocyte subsets and a lower inflammatory response. This finding indicates that remifentanil has advantages in reducing the postoperative inflammatory response and immunosuppression and can also shorten the postoperative awakening time, making it a safe and effective anesthesia option, which is consistent with the findings of this study. Furthermore, propofol exhibits immunomodulatory properties through the suppression of inflammatory mediator release and attenuation of immune system hyperactivation. The combined use of the two may produce a synergistic effect on immune protection. Yang X et al[26] compared the effects of propofol-remifentanil versus propofol-ketamine anesthesia on 126 children undergoing tonsillectomy and adenoidectomy and reported that propofol-remifentanil can more effectively stabilize hemodynamics and significantly reduce inflammatory indicators such as CRP, IL-6, and TNF-α, and stress indicators such as adrenaline and cortisol. Although both groups presented similar decreases in the $CD3^+$, $CD4^+$, and $CD4^+/CD8^+$ T cell ratios, the observation group presented a shorter anesthesia recovery time and a lower incidence of emergence agitation, confirming the comprehensive advantages of this propofol-remifentanil anesthesia regimen in inhibiting the inflammatory stress response and promoting rapid postoperative awakening. For pancreatic cancer patients, maintaining good postoperative immune function is particularly important. Tumor patients often are immunocompromised, and surgical trauma further weakens immune function, making patients prone to complications such as infection after surgery, which may also affect tumor recurrence and metastasis.[27] The relatively high levels of immune cells in the study group suggest that propofol-remifentanil anesthesia helps maintain the patient's immune function in the early postoperative period, reducing the risk of infection, and may have positive implications for inhibiting tumor recurrence and metastasis in the long term.

Compared with the control group, the study group presented a shorter postoperative eye-opening time, extubation time, and spontaneous breathing recovery time, which may be attributed to the pharmacological properties of remifentanil. Owing to its rapid metabolism and elimination, the plasma concentration of remifentanil decreases swiftly after drug discontinuation at the end of surgery, leading to a rapid reduction in anesthetic depth and faster recovery of consciousness and spontaneous breathing function.[28] Additionally, the rapid metabolic characteristics of propofol enable patients to regain consciousness more quickly after surgery. The combined use of these two drugs further shortens the postoperative recovery time and enhances

postoperative comfort.[29] The early postoperative rehabilitation process holds significant clinical importance for patient safety and the improvement of prognosis. Shortening the time to eye-opening and tracheal extubation during the anesthesia recovery period can effectively reduce the risk of adverse events such as convulsions and reflux aspiration during this phase. Moreover, early tracheal extubation can shorten the duration of invasive mechanical ventilation, facilitate the early recovery of patients' spontaneous breathing function and language communication ability, and accelerate respiratory rehabilitation to optimize the perioperative management process.[30] Timely restoration of spontaneous breathing helps maintain gas exchange and acid–base balance, reduces the duration of respiratory support equipment use, and decreases the incidence of ventilator-related complications.[31] Furthermore, early awakening enables patients to resume communication and interaction with the external environment more quickly, which is beneficial for postoperative psychological recovery.[32] The prolonged duration of action of fentanyl may result in delayed postoperative recovery. After surgery, fentanyl continues to exert pharmacological effects on the body, inhibiting the functional recovery of the central nervous system and thereby prolonging the recovery time and spontaneous breathing recovery time. This not only increases the difficulty of management during anesthetic recovery but also may pose potential adverse effects to patients.[33]

Postoperative pain management constitutes an essential component of postoperative care. Effective sedation and analgesia can alleviate patient suffering and promote postoperative recovery. In this study, the VAS scores at 6 and 12 hours postoperatively were greater than those at 1 h, whereas the Ramsay scores were lower in both groups. This result reflects the gradual emergence of pain caused by surgical trauma and the gradual weakening of the sedative effects of anesthetic drugs over time. In the analysis, no statistically significant intergroup disparities were detected, indicating that the two anesthetic regimens of propofol-fentanyl and propofol-remifentanil have similar effects in terms of postoperative pain control and sedation. Patients in the study group exhibited markedly fewer postoperative complications than did those in the control group. This may be related to the fewer side effects of remifentanil. Remifentanil has relatively mild respiratory depression, and its rapid metabolism prevents its accumulation in the body, thereby reducing the incidence of postoperative adverse reactions such as respiratory depression.[34] Furthermore, remifentanil induces lower phosphorylation of μ receptors and reduces activation of the β-arrestin pathway, thereby decreasing side effects such as nausea and vomiting.[35] Additionally, the pKa value of remifentanil is close to the physiological pH, making it easier to cross the blood–brain barrier and requiring lower doses to achieve equivalent analgesic effects.[36]

Surgical injury initiates a systemic inflammatory cascade, stimulating the production of multiple inflammatory cytokines and chemotactic factors. Among these, CXCL10, which is primarily upregulated by interferon-γ, functions as a potent chemoattractant for T cells and NK cells, thereby modulating both immune surveillance and inflammatory processes at the injury site.[37] CXCL10 may exert certain anti-tumor effects in pancreatic cancer by promoting the aggregation of immune cells, specifically T cells, into the tumor microenvironment.[38] However, more commonly, its overexpression exacerbates local inflammation, promotes tumor angiogenesis, invasion, and metastasis, and is associated with tumor progression and poor prognosis.[39] High levels of CXCL10 often indicate a large tumor burden and a strong inflammatory response. CXCL13 mainly chemoattracts B lymphocytes and acts as a key regulator in the development of lymphoid tissues, immune cell homing, and humoral immune responses.[40] In this study, the postoperative decrease in plasma CXCL10 and CXCL13 levels may be related to the immunosuppressive state caused by surgical trauma. When the body is in an immunosuppressive state, the activity of immune cells is inhibited, and the production and release of chemokines are correspondingly reduced. The lower CXCL10 and CXCL13 levels in the study group may reflect the greater ability of propofol-remifentanil anesthesia to inhibit inflammatory responses and immune regulation. The metabolism of remifentanil does not depend on liver or kidney function, and it is rapidly hydrolyzed by plasma esterases, avoiding prolonged drug accumulation. This characteristic may reduce continuous immunosuppression of the immune system, thereby decreasing the release of proinflammatory cytokines such as CXCL10 and CXCL13.[41] Furthermore, remifentanil has greater selectivity for μ-opioid receptors, which may reduce surgical stress responses through more precise analgesic effects, whereas fentanyl may have more significant

immunomodulatory effects owing to its longer duration of action.[42] Additionally, propofol has certain anti-inflammatory effects, as it can inhibit the synthesis and release of inflammatory factors and alleviate inflammatory responses. The combined use of these two drugs may produce synergistic anti-inflammatory effects, further reducing the inflammatory response caused by surgical trauma.[43] In individuals with pancreatic carcinoma, uncontrolled inflammatory processes can facilitate neoplastic growth, invasion, and distant metastasis. Reducing plasma CXCL10 and CXCL13 levels may help alleviate the stimulation of the inflammatory microenvironment on tumor cells and, theoretically, may have potential benefits in inhibiting tumor progression.[44,45] However, this hypothesis requires further basic research and long-term clinical follow-up to be confirmed.

Operative injury activates programmed cell death mechanisms, leading to the upregulation of apoptosis-promoting proteins and the downregulation of apoptosis-inhibiting proteins.[46] The study group exhibited significant fluctuations in the levels of apoptotic molecules, possibly influenced by remifentanil. This potent μ-opioid agonist has been shown to regulate apoptotic protein expression, extending beyond its primary analgesic role. Experimental data support that remifentanil inhibits apoptosis by blocking *Bax*-mediated pathways, attenuating cytochrome C release, and upregulating the expression of protective proteins such as *Survivin* and *Bcl-2*.[47] Furthermore, remifentanil preconditioning can alleviate damage to brain nerves caused by extracorporeal circulation by blocking the *AKT/NRF2* signaling pathway.[48] The observed suppression of apoptosis-promoting proteins accompanied by increased expression of apoptosis-inhibiting proteins suggests that remifentanil may intervene in apoptotic pathways through multiple targets to reduce the excessive activation of apoptosis caused by surgical trauma, providing a new theoretical basis for elucidating the organ-protective mechanism of remifentanil. Subsequent studies can further explore the specific signal transduction mechanisms by which remifentanil regulates these apoptosis-related molecules and their correlation with the clinical prognosis.

The current study provides valuable insights into the potential immunomodulatory and anti-tumor effects of anesthesia by assessing apoptosis-related markers such as *Bax*, *Bcl-2*, *Caspase-4*, and *Survivin*, as well as inflammatory markers like CXCL10 and CXCL13. However, several limitations must be acknowledged. Firstly, these proteins are primarily intracellular, and their detection in plasma via ELISA only offers an indirect reflection of tissue-level apoptotic activity. Thus, the observed changes in plasma levels, although statistically significant, may not fully represent the actual apoptotic activity within the tumor or immune cells. Future studies could consider more direct measures of apoptosis, such as immunohistochemical analysis of tissue samples or flow cytometry of isolated cells. Secondly, the study lacks direct mechanistic evidence to support the observed alterations in these markers. The associations between the anesthesia regimen and the changes in apoptotic and inflammatory markers are preliminary and hypothesis-generating. Further research is needed to elucidate the underlying mechanisms and to determine whether these changes translate into definitive anti-tumor or immunoprotective effects. Thirdly, our study did not fully address several perioperative variables that could influence the outcomes, such as fluid management and opioid rescue doses. These variables are critical in perioperative care and can significantly impact hemodynamic stability, pain control, and overall recovery. Their absence from our analysis limits the comprehensiveness of our findings. Future studies should consider incorporating detailed assessments of these variables. As a retrospective study, our findings should be interpreted with caution due to inherent limitations, including the lack of randomization and potential selection bias, which may influence the generalizability of our results. The relatively limited sample size may have constrained the statistical power and broader generalizability of the findings. Additionally, the 24-hour postoperative follow-up restricts the comprehensive assessment of long-term recovery, as it only describes short-term biomarker changes and lacks medium- or long-term clinical outcomes (e.g., infection rates, cancer recurrence, survival). We also did not conduct subgroup analyses based on tumor stage or ASA grade, which may have obscured potential heterogeneous effects across different patient groups. Future prospective, randomized controlled trials with larger sample sizes, longer follow-up periods, and subgroup analyses are warranted to further validate these findings and optimize clinical anesthesia practices for pancreatic cancer surgery. Finally, the study's analytical approach is primarily descriptive, focusing on endpoint comparisons without

integrating the findings into a broader mechanistic framework. Future work should consider more interpretive analyses grounded in current literature to enhance the understanding of the observed effects.

The results of this study indicate that the combination of propofol and remifentanil in patients undergoing pancreatic cancer surgery provides effective sedative and analgesic effects, controls the levels of apoptotic molecules and plasma CXCL10 and CXCL13, and improves postoperative recovery.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of The Fourth People's Hospital of Jinan. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki declaration.

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

The datasets generated during this study are available from the corresponding author, Dr. Yanchun Tian, upon reasonable request. Requests should be submitted via email to tianyanchun750228@163.com.

AI ASSISTANCE DISCLOSURE

The authors did not use any artificial intelligence (AI) tools in the preparation of this manuscript.

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