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Differential effects of sevoflurane versus propofol on calmodulin expression in breast cancer patients

Jiahui Wang, Bichen He, Gulibanumu Kuerban, Chentong Gao and Bing Zhang*
The 3rd Affiliated Teaching Hospital of Xinjiang Medical University (Affiliated Cancer Hospital), Xinjiang Urumqi, 8300000 China

Abstract: **Background**: Evidence from experimental and clinical studies suggests that anesthetic drugs may modulate tumor biology by influencing immune regulation, inflammation and intracellular calcium signaling. However, the extent to which sevoflurane or propofol alters calcium-related molecular expression in human breast cancer tissue remains unclear. **Objectives**: This study aimed to compare the effects of sevoflurane- versus propofol-based anesthesia on calcium signaling pathway–related gene and protein expression in breast cancer tissues and to evaluate their association with early - postoperative recovery and short-term oncologic outcomes. **Methods**: A total of 38 female patients undergoing breast cancer surgery were prospectively randomized to the sevoflurane group (S group, n=19) or the propofol group (P group, n=19). Paired tumor and adjacent normal tissues were collected intra-operatively. mRNA expression of RYR2 and CALML5 was quantified using RT-qPCR and protein levels were assessed by Western blotting. Postoperative pain was evaluated using the 24-hour resting numerical rating scale (NRS), recovery quality using the quality of recovery-15 (QoR-15) on post-operative day 1 and incision pain at post-operative months 3 and 6. Tumor recurrence or metastasis was monitored for 6 months. **Results**: Compared with the propofol group, sevoflurane anesthesia demonstrated a nonsignificant upward trend in RYR2 mRNA and protein expression (P>0.05), whereas CALML5 expression showed a significant increase under sevoflurane (P<0.001). No significant intergroup differences were detected in 24-hour NRS scores, post-operative QoR-15, chronic incision pain at 3 or 6 months, or 6-month recurrence/metastasis rates (all P>0.05). **Conclusion**: Sevoflurane anesthesia induced a selective increase in CALML5 expression compared with propofol, suggesting potential differential modulation of calcium-associated molecular pathways. However, these molecular changes did not translate into measurable differences in early recovery, post-operative pain, or short-term oncologic prognosis. The findings support the clinical non-inferiority of sevoflurane compared with propofol and provide preliminary molecular evidence to guide future mechanism-based perioperative investigations.

Keywords: Breast cancer calcium signaling pathway; Clinical prognosis; Propofol; Post-operative pain; Sevoflurane

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INTRODUCTION

Breast cancer, one of the most prevalent malignancies among women, is primarily treated through surgical intervention (Martín *et al*., 2022). Previous studies have suggested that the choice of anesthetic agents during the perioperative period may modulate tumor biological behavior (Alam *et al*., 2021), including proliferation (Sun *et al*., 2022), invasion (Chang *et al*., 2022), immune evasion (Lan *et al*., 2025; Jiang *et al*., 2024) and alterations of the tumor microenvironment (Zhou *et al*., 2022), thereby influencing patients' long-term survival outcomes (Yan *et al*., 2023). Propofol and sevoflurane, representative agents of intravenous and inhalational anesthesia, respectively, are both widely used in perioperative anesthesia. However, their differential effects on postoperative metastasis, recurrence and prognosis in breast cancer patients remain unclear (Sun P *et al*., 2024).

Sevoflurane, a volatile halogenated ether, can directly interact with the hydrophobic pocket of the sarcoplasmic reticulum RyR2 channel, increasing its open probability (Osman *et al*., 2023). Meanwhile, it upregulates CALML5, serving as an "amplifier" of calcium signaling (Ling *et al*., 2021). This dual upregulation may induce intracellular calcium oscillations in breast cancer cells during the perioperative period, activating calcium-dependent transcription factors such as NFAT and CREB, thereby influencing the expression of metastasis-related genes (Cui *et al*., 2017).

The inhibitory effect of propofol on CALML5 expression may be mediated through several mechanisms: (1) direct transcriptional regulation, such as the suppression of miR-155-5p(Hu *et al*., 2025) ; (2) reduction of oxidative stress, thereby decreasing calcium release from the endoplasmic reticulum (ER) stores (Lukoseviciene *et al*., 2018); (3) inhibition of calcium influx via GABA receptors and reactive oxygen species (ROS) modulation(Liu *et al*., 2021)—a biphasic process characterized by initial suppression followed by compensatory upregulation, during which the induced increase in CALML5 expression may serve as a homeostatic response to maintain calcium balance; and (4) cancer tissue specificity—ER stress in tumor cells can intrinsically induce CALML5 expression to alleviate calcium depletion and propofol may further potentiate this compensatory mechanism (Oh *et al*., 2022). Previous studies have confirmed that aberrant activation of the calcium signaling pathway is involved

**Corresponding author:* e-mail: drzhangbing@xjmu.edu.cn

in the pathogenesis of tumor invasion, metastasis and pain sensitization (Shapovalov *et al*., 2021). RYR2, as a key intracellular calcium-release channel, can promote calcium oscillations when overexpressed, thereby activating pro-metastatic pathways such as CaMKII and STAT3 (Xu *et al*., 2021). Meanwhile, CALML5, a member of the calmodulin-like protein family, may influence prognosis by enhancing tumor cell motility and contributing to chemoresistance (Taniwaki *et al*., 2025). Therefore, this study focuses on the calcium signaling pathway as a critical regulatory axis. By examining the transcriptional and protein expression profiles of pivotal calcium-signaling molecules, RYR2 and CALML5, in paired tumor and adjacent normal tissues from breast cancer patients receiving either sevoflurane or propofol anesthesia (Montazeri, 2024) and by integrating postoperative pain assessments,recurrence status and survival outcomes, this study seeks to clarify the distinct regulatory effects of different anesthetic agents on calcium signaling and to investigate how these molecular variations relate to clinical prognosis. The findings are expected to provide robust evidence for optimizing perioperative anesthetic strategies in breast cancer patients.

MATERIALS AND METHODS

General information

The approval explicitly covered all components of the research protocol, including intraoperative acquisition of paired tumor and adjacent non-tumor breast tissues, postoperative follow-up assessments and molecular analyses (RT-qPCR and Western blot) performed on the collected human samples. All clinical procedures were carried out in strict accordance with institutional ethical requirements to ensure scientific validity and regulatory compliance. To safeguard patient autonomy and informed decision-making, each participant or their legal representative signed a written informed consent form prior to enrollment. The document clearly described the study objectives, procedural details, potential risks, data-privacy protection and the planned use of surgical tissues for molecular testing, thereby fully meeting the ethical principle of informed consent. Participant enrollment occurred between September 2024 and March 2025 and eligible subjects were women scheduled to undergo breast cancer surgery during this period. No additional ethical submissions were required because all analytic procedures were pre-specified in the approved protocol. If future analyses extend beyond the scope of the protocol—such as genomic sequencing or prolonged follow-up—supplemental ethical approval will be obtained accordingly.

This study was designed as an exploratory randomized controlled clinical trial; therefore, a formal hypothesis-driven sample size calculation for clinical endpoints was not performed. Instead, the target sample size was determined by feasibility considerations, including the number of breast cancer patients eligible for tissue collection during the recruitment period, willingness to provide paired tumor and adjacent specimens for molecular analysis and the requirement of completing a 6-month follow-up.To ensure that the study size remained within an acceptable methodological range, reference was made to previously published mechanistic perioperative studies evaluating anesthetic-related molecular alterations in breast cancer, in which 20-40 subjects were typically enrolled (Wang *et al*., 2023;). A final cohort of 38 patients was included, which fell within this range and provided sufficient biological material to detect large-magnitude differences in mRNA and protein expression between anesthetic regimens.

Inclusion criteria: Female patients aged 18–65 years; American Society of Anesthesiologists (ASA) physical status classification I–III; preoperative biopsy confirming breast cancer and eligibility for surgical treatment; and patients who were fully informed and voluntarily agreed to participate in the study.

Exclusion criteria: Patients with major diseases involving vital organs such as the heart, brain, or lungs; those with hepatic or renal dysfunction; individuals with severe systemic diseases; patients with poorly controlled blood pressure or blood glucose; those with concurrent malignant tumors; patients with a history of radiotherapy or chemotherapy; To avoid pharmacologic confounding related to calcium signaling, all enrolled patients were screened preoperatively for the use of calcium-channel-active medications and supplements. During the pre-anesthesia evaluation, patients were specifically asked about regular or recent intake of: calcium channel blockers (e.g., verapamil, diltiazem, nifedipine), herbal products known to modulate Ca^{2+} homeostasis (e.g., ginseng, ginkgo biloba, astragalus-based supplements) and over-the-counter agents reported to affect Ca^{2+}-dependent signaling or calmodulin binding. Patients who had used any of these agents within two weeks before surgery were excluded from participation to minimize interference with calcium-dependent molecular outcomes. This screening procedure was incorporated into the exclusion criteria and documented in the anesthetic assessment records.

Elimination criteria

Failure to obtain intraoperative tissue samples, occurrence of intraoperative drug allergy, or withdrawal from the study before completion.A total of 56 patients were assessed for eligibility between September 2024 and March 2025. Eighteen patients were excluded before randomization, including 11 who did not meet the inclusion criteria, 5 who declined participation and 2 for other reasons. Finally, 38 patients were randomized equally into the propofol and sevoflurane groups. One patient in each group was lost to follow-up at 3 months and no additional loss occurred between 3 and 6 months. Tissue availability for molecular analysis is shown in figure 1.

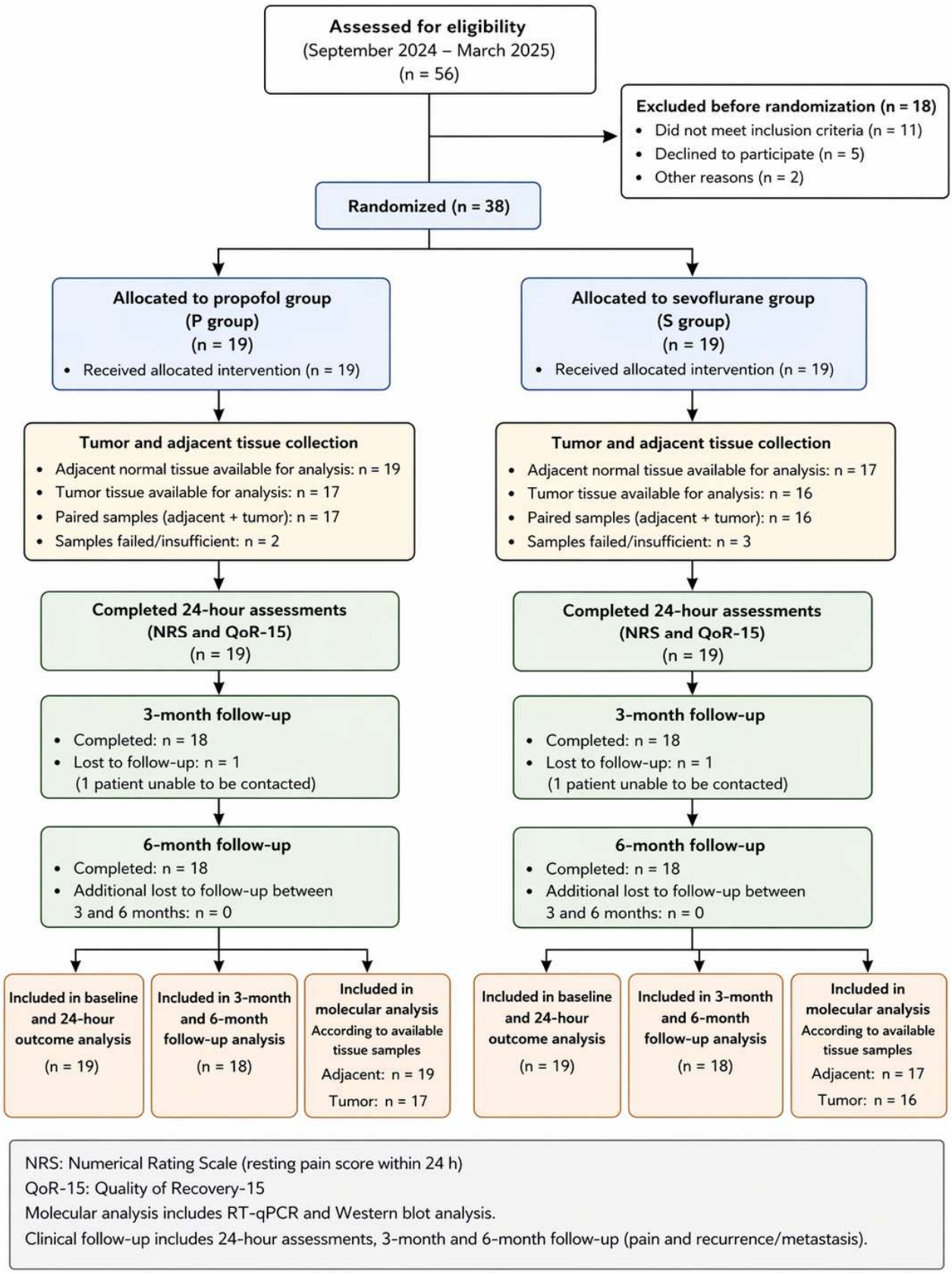

Fig. 1: Study flow diagram of patient enrollment, randomization, tissue collection, follow-up and final analysis.

Grouping and intervention

To ensure methodological rigor and comparability between treatment arms, patients scheduled for breast cancer surgery were randomly allocated in a 1:1 ratio to either propofol-based anesthesia (P group) or sevoflurane-based anesthesia (S group) using a computer-generated random number table. This randomization strategy minimized selection bias and ensured balanced baseline demographic and clinical characteristics, thereby providing a valid platform for comparing anesthetic-related molecular effects and postoperative recovery profiles.

Preoperative preparation followed standard enhanced-recovery protocols. All patients underwent at least 8 hours of fasting and fluid deprivation before surgery and no sedative premedication was administered to avoid confounding anesthetic depth. Patient identity and surgical consent were verified using a three-point confirmation system to ensure procedural accuracy. Intraoperative monitoring complied with international anesthetic safety guidelines and included continuous electrocardiography, noninvasive blood pressure, pulse oximetry and end-tidal carbon dioxide ($ETCO_2$). Depth of anesthesia was titrated using a bispectral index (BIS) monitor to maintain precise hypnotic control. To avoid perioperative hypothermia, forced-air warming and thermal insulation were employed to maintain stable core temperature throughout anesthesia management.

Anesthesia induction

Anesthetic induction was tailored according to the characteristics of each regimen. In the P group, anesthesia was induced intravenously with propofol 1.5~2.0 mg/kg, administered together with sufentanil 0.3~0.5 μg/kg and rocuronium 0.6 mg/kg to enhance analgesia and facilitate neuromuscular relaxation. In the S group, anesthesia was induced via inhalation of sevoflurane at 6~8 vol% in 100% oxygen through a face mask at a fresh gas flow of 6 L/min until the loss of consciousness and eyelash reflex. After induction, identical adjunctive doses of sufentanil 0.3~0.5 μg/kg and rocuronium 0.6 mg/kg were administered and sevoflurane concentration was subsequently reduced to a maintenance range based on clinical response. All patients received 3 minutes of preoxygenation prior to induction. Endotracheal intubation was performed under direct visualization once BIS values stabilized between 40 and 50, ensuring airway safety and procedural efficiency. Following successful intubation, mechanical ventilation was initiated. Ventilatory parameters followed standard clinical guidelines: tidal volume 6~8 mL/kg, respiratory rate 10~12 breaths/min, inspired oxygen concentration 50% and end-tidal carbon dioxide maintained at 35~45 mmHg by appropriate ventilatory adjustments.

Anesthesia maintenance

During anesthetic maintenance, the P group received propofol via target-controlled infusion to sustain a stable predicted plasma concentration, whereas the S group was maintained on sevoflurane at an end-tidal concentration of 1.5–2.5%. Both groups received a continuous infusion of remifentanil to provide baseline analgesia. Rocuronium was administered in incremental doses according to surgical requirements and all patients were given sufentanil prior to skin incision to reinforce anesthetic depth and ensure adequate muscle relaxation.

Perioperative fluid administration was titrated to preserve hemodynamic homeostasis, avoiding both hypovolemia and fluid overload. Anesthetic depth was controlled with bispectral index monitoring, targeting BIS values between 40 and 60. Blood pressure and heart rate were maintained within ±20% of pre-induction baseline values. Any hemodynamic deviation, including hypotension, hypertension, tachycardia, or bradycardia, was promptly managed with vasoactive agents to prevent tissue hypoperfusion and cardiovascular instability.

Recovery from anesthesia

To facilitate a smooth emergence from anesthesia and avoid opioid-related hyperalgesia, the remifentanil infusion was discontinued approximately 10 minutes before the anticipated end of surgery and sufentanil was administered as a transition analgesic. Routine postoperative patient-controlled analgesia was not used. Postoperative nausea or vomiting, when present, was treated with intravenous dolasetron according to institutional antiemetic protocols. Upon completion of surgery, all patients were transferred to the post-anesthesia care unit (PACU) for standardized recovery monitoring. Tracheal extubation was performed after full restoration of spontaneous ventilation and protective airway reflexes. Patients achieving an Aldrete score ≥9 were subsequently transferred to the surgical ward for continued recovery. This perioperative management strategy reflects a patient-centered anesthetic approach aligned with enhanced recovery after surgery (ERAS) principles, prioritizing analgesic safety, hemodynamic stability and optimized postoperative recovery.

Specimen collection and storage

After surgical excision of the breast cancer lesion, tissue procurement followed a standardized spatial protocol. Tumor samples were obtained from the viable central region of the mass, avoiding necrotic, cystic, or hemorrhagic areas to minimize intratumoral heterogeneity. Correspondingly, adjacent non-tumorous breast tissues were collected 2–3 cm away from the gross tumor margin and visually confirmed to be free of malignant infiltration. Immediately after removal, connective and adipose tissues were trimmed to eliminate nonessential components. Each specimen was briefly rinsed with sterile normal saline to remove residual blood and debris. Using sterile forceps and scissors, the tissues were cut into blocks of approximately 0.5 cm^3, transferred into pre-cooled cryogenic tubes and

rapidly immersed in liquid nitrogen. All specimens were subsequently stored at −80 °C until RT-qPCR and Western blot analyses were performed.

Laboratory procedures

To elucidate anesthesia-related molecular alterations at the tissue level, two complementary molecular biology techniques-quantitative real-time polymerase chain reaction (RT-qPCR) and Western blotting-were performed to quantify mRNA and protein expression, respectively. RT-qPCR analysis: Total RNA was extracted from frozen tissue using TRIzol reagent (Invitrogen, USA) in accordance with the manufacturer's protocol. RNA purity and concentration were assessed using a NanoDrop 2000 spectrophotometer (Thermo Scientific, USA) and 1 μg of RNA was reverse-transcribed into cDNA using the PrimeScript™ RT reagent kit (Takara, Japan; Cat. No. RR037A).RT-qPCR was conducted on a QuantStudio™ 5 Real-Time PCR System (Applied Biosystems, USA) using TB Green® Premix Ex Taq™ II (Takara, Japan; Cat. No. RR820A) in a total reaction volume of 20 μL, containing 2 μL of cDNA template.

Primer sequences were as follows: 1. CALML5: Forward 5′-AGG AGA GGA TGG CAA GAA GG-3′; Reverse 5′-CTG GCT TCA GGT AGA CTT GG-3′;2. RYR2: Forward 5′-TGG ACT TCT CCA GCA TCC TT-3′; Reverse 5′-GGA GAT GAC TGC CTC ATC CT-3′;3. GAPDH (reference gene): Forward 5′-GGA GCC AAA AGG GTC ATC AT-3′; Reverse 5′-GTG ATG GCA TGG ACT GTG GT-3′. All measurements were performed in triplicate and a no-template control (NTC) was included in every run to exclude contamination and nonspecific amplification. A melting-curve analysis confirmed the specificity of each amplicon. Relative mRNA expression was calculated using the $2^{-\Delta\Delta Ct}$ method, with GAPDH as the internal control. Western blot analysis: Total protein was extracted using RIPA lysis buffer supplemented with protease inhibitors (Beyotime Biotechnology, China) and quantified by BCA assay (Thermo Scientific, USA). Equal amounts of protein were separated via SDS-PAGE and transferred to PVDF membranes (Millipore, USA). After blocking with 5% non-fat milk, membranes were incubated overnight at 4 °C with primary antibodies targeting CALML5 and RYR2, followed by incubation with HRP-conjugated secondary antibodies. Chemiluminescent signals were detected using an ECL substrate (Millipore, USA). Band intensity values were analyzed using ImageJ software (NIH, version 1.53). Densitometric values were normalized to the internal control β-actin and the expression of each protein was reported as the target-to-β-actin ratio. All samples were processed under identical exposure settings to ensure consistency.

Postoperative prognostic assessment

Postoperative pain was evaluated using the 11-point numerical rating scale (NRS-11), which ranges from 0 to 10. The scale was verbally administered by trained nursing staff at rest, where 0 indicates no pain and 10 represents the worst imaginable pain. Patients were instructed to select the single number that best reflected their pain intensity at the time of assessment. In accordance with commonly accepted clinical cut-off values, NRS 1~3 was classified as mild pain, 4~6 as moderate pain and ≥7 as severe pain and an NRS ≥4 was considered clinically meaningful pain requiring analgesic attention. This procedure is widely recommended in perioperative pain assessment and has demonstrated good validity and responsiveness in postoperative settings. Pain assessments in this study were performed at 24 hours after surgery to standardize evaluation and minimize inter-observer variability (Breivik *et al*., 2008; Stark *et al*., 2013); Postoperative recovery quality was assessed using the validated quality of recovery-15 (QoR-15) questionnaire, which contains 15 items covering physical comfort, emotional state, psychological support, physical independence and pain. Each item is rated on an 11-point numerical scale (0~10), yielding a total score range of 0~150, with higher scores indicating better recovery. The questionnaire was administered face-to-face by trained research nurses at postoperative 24 hours and patients were instructed to rate each item based on their overall recovery experience during the preceding day. Because this study was conducted in a Chinese-speaking population, an officially translated and psychometrically validated Chinese version of the QoR-15 was used, which has demonstrated high internal consistency, construct validity and responsiveness in perioperative settings. The cultural and semantic equivalence of the Chinese QoR-15 was previously established through forward–backward translation, expert consensus review and pilot cognitive testing among surgical patients, as reported in validation studies. Therefore, no additional linguistic modification was required for the present trial (Bu *et al*., 2014); and during follow-up, data on incision pain at 3 and 6 months, as well as tumor recurrence and patient survival, were systematically recorded.

Statistical analysis

Data were analyzed using SPSS version 26.0. The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and compared using independent-samples t-tests or paired t-tests when appropriate. Non-normally distributed variables were expressed as M (P_{25}, P_{75}) and analyzed using the Mann–Whitney U test or the Wilcoxon signed-rank test. Categorical variables were reported as frequencies and percentages and compared using χ^2 tests or Fisher's exact tests when expected cell counts were <5. In addition to hypothesis testing, effect sizes (Cohen's d for continuous variables and Cramer's V for categorical variables) were calculated to quantify the magnitude of group differences. Repeated-measure outcomes such as NRS and QoR-15

scores were further analyzed using repeated-measures ANOVA for normally distributed data or the Friedman test for non-normal data, with Bonferroni correction applied for multiple comparisons. All statistical tests were two-tailed and a *P*-value <0.05 was considered statistically significant.

Baseline data

This study included a total of 38 patients, divided equally into two groups (n = 19 each). Statistical analysis revealed no significant differences in baseline characteristics between the two groups ($P > 0.05$).

Comparison between groups: No significant difference was observed in preoperative serum calcium levels between the two groups (P = 0.609). Postoperatively, serum calcium levels in Group 2 were slightly higher than those in Group 1; however, the difference was not statistically significant ($P = 0.110$).

Comparison within groups: Paired comparisons of pre- and postoperative calcium concentrations within each group revealed no significant changes in either group. Postoperative calcium levels showed no statistically significant difference from preoperative values in Group 1 ($P = 0.354$) or Group 2 ($P = 0.643$).

RESULTS

Baseline characteristics

A total of 38 patients were included in this study, with 19 patients in each group. No statistically significant differences were found between the two groups in baseline demographic characteristics, clinicopathological features, or perioperative variables (all $P>0.05$, Table 1).

qRT-PCR analysis of RYR2 and CALML5 gene expression in the two groups

Comparison of RYR2 and CALML5 gene expression between the propofol and sevoflurane groups

CALML5 (calmodulin-like protein 5) belongs to the calmodulin-like protein family, whereas RYR2 (ryanodine receptor 2) serves as a pivotal calcium-release channel located in the sarcoplasmic reticulum.

Comparison of RYR2 and CALML5 gene expression between the propofol and sevoflurane groups

Expression of the RYR2 gene showed an increasing tendency in the sevoflurane group compared with the propofol group, although the difference was not statistically significant ($P > 0.05$). Conversely, CALML5 expression was markedly elevated in the sevoflurane group relative to the propofol group ($P < 0.001$), suggesting that sevoflurane anesthesia significantly enhances CALML5 expression in breast cancer tissue. (Table 2; Fig. 2)

Expression levels of RYR2 and CALML5 genes in the propofol group

In the propofol group, RYR2 expression in tumor tissues showed an upward trend that approached statistical significance, suggesting that propofol may mildly induce RYR2 expression within the tumor microenvironment. In contrast, CALML5 expression was significantly elevated in tumor tissues compared with adjacent normal tissues. Combined with the findings in Table 2, these results indicate that propofol upregulated CALML5 expression; however, the degree of upregulation was lower than that observed with sevoflurane anesthesia overall (1.737 vs. 2.053) (Table 3; Fig. 3).

Expression levels of RYR2 and CALML5 genes in the sevoflurane group

In the sevoflurane group, overall RYR2 expression levels were higher and their pronounced elevation in tumor tissues implies that sevoflurane could further enhance RYR2 activation within the tumor microenvironment. Conversely, CALML5 expression in tumor tissues was marginally reduced compared with adjacent normal tissues, although the difference was not statistically significant (Table 4; Fig. 4).

Western blot analysis of RYR2 and CALML5 protein expression

Western blot analysis demonstrated that the protein expression levels of both RYR2 and CALML5 were significantly higher in the propofol group than in the sevoflurane group (both P = 0.001), indicating distinct regulatory patterns of calcium-related proteins between the two anesthetic regimens (Table 5; Fig. 5).

Comparison of perioperative serum calcium concentrations

No significant between-group differences were observed in preoperative or post-operative serum calcium concentrations. In addition, paired comparisons within each group showed no significant perioperative change in serum calcium levels in either the propofol group or the sevoflurane group (Table 6).

Postoperative outcomes and follow-up results

The median post-operative NRS pain score in Group 1 was slightly higher than that in Group 2, with the difference approaching statistical significance (P=0.067). The incidence of incision pain at 3 and 6 months after surgery showed no significant difference between the two groups (P>0.05). Similarly, QoR-15 scores and five-point Likert scale ratings indicated no significant variation in overall recovery quality between groups (P> 0.05). During follow-up, the rates of tumor recurrence and metastasis were low in both groups and no statistically significant differences were observed ($P > 0.05$) (Table 7).

DISCUSSION

The analysis demonstrated a pronounced difference in CALML5 mRNA expression between the two anesthetic regimens, with significantly higher transcript levels observed in the sevoflurane group (P < 0.001).

Table 1: Baseline characteristics of patients in the two groups

Variables	1(*n*=19)	2(*n*=19)	t/Z/χ^2	*P*
Ethnicity, n(%)			-	>0.999
Han	12 (63.16)	12 (63.16)		
Uygur	5 (26.32)	6 (31.58)		
Kazakh	1 (5.26)	1 (5.26)		
Hui	1 (5.26)	0 (0.00)		
Age(years)	58.00±5.63	55.00±6.98	1.458	0.154
ASA classification			-	>0.999
II	18 (94.74)	18 (94.74)		
III	1 (5.26)	1 (5.26)		
BMI (kg/m²)	24.57±3.94	26.62±4.04	-1.586	0.122
Height (m)	1.62±0.06	1.60±0.06	0.796	0.431
Weight (kg)	64.16±9.14	68.05±8.49	-1.360	0.182
Parity, n(%)			-	0.232
<3	13 (68.42)	17 (89.47)		
≥3	6 (31.58)	2 (10.53)		
Dysmenorrhea, n(%)			-	0.194
No	12 (63.16)	7 (36.84)		
Yes	7 (36.84)	12 (63.16)		
Menopause, n(%)			-	0.330
No	7 (36.84)	11 (57.89)		
Yes	12 (63.16)	8 (42.11)		
Menstrual cycle (days)	4.32±0.58	4.32±0.48	0.000	>0.999
Tumor location, n(%)			-	0.746
Left	11 (57.89)	9 (47.37)		
Right	8 (42.11)	10 (52.63)		
Molecular subtype			-0.062	0.951
Luminal A	15 (78.95)	15 (78.95)		
Luminal B	3 (15.79)	2 (10.53)		
Triple-negative	1 (5.26)	2 (10.53)		
Pathological type, n(%)			-	0.230
Invasive special type	0 (0.00)	3 (15.79)		
Invasive non-special type	19 (100.00)	16 (84.21)		
Metastasis, n(%)			-	0.325
No	9 (47.37)	13 (68.42)		
Yes	10 (52.63)	6 (31.58)		
ER (%)	90.00 (75.00, 90.00)	80.00 (80.00, 90.00)	0.785	0.432
PR (%)	80.00 (25.00, 90.00)	70.00 (17.50, 90.00)	0.044	0.965
HER2 (IHC score)	2.00 (0.00, 2.00)	2.00 (0.00, 2.00)	-0.111	0.911
KI67 (%)	47.63±24.69	45.79±22.00	0.243	0.810
AR (%)	70.00 (0.00, 90.00)	80.00 (0.00, 90.00)	-0.799	0.424
Histological grade, n(%)			0.467	0.640
Grade I	0 (0.00)	1 (5.26)		
Grade II	10 (52.63)	10 (52.63)		
Grade III	9 (47.37)	8 (42.11)		
Surgical method, n(%)			-	0.515
Breast-conserving surgery	12 (63.16)	9 (47.37)		
Mastectomy	7 (36.84)	10 (52.63)		
Anesthesia time (min)	89.74±25.47	84.21±27.70	0.640	0.526
Blood loss (ml)	20.00 (15.00, 50.00)	30.00 (15.00, 50.00)	-0.408	0.683
Fluid infusion (ml)	750.00 (750.00, 1000.00)	1000.00 (750.00, 1250.00)	-1.423	0.155

Comparison between groups: No significant difference was observed in preoperative serum calcium levels between the two groups (P = 0.609). Postoperatively, serum calcium levels in Group 2 were slightly higher than those in Group 1; however, the difference was not statistically significant (P = 0.110). Comparison within groups: Paired comparisons of pre- and postoperative calcium concentrations within each group revealed no significant changes in either group. The postoperative calcium levels showed no statistically significant difference compared with preoperative values in Group 1 (P = 0.354) or Group 2 (P = 0.643).

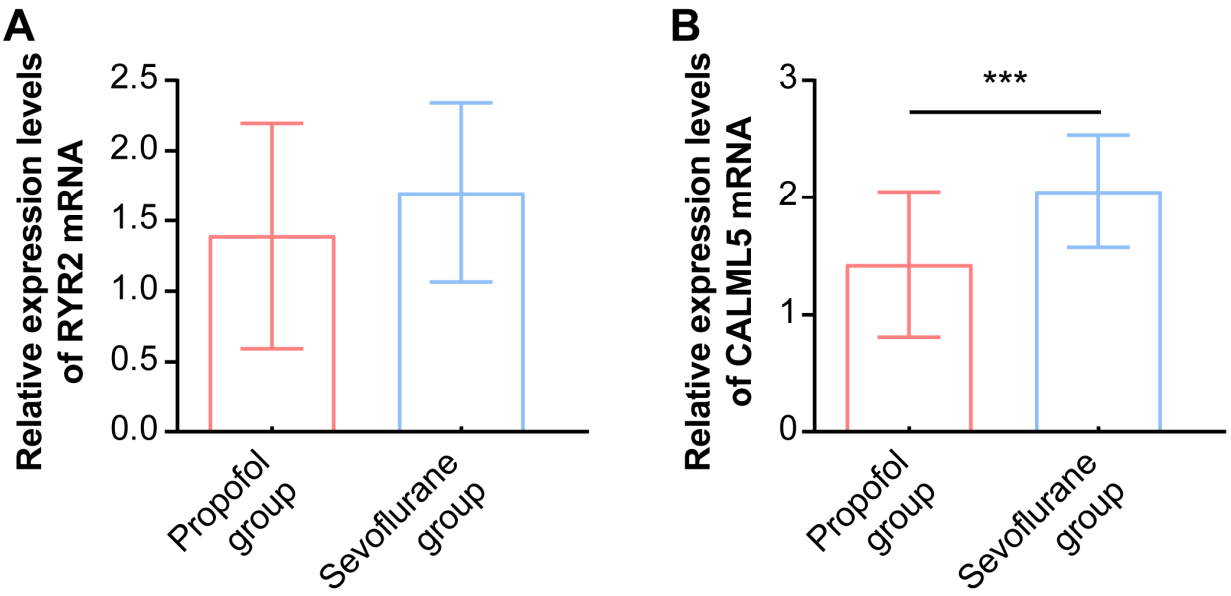

Fig. 2: Comparison of RYR2 and CALML5 mRNA expression levels between the propofol and sevoflurane groups. (a) Relative RYR2 mRNA expression in breast tissue samples from the propofol and sevoflurane groups; (b) Relative CALML5 mRNA expression in breast tissue samples from the propofol and sevoflurane groups. Data are presented as mean ± SD. Statistical comparisons between groups were performed using the independent-samples t test. **P*<0.05, ***P*<0.01, ****P*<0.001; ns, not significant. RYR2, ryanodine receptor 2; CALML5, calmodulin-like protein 5; SD, standard deviation.

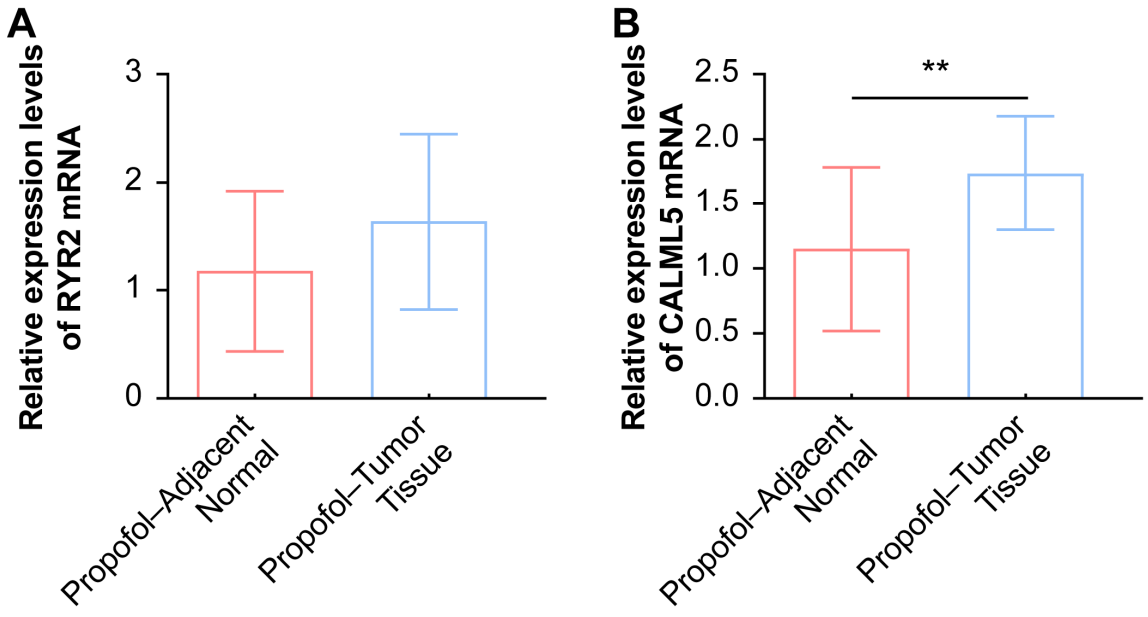

Fig. 3: Comparison of RYR2 and CALML5 mRNA expression between adjacent normal tissue and tumor tissue in the propofol group.
(a) Relative RYR2 mRNA expression in adjacent normal tissue and tumor tissue from patients receiving propofol-based anesthesia; (b) Relative CALML5 mRNA expression in adjacent normal tissue and tumor tissue from patients receiving propofol-based anesthesia. Data are presented as mean ± SD. Statistical comparisons were performed between tissue types within the propofol group. **P* < 0.05, ***P*< 0.01, ****P*<0.001; ns, not significant. RYR2, ryanodine receptor 2; CALML5, calmodulin-like protein 5; SD, standard deviation.

Table 2: Comparison of RYR2 and CALML5 mRNA expression levels between groups

Group	RYR2	CALML5
Propofol group (n = 36)	1.393±0.800	1.428±0.618
Sevoflurane group (n = 33)	1.702±0.638	2.053±0.480
t	-1.762	-4.660
P	0.083	0.000

Note: The *t* value represents the test statistic from the t-test, while the *P* value indicates the level of statistical significance. A *P* value < 0.05 was considered to indicate a statistically significant difference between the two groups.

Table 3: Analysis of RYR2 and CALML5 mRNA expression levels in propofol-treated tissues

Subgroup	RYR2	CALML5
Propofol–adjacent normal tissue (n = 19)	1.178±0.743	1.151±0.633
Propofol–tumor tissue (n = 17)	1.634±0.814	1.737±0.439
t	-1.758	-3.190
P	0.088	0.003

Note: The *t* value represents the statistic derived from the *t*-test, and the *P* value reflects the level of statistical significance. A *P* value < 0.05 was considered to indicate a statistically significant difference between the two groups.

Table 4: Analysis of RYR2 and CALML5 mRNA expression levels in sevoflurane-treated tissues

Subgroup	RYR2	CALML5
Sevoflurane–adjacent normal tissue (n = 17)	1.364±0.440	2.159±0.492
Sevoflurane–tumor tissue (n = 16)	2.062±0.629	1.940±0.456
t	-3.671	1.324
P	0.001	0.195

Note: The *t* value corresponds to the statistic obtained from the t-test, while the *P* value reflects the probability of significance. Differences between the two groups were regarded as statistically significant when $P < 0.05$.

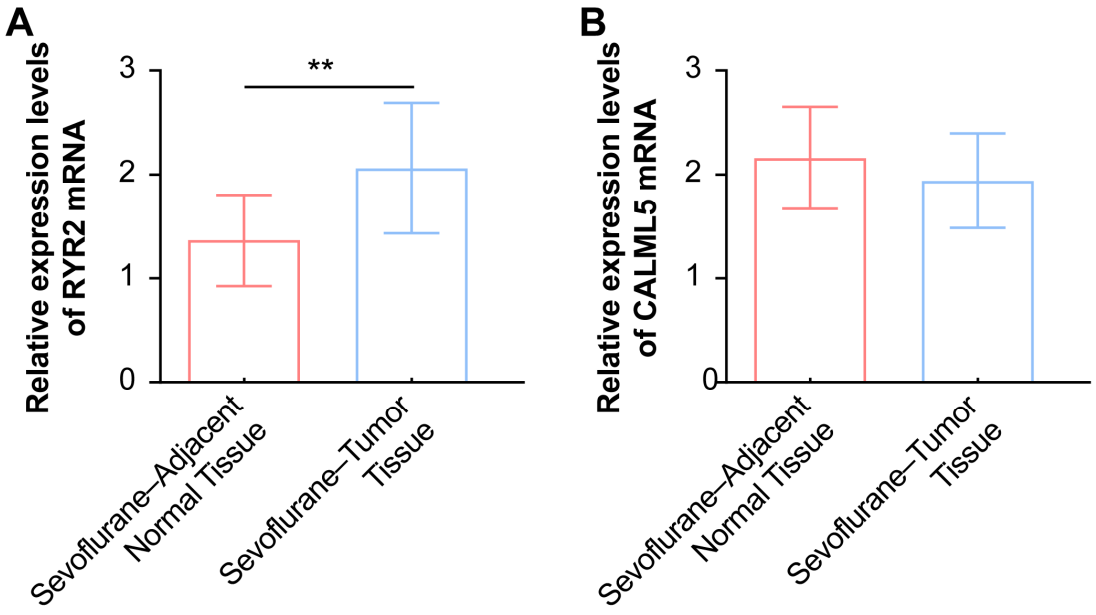

Fig. 4: Comparison of RYR2 and CALML5 mRNA expression between adjacent normal tissue and tumor tissue in the sevoflurane group.
(a) Relative RYR2 mRNA expression in adjacent normal tissue and tumor tissue from patients receiving sevoflurane-based anesthesia; (b) Relative CALML5 mRNA expression in adjacent normal tissue and tumor tissue from patients receiving sevoflurane-based anesthesia. Data are presented as mean ± SD. Statistical comparisons were performed between tissue types within the sevoflurane group. **P*<0.05, ***P*< 0.01, ****P*<0.001; ns, not significant. RYR2, ryanodine receptor 2; CALML5, calmodulin-like protein 5; SD, standard deviation.

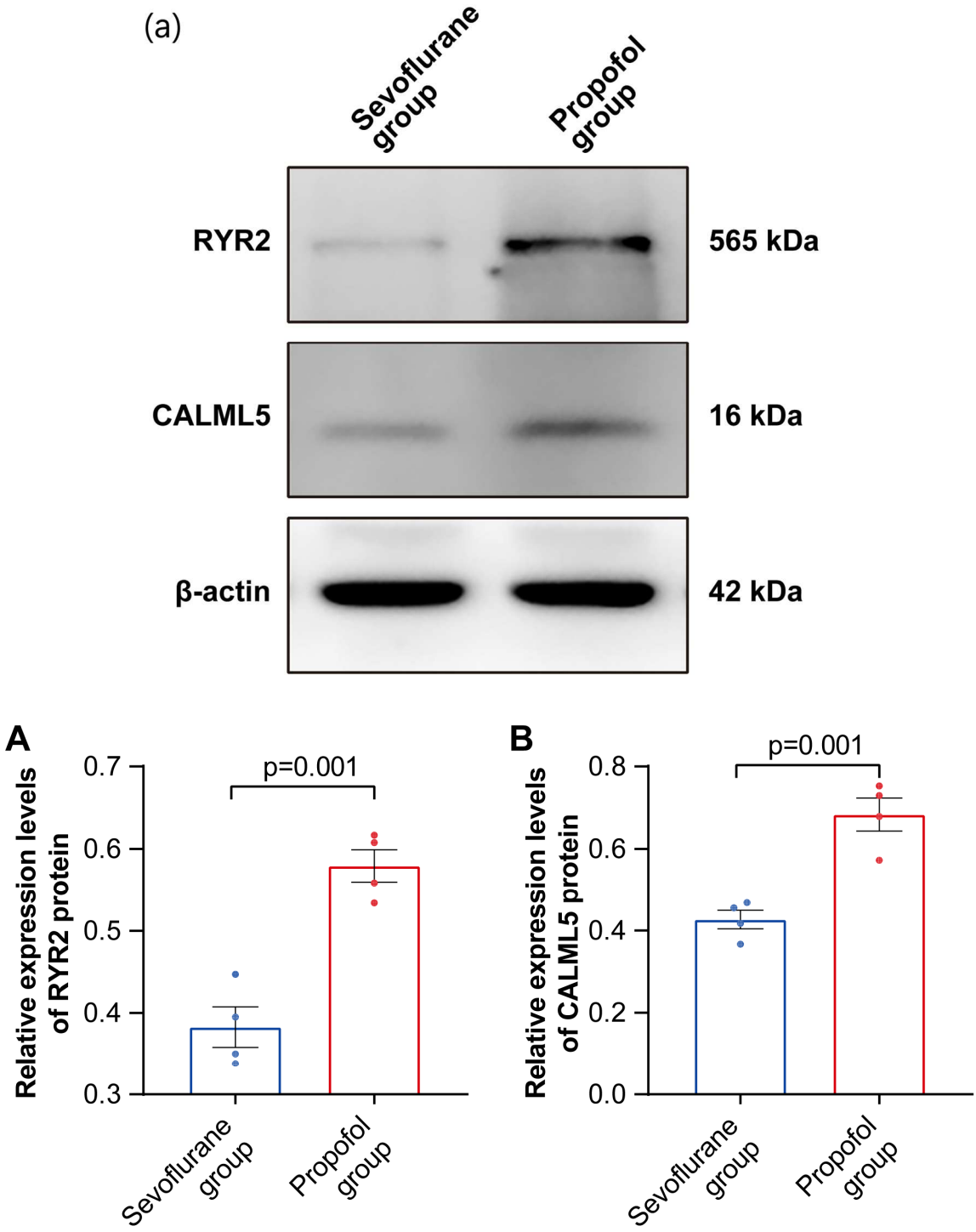

Fig. 5: Representative Western blot images and quantitative analysis of RYR2 and CALML5 protein expression in the sevoflurane and propofol groups.
(a) Representative Western blot bands of RYR2, CALML5 and β-actin in the sevoflurane and propofol groups; (b) Quantitative analysis of RYR2 protein expression normalized to β-actin; (c) Quantitative analysis of CALML5 protein expression normalized to β-actin. Data are presented as mean ± SD. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. RYR2, ryanodine receptor 2; CALML5, calmodulin-like protein 5.

Table 5: Western blot analysis of RYR2 and CALML5 protein expression in the two groups

Group	RYR2	CALML5
Sevoflurane group	0.383±0.050	0.427±0.045
Propofol group	0.580±0.040	0.684±0.080△
t	-6.214	-5.572
P	0.001	0.001

Note: ≥ Indicates a statistically significant difference compared with the sevoflurane group ($P < 0.05$).

Table 6 Comparison of perioperative serum calcium concentrations between the two groups

Variables	1(*n*=19)	2(*n*=19)	Z	*P*
Preoperative calcium concentration (mmol/L)	2.23 (2.18, 2.25)	2.23 (2.21, 2.27)	-0.512	0.609
Post-operative calcium concentration (mmol/L)	2.20 (2.15, 2.25)	2.23 (2.21, 2.31)	-1.597	0.110
Z	-0.927	-0.463		
P	0.354	0.643		

Note: Between-group comparisons were performed using the Mann-Whitney U test.
Within-group paired comparisons showed no significant difference between preoperative and post-operative calcium concentrations in Group 1 ($Z = -0.927$, $P = 0.354$) or Group 2 ($Z = -0.463$, P=0.643).

Table 7: Comparison of postoperative outcomes between the two groups

Variable	1(*n*=19)	2(*n*=19)	t/Z/χ2	*P*
Post-operative NRS pain score	5.00 (4.00, 5.00)	4.00 (3.00, 4.50)	1.835	0.067
Incision pain at 3 months, n(%)			-	>0.999
No	14 (73.68)	13 (68.42)		
Yes	5 (26.32)	6 (31.58)		
Incision pain at 6 months			-	>0.999
No	18 (94.74)	18 (94.74)		
Yes	1 (5.26)	1 (5.26)		
QoR-15 total score	142.00 (140.50, 143.50)	142.00 (140.50, 144.00)	-0.491	0.623
5-point Likert scale	4.00 (4.00, 5.00)	4.00 (4.00, 5.00)	-0.327	0.743
Postoperative recurrence			-	>0.999
No	15 (78.95)	16 (84.21)		
Yes	4 (21.05)	3 (15.79)		
Postoperative metastasis			-	>0.999
No	17 (89.47)	18 (94.74)		
Yes	2 (10.53)	1 (5.26)		
Yes	5 (26.32)	6 (31.58)		
Incision pain at 6 months, n(%)			-	>0.999
No	18 (94.74)	18 (94.74)		
Yes	1 (5.26)	1 (5.26)		
QoR-15 total score	142.00 (140.50, 143.50)	142.00 (140.50, 144.00)	-0.491	0.623
5-point Likert scale	4.00 (4.00, 5.00)	4.00 (4.00, 5.00)	-0.327	0.743
Postoperative recurrence, n(%)			-	>0.999
No	15 (78.95)	16 (84.21)		
Yes	4 (21.05)	3 (15.79)		
Postoperative metastasis, n(%)			-	>0.999
No	17 (89.47)	18 (94.74)		
Yes	2 (10.53)	1 (5.26)		

The median post-operative NRS pain score in Group 1 was slightly higher than that in Group 2, with the difference approaching statistical significance ($P = 0.067$). The incidence of incision pain at 3 and 6 months after surgery showed no significant difference between the two groups ($P > 0.05$). Similarly, QoR-15 scores and five-point Likert scale ratings indicated no significant variation in overall recovery quality between groups ($P > 0.05$). During follow-up, the rates of tumor recurrence and metastasis were low in both groups, and no statistically significant differences were observed ($P > 0.05$).

Within the propofol cohort, CALML5 expression was elevated in tumor specimens compared with paired adjacent noncancerous tissues, indicating tumor-associated upregulation. A similar trend was noted for RYR2 in the sevoflurane cohort, in which tumor tissues exhibited higher expression than corresponding normal tissues. Across both anesthetic conditions, gene expression was consistently increased in malignant rather than adjacent benign tissues,

suggesting that anesthetic exposure may preferentially interact with calcium-regulatory molecular targets in tumor microdomains rather than in normal parenchyma. Notably, propofol exerted a comparatively greater suppressive effect on CALML5 expression than sevoflurane, supporting the hypothesis that distinct anesthetic modalities may differentially modulate calcium-dependent signaling pathways and thereby influence the molecular phenotype and biological behavior of breast cancer cells.

Notably, propofol produced a marked suppression of CALML5 expression relative to sevoflurane, providing a potential molecular explanation for divergent anesthetic effects on tumor biological behavior. Given that CALML5 participates in calcium-mediated signaling, cytoskeletal dynamics, cell motility and proliferation, its down-regulation under propofol anesthesia may indicate a comparatively attenuated activation of calcium-dependent pathways within breast cancer tissues. At the clinical level, however, postoperative assessments—including 24-hour NRS pain scores, QoR-15 recovery indices and the rates of tumor recurrence or metastasis within six months—did not differ significantly between groups. Several factors may account for these comparable outcomes: the six-month follow-up interval may be too brief to capture survival-relevant oncologic differences; postoperative adjuvant therapies such as chemotherapy, radiotherapy, or endocrine treatment may dilute anesthesia-related effects; and the modest sample size may have limited statistical power to detect subtle clinical differences.

Recent narrative and mechanistic reviews have suggested that the choice between propofol and sevoflurane may influence oncologic outcomes in breast cancer through immunomodulation, inflammation and tumor microenvironment remodeling; however, the currently available clinical evidence remains heterogeneous. No consistent survival advantage has been demonstrated for either propofol- or sevoflurane-based anesthesia in breast cancer surgery, despite biologically plausible differences in immune and inflammatory pathways (Fang *et al*., 2022). Broader evidence has also indicated that anesthetic agents and anesthetic techniques used during cancer surgery may modulate immune surveillance, inflammatory cytokines, angiogenesis and circulating tumor cells, whereas their long-term impact on recurrence and survival remains uncertain and requires further high-quality studies (Iqbalbhai *et al*., 2025). At the cellular level, breast cancer cell survival has been reported to be altered by sevoflurane through perturbation of intracellular calcium homeostasis, suggesting that calcium signaling may represent a relevant but still underexplored target of anesthetic action in breast cancer (Deng *et al*., 2020).In addition, perioperative immunologic observations have suggested that propofol-based anesthesia may better preserve $CD4^+$ T-cell activity than inhalational anesthesia during the immediate postoperative period, indicating potential differential effects on adaptive immunity (Sun D *et al*., 2024).The differential regulation of CALML5 observed in the present study is biologically consistent with previous evidence suggesting that propofol may interfere with tumor-related signaling pathways (Xu *et al*., 2020). Mechanistic and clinical evidence has indicated that propofol may suppress cancer-related progression by modulating mitochondrial function, attenuating NF-κB-mediated inflammation, reducing circulating tumor cells and enhancing antitumor immunity in human subjects (Xu *et al*., 2020). Propofol has also been associated with down-regulation of proliferation-related signaling cascades and possible reduction in metastatic potential through effects on epithelial-mesenchymal transition and cytoskeletal remodeling (Xu *et al*., 2020). These molecular features are in line with the present observation that propofol was associated with lower CALML5 expression than sevoflurane, which may reflect a relatively restrained activation of calcium-dependent pathways in breast cancer tissues.Volatile anesthetics, including sevoflurane and isoflurane, have also been reported to modulate tumor immunity and cancer-cell behavior in a context-dependent manner, with both inhibitory and potentially tumor-promoting findings described in the literature (Xu *et al*., 2020). Nevertheless, most previous reports were based on narrative syntheses, in vitro experiments, or short-term immune endpoints and rarely integrated direct measurements of calcium-signaling-related molecules in human tumor tissues with prospectively collected perioperative outcomes. In this context, the present randomized clinical study focused on the calcium signaling pathway as a defined mechanistic axis and quantitatively compared RYR2 and CALML5 expression in paired tumor and adjacent normal tissues from breast cancer patients receiving propofol- versus sevoflurane-based anesthesia, while simultaneously assessing postoperative pain, early recovery quality and 6-month recurrence/metastasis. By integrating tissue-level molecular readouts with short-term clinical outcomes, these findings help refine previous research from asking whether anesthetic choice matters to clarifying how specific anesthetic regimens may differentially modulate calcium-dependent signaling in vivo and whether such changes translate into measurable clinical differences. Several limitations should also be acknowledged. First, the relatively small sample size increases the possibility that the observed molecular differences may partly reflect sampling variation and it may also limit representation of different tumor subtypes and perioperative biological heterogeneity. Second, the single-center design improves internal consistency but restricts external generalizability and may introduce institutional practice bias. Third, the 6-month follow-up period reflects only short-term recurrence and recovery and cannot substitute for long-term oncologic evaluation in breast cancer, particularly in the context of adjuvant therapies that may confound anesthesia-related effects. Therefore, larger multicenter studies with longer follow-up durations are warranted to confirm the

reproducibility and clinical significance of the present findings.

In summary, by integrating mRNA and protein profiling with perioperative clinical assessment, measurable differences were identified in the molecular responses of breast cancer tissue to propofol- and sevoflurane-based anesthesia. These observations provide preliminary evidence that anesthetic choice may influence calcium-dependent regulatory pathways in malignant tissue. Although short-term clinical equivalence was observed within the 6-month follow-up period, the molecular findings highlight a potentially relevant biological signal that may help inform future mechanism-oriented optimization of perioperative anesthetic strategies in breast cancer surgery.

CONCLUSION

In this randomized controlled study comparing two commonly used anesthetic agents in breast cancer surgery, sevoflurane and propofol demonstrated distinct regulatory effects on calcium-signaling–related molecules, which represented the primary mechanistic objective of the research. Sevoflurane anesthesia significantly up-regulated CALML5 gene and protein expression, whereas propofol showed a comparatively suppressive profile, while changes in RYR2 expression remained statistically nonsignificant between groups. These findings confirm that inhalational and intravenous anesthetics exert differential molecular influences on calcium-dependent pathways within breast cancer tissues, supporting the biological hypothesis addressed in this study. Despite these molecular differences, no statistically significant differences were detected in postoperative pain scores (NRS), early recovery quality (QoR-15), incision pain at 3–6 months, or 6-month recurrence/metastasis rates, indicating that short-term clinical outcomes were not modified by anesthetic selection within the observation period. Taken together, the current findings suggest that sevoflurane alters calcium-regulatory signaling at the tumor tissue level but does not translate into measurable short-term clinical advantages or disadvantages compared with propofol. These results refine current understanding regarding perioperative anesthetic choice in breast cancer surgery —highlighting a molecular divergence without corresponding early clinical divergence. Given the limited sample size, single-center design and short follow-up duration, the present observations should be interpreted cautiously. Longer follow-up, molecular mechanistic studies and multicenter trials are warranted to determine whether perioperative modulation of calcium signaling could influence long-term oncologic outcomes.

Acknowledgments
All authors declare no conflicts of interest related to this study. The study was conducted in strict accordance with the Declaration of Helsinki (2022 Revision) and written informed consent was obtained from all enrolled subjects or their legally authorized representatives prior to any study-related interventions.

Authors' contributions
Jiahui Wang: Contributed to conceptualization, methodology, investigation (clinical data collection and experimental performance), formal analysis and drafting of the original manuscript; Bichen He: Contributed to data curation, validation and visualization. Gulibanumu Kuerban: Contributed to methodology optimization, resources (laboratory reagents and clinical samples) and investigation. Chentong Gao: Contributed to formal statistical analysis and manuscript review and editing; Bing Zhang: Led conceptualization, acquired funding, supervised the overall study, critically reviewed and edited the manuscript and approved the final version for submission. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Data availability statement
The datasets generated and analyzed during the current study are not publicly available due to patient privacy and institutional data-protection policies, but are available from the corresponding author on reasonable request. Qualified researchers may obtain access after submitting a justified request and signing a data-use agreement in accordance with ethical guidelines.

Ethical approval
This study was formally approved by the Ethics Review Committee of the Affiliated Tumor Hospital of Xinjiang Medical University (approval no. K-2025029). This study was performed in adherence with the STROBE guidelines. See supplementary file for the STROBE checklist.

Conflict of interest
The authors declare that there are no conflicts of interest regarding the publication of this manuscript. All authors have no financial, personal, academic, or institutional relationships that could be perceived as influencing the work. No industry support, commercial funding, or external sponsorship was involved in the study design, data collection, analysis, interpretation, or manuscript preparation.

Supplementary data
https://www.pjps.pk/uploads/2026/06/SUP1780830178.pdf

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