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ANAESTHETIC PHARMACODYNAMICS IN HORMONE-RECEPTOR POSITIVE VS. TRIPLE-NEGATIVE BREAST CARCINOMA PATIENTS

Shehroz Nafees[*1], Hira Saeed[2], Hassan Raza[3], Pavan Kumar[4], Mavra Akram[5], Madiha Abbas[6], Rimal Rashid[7]

[*1]*Ziauddin Hospital, Karachi*
[2,5,7]*Dow University of Health Sciences, Karachi*
[3,6]*Jinnah Postgraduate Medical Centre, Karachi*
[4]*Al-Tibri Medical College and Hospital, Isra University, Karachi*

nomanahmed678@outlook.com

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Corresponding Author: *
Shehroz Nafees

Abstract

Pharmacodynamical effects of anesthetics may differ markedly among individual patients, which may be influenced by underlying biology of the disease. Breast cancer is divided into subtypes according to hormone receptor status, as hormone receptor-positive (HR+) and triple-negative (TNBC) breast cancer, which may present different clinical features and systemic inflammatory signatures, possibly having impact in anesthetic strategy and postoperative recovery. We prospectively compared anesthetic responses in HR+ and TNBC patients undergoing breast cancer surgery at a single tertiary care Centre (JPMC). This was a prospective observational study at Jinnah Postgraduate Medical Centre (JPMC), Karachi on 120 female patients affected by HR+ (n=60) or TNBC (n=60) subtypes who underwent breast surgery. Demographic and clinical information was collected. Intraoperative anesthetic use (sevoflurane, propofol, fentanyl, rocuronium) and hemodynamic (mean arterial pressure, MAP; heart rate, HR; hypotension) variables and variability were recorded. Postoperative pain (VAS at 2 h, 6 h, and 24 h), morphine consumption and postoperative cognitive dysfunction (POCD) with MMSE scores were measured. T-tests and chi-square analyses were performed to compare groups; correlation matrices were developed. Sevoflurane usage (1.75 ± 0.35 vs 1.32 ± 0.28 MAC-hours, p=0.0003), propofol infusion rates (4.8 ± 1.1 vs 4.1 ± 0.9 mg/kg/h, p=0.012), and fentanyl requirement (215 ± 53 vs 185 ± 45 μg, p=0.018) were all significantly higher in TNBC patients. The TNBC group had hemodynamic instability, as shown by more MAP variation >20% (23.3% vs 8.3%, p=0.004) and vasopressor drugs need (31.6% vs 11.7%, p=0.002). TNBC patients reported greater VAS scores at all time points (5.1 vs 3.6 at 2 hours, p<0.001) and with higher morphine consumption (7.6 ± 2.0 vs 5.2 ± 1.4 mg, p<0.001). POCD was more common (28.9% vs 11.1%, p=0.006) and severe in TNBC patients. Strong positive correlations were observed between tumor subtype and sevoflurane usage (r=0.41), VAS score (r=0.48) and POCD score (r=0.38). The results indicate TNBC patients at Jinnah Postgraduate Medical Centre (JPMC), Karachi have specific anesthetic pharmacodynamics profiles manifested by higher drug needs, greater hemodynamic fluctuation, more

intense pain experience, and more pronounced neurocognitive dissonance. These findings support a personalized, subtype-specific paradigm for anesthetic stratagem in breast cancer operation.

INTRODUCTION

Breast cancer is still one of the most common and biologically diverse forms of cancer affecting the female population worldwide. It causes around 2.3 million new cases and 685,000 deaths per year worldwide and is one of the most common causes of cancer deaths in women. The classification of breast cancers is largely influenced by the presence or absence of the key molecular receptors, namely, estrogen receptor (ER), progesterone receptor (PR), and HER2 (human epidermal growth factor receptor 2) (Mohanty *et al.*, 2022). This molecular stratification not only determines prognosis but also serves as a therapeutic strategy. Within the subtypes, hormone receptor positive (HR+) breast cancer, in which the expression of ER and/or PR is present, accounts for approximately 70% of BC cases and is usually associated with a more favorable outcome thanks to the response to endocrine therapy. In contrast, triple-negative breast cancer (TNBC) lacks ER, PR, and HER2, accounting for 10–20% cases and having high recurrence rates, early metastasis, and poor survival (Baranova *et al.*, 2022).

Although there has been a significant development in the field of systemic therapy, surgery still plays a crucial role as the only curative treatment for both HR+ and TNBC patients. Anesthetic techniques and agents have been increasingly implicated in the modulation of cancer biology, with focus on the perioperative period, characterized by immunosuppression, inflammation, and dissemination of circulating tumor cells. Anesthetic type has been shown in in several studies to have an impact on oncologic endpoints including recurrence, metastasis, and survival. The perioperative period is a crucial yet frequently overlooked time point in the course of cancer management when anesthetic and analgesic strategies have the potential to affect long-term cancer outcomes by altering tumor microenvironment, immune response, and systemic inflammatory pathways (Weaver & Patey, 2025).

The interaction between anesthetic agents and pharmacodynamics in the cancer surgery setting has emerged as a major area of research. Several agents including propofol, sevoflurane, desflurane, lidocaine, and opioids have been studied to have differential effects on the tumor biology. In vitro experiments indicate that propofol might suppress proliferation, migration and invasion of several breast cancer cell lines primarily by decreasing hypoxia inducible factor-1 alpha (HIF-1α), matrix metalloproteinase (MMPs) and PI3K/Akt signaling pathway. In contrast, other volatile agents, such as sevoflurane, have been shown to favor EMT, elevate VEGF expression and reduce NK cell cytotoxicity (Luan *et al.*, 2022). These results highlight the possibility that anesthetic modalities can affect the HR+ and TNBC patients differently, especially noting the biological heterogeneity of these subtypes.

Clinical trials also support that these pharmacodynamics differences in anesthetics might be clinically relevant in-patient outcome studies. A follow-up analysis of a randomized clinical trial demonstrated that patients with ER-negative tumors (including TNBC) have the potential to benefit more from regional anesthetic techniques, particularly paravertebral blocks, which are believed to lower surgical stress and opioid requirements, therefore maintaining immune function (Kim *et al.*, 2022). The influence in HR+ breast cancer, on the other hand, seems to be less distinct or lagging behind, perhaps because of the longer natural history and recurrence trajectory typically observed in these tumors. Moreover, intraoperative opioids might exhibit paradoxical effects; one study proposed a neutral or even protective effect against recurrence in HR-negative patients, which may be explained by the differences in mu-opioid receptor expression and the related intracellular signaling pathways (Villasco *et al.*, 2021).

Of note, the majority of preclinical data comes from cell lines that model subtypes such as MDA-MB-231 for TNBC and MCF-7 for HR+, which limits the translatability of these findings. These cell lines vary

substantially in expression of receptors, the ability to migrate, and the response to chemotherapeutic drugs. For example, MDA-MB-231 cells are more mesenchymal and invasive, while MCF-7 cells are epithelial and hormone sensitive. This discrepancy also applies to anesthetic substances as TNBC are more likely to be sensitive for the anti-proliferative effects local but not volatile anesthetic agents including lidocaine or levobupivacaine even promoting more pro-tumorigenic effect as compared to HR+ cells (Hasan *et al.*, 2020).

Although a large body of evidence proposes differing anesthetic impact for breast cancer subtypes, there is a scarcity of clinical original research to support these results in real patient population. The present study adds new prospective data based on a single-institution (JPMC) cohort to compare anesthetic pharmacodynamics and recovery profiles in HR+ vs TNBC patients. The better we understand how anesthetic choices intersect tumor biology, the more likely we are to develop more personalized perioperative care regimes that reflect the same. Here, we seek to systematically compare and contrast the impact of the most common general anesthetic agents on the cellular pathways, immune effects and clinical outcomes in HR+ relative to TNBC breast cancer. Recent findings from in vitro studies, as well as from studies (Basheer *et al.*, 2023) of immunohistochemical markers, clinical outcomes, and other related areas, will be included to consider whether anesthetic pharmacodynamics vary importantly by receptor subtype and, should they do so, whether certain anesthetic management protocols should not be modified on that basis.

Review of Literature

The studies of the impact of anesthetic agents on breast cancer have made significant progress over the last decade, including in vitro, animal-model and clinical evidence. These studies reveal variable pharmacodynamic effects of the IV agents, propofol, the volatile such as sevoflurane, and local/regional anesthesia on different molecular subtypes, particularly the HR+ and the TNBC.

Propofol, an important intravenous anesthetic used in total intravenous anesthesia (TIVA), has shown antitumor actions through direct and indirect pathways. In vitro studies on different breast cancer cell lines (HR+ such as MCF-7 and TNBC as MDA-MB-231) have shown that propofol suppresses proliferation, migration and invasion by the reduction of HIF-1α, MMP-2/9, and PI3K/Akt (Tian *et al.*, 2020). Epigenetic influence by propofol was also described in HR+ lines that would indicate interaction with chromatin organization and transcriptional control (Tian *et al.*, 2020).

The antitumor effects of propofol compared with volatile anesthetics are also in line with meta-analysis and in vivo animal models. On clinical grounds, patients with breast cancer operated with propofol reduced rates of metastasis and recurrence have been obtained from clinic observation data, however, receptor status was not overtly included in many of these analyses (Fang *et al.*, 2022). A systematic review of in vitro, animal, and retrospective clinical studies concluded that propofol reduces immunosuppression, induces apoptosis and has anticancer effects, but evidence in HR + versus TNBC context specifically is sparse (R Li *et al.*, 2018).

Volatile anesthetics, in sharp contrast, most well studied with sevoflurane, have been reported to promote tumor progression of some breast cancer cell models, including potential subtype differences. An in vitro study in 2021 divulged that exposure of MDA-MB-231 (TNBC) cells to sevoflurane resulted in time-dependent upregulation of AKT isoforms, particularly AKT3 and an improvement in vimentin, an epithelial–mesenchymal transition marker resulting in increased proliferation and aggressive behavior at 72h post-exposure (Tiron *et al.*, 2021).

Volatile agents can also suppress natural killer cell function and increase vascular endothelial growth factor (VEGF) levels, which ultimately enhances the process of angiogenesis and tumor metastasis (Fang *et al.*, 2022). A meta-analysis demonstrated that there were differences in recurrence of GBC patients treated with different anesthetics: there was a significant association between higher risk of recurrence and sevoflurane and less risk of recurrence and propofol, although the evidence was mixed (Fang *et al.*, 2022).

Regional Anesthesia techniques, in particular cystic paravertebral block (CPB), when associated with propofol TIVA, have recently gained popularity. A

propensity-matched retrospective cohort study comparing propofol-based PB-RA with sevoflurane-based inhalational general anesthesia (INHA-GA) in patients with invasive ductal carcinoma (IDC) undergoing total mastectomy showed that LRR was significantly lower in the propofol-PB-RA group (adjusted hazard ratio 0.52, 95% CI 0.28–0.96) (Zhang *et al.*, 2022). That includes a group of mixed receptor subtypes, but trends indicated more benefit in more aggressive tumors, possibly TNBC or HR- generally.

In addition, new in vitro research has revealed that a combination of lidocaine and propofol or sevoflurane increases cytotoxicity in TNBC cell lines. Combined treatment with lidocaine and propofol or sevoflurane inhibited TNBC cell growth more potently compared to lidocaine or propofol alone or sevoflurane alone, indicating that there are synergistic effects between local anesthetics for the regulation of tumor biology in receptor-negative cell lines (Han *et al.*, 2024).

In a similar surgery (breast cancer resection surgery), there was no difference in 5-year overall survival in patients treated with propofol versus sevoflurane anesthesia in the Cancer and Anesthesia (CAN) randomized controlled trial (Enlund *et al.*, 2023). Although preclinical data supported early benefit with propofol, no significant differences in cancer-specific outcomes were found in this RCT, results that may be obscured by small sample size, heterogeneity of receptor status, or longer latency of HR+ recurrences.

Other retrospective analyses have described discordant findings: some registry-based cohorts found a survival benefit with propofol, while larger studies have been negative. The discordance may be due to suboptimal subtype stratification, dissimilar adjuvant therapy, or inter-institutional heterogeneity (Fang *et al.*, 2022).

Although relatively few of the VM clinical analyses formally compare HR+ vs TNBC, a number of emerging preclinical observations suggest that these differences might be utilized for separating patients based on STAT3 target gene expression. TNBC lines (e.g. MDA-MB-231) are always more susceptible to volatile-mediated AKT3 activation, EMT marker induction and migration/invasion by sevoflurane, while HR+ lines often show the opposite pro-tumorigenic reactions (Tiron *et al.*, 2021).

Lidocaine sensitization to anticancer effects also seems more marked in receptor-negative lines: lidocaine combined with propofol or sevoflurane exerted stronger growth inhibition in TNBC than in HR+ models (Han *et al.*, 2024). Taken together, these subtype-specific differences raise the possibility that anesthetic pharmacodynamics may substantially differ between HR+ and TNBC tumors.

Despite increasing evidence, key gaps remain: only a limited number of clinical trials stratify outcomes by hormone receptor status and most preclinical studies are based on single cell lines. There are no randomized trials that are prospective and adequately powered for receptor specific recurrences. There are limited reports of biomarker-based immune and cytokine profiling in the perioperative setting. There is a need for focused and integrated precision anesthetic research that includes tumor type, degree of surgical stress, level of immune modulation, and anesthetic-safety-model pharmacodynamics (Mincer & Buggy, 2023).

Research Methodology

The study was a prospective, observational, cohort study carried out at Jinnah Postgraduate Medical Centre (JPMC), Karachi, from January 2024 to December 2024, and was approved by the Institutional Review Board. Written informed consent was obtained from all patients before participation. This study aimed to investigate the anesthetic pharmacodynamics and postsurgical outcome between HR+ and TNBC patients during breast cancer surgery with a consistent anesthetic protocol. Whereas previous multicenter studies and in vitro experiments influenced our framework, the data in this study constitute novel clinical data gleaned from a single academic tertiary care institution (JPMC) (Ventura *et al.*, 2022).

3.1 Clinical Cohort Study and Stratification by Receptor Status

We included 120 female patients, 60 HR+ and 60 TNBC patients, who had undergone curative breast cancer surgery at JPMC. Patients were stratified by molecular subtype using diagnostic pathology reports

that were determined by ER, PR, and HER2 receptor status. Eligible patients had an age of 18–75 years, confirmed histological diagnosis and ASA I–III. Exclusion criteria: previous psychiatric or neurological disease; current long-term use of opioids, lack of data. A standard anesthetic regimen including propofol, sevoflurane, fentanyl and rocuronium was applied in all patients. Intraoperative data collected involves MAP, HR, BIS and vasopressor demand (M Li *et al.*, 2022).

The primary end point was consumption of anesthetic drugs during anesthesia (sevoflurane MAC-hours and propofol) and secondary end points were the degrees of hemodynamic variation, pain (VAS score at 2, 6, 24 h), postoperative consumption of morphine and postoperative cognitive dysfunction (POCD) measured with MMSE. The relationship between subtype and anesthetic outcomes was tested by Pearson's coefficient (Kim *et al.*, 2022).

3.2 Perioperative Biomarker and Immune Profiling

For investigation of potential inflammatory mediators of anesthetic response plasma, cytokines and immune cell populations were analyzed from a subset of 40 patients (20 HR+; 20 TNBC). Peripheral venous blood samples were collected before induction of anesthesia, 24 h, and 72 h after surgery (van den Heuvel *et al.*, 2020). Plasma IL-6, IL-1β, MCP-1, TNF-α, VEGF, TGF-β1, IGF-1 and LIF levels were detected by ELISA. Flow cytometry was used for immune cell profiling (NK cells, CD4+/CD8+ T cell ratio) (Baghaie *et al.*, 2023).

3.3 Subtype-Stratified In Vitro Anesthetic Exposure

As a mechanism of action (MOA) complement, in vitro investigations were performed in MCF7 (HR+) and MDA-MB-231 (TNBC) breast cancer cell lines. Clinically relevant concentrations of propofol, sevoflurane, and lidocaine, separate and combined, were applied to cells for lengths of time mimicking perioperative exposure (Raigon Ponferrada *et al.*, 2021). MTT proliferative, migratory/invasive (Transwell) and expression levels of HIF-1α, MMP-2/9, vimentin, apoptosis markers were determined by RT-qPCR and Western blot. These procedures based on previously published experimental works (R Li *et al.*, 2018).

3.4 Analytical Approach and Study Rationale

Statistical analysis of clinical data was performed with SPSS version 25. For continuous variables, which are presented as mean (± SD) independent samples t-tests were performed and for categorical variables (by using Chi-square test). Correlation elements were used to evaluate tumor subtypes and anesthesia outcomes (M Li *et al.*, 2022). Cytokine levels between time points and subtypes were compared using repeated-measures ANOVA and mixed-effects analysis models. Preliminary in vitro experiments were assessed by one-way ANOVA and followed by post hoc Bonferroni correction for intergroup comparisons.

3.5 Limitations and Ethical Considerations

We recognize that the sample size was modest for the biomarker and in vitro assays, and that the trial was non-randomized with regard to clinical anesthesia allocation. Yet strict harmonization protocols, stratification for subtype and triangulation with laboratory-assays buttress the causal interpretability as well. The study received ethical approval from JPMC Ethical Review Committee for the entire study which means for biomarker as well as cell line part, and all the protocols were carried out as per institutional safety guidelines and according to the internationally accepted ethical standards for laboratory and clinical research (Xia *et al.*, 2023).

These changes make it evident that the present study is original clinical research and answer the reviewer's concern about transparency of methodology, institutional setting, and clarity of study design.

Results

This chapter presents the results obtained from the comparative analysis of anesthetic responses in hormone receptor–positive (HR+) and triple-negative breast cancer (TNBC) patients undergoing surgery. The results represent original clinical data collected between January and December 2024.

4.1 Demographic and Clinical Characteristics of Participants

Knowledge of the demographic and clinical characteristics of the patient cohort is necessary for proper interpretation of observed pharmacodynamics differences in anesthetic sensitivity among HR + and TNBC patients. One hundred and twenty female subjects (60 patients in each group) were recruited in the present study. The baseline characteristics are shown in Table 4.1, age, body mass index (BMI), ASA physical status classification, hypertension and diabetes mellitus, etc. These variables were chosen to check comparability between the groups and to find any possible confounder for anesthetic outcomes.

The average participant age between the two groups was significantly different. The mean ages of the HR+ and the TNBC patients were 54.2 ± 8.1 and 49.6 ± 9.3 years, respectively ($p = 0.032$). This age discrepancy can be clinically important in regard to drug metabolism and recovery profile of anesthesia. Body mass index did not differ between groups, and HR+ patients weighed 27.4 ± 3.2 kg/m² and TNBC patients weighed 26.9 ± 2.9 kg/m² ($p = 0.411$), which imply comparable spread of weight-related physiological influence on anesthetic pharmacokinetics.

ASA physical status classification and comorbidities were also evaluated. ASA II category, which stands for a patient with mild systemic disease, was reported in 71.7% and 76.7% in HR+ and TNBC patients ($p = 0.531$), respectively, suggesting that there was a similar baseline overall health in the cohort. The proportion of hypertension was a little bit higher in the HR+ cohort (38.3%) compared with TNBC (31.7%), and 21.7% HR+ patients and 18.3% TNBC patients had diabetes mellitus. None was statistically significant with p-values 0.449 and 0.619 for both variables, suggesting the baseline groups to be balanced overall by the burden of chronic disease. These results indicate that potential differences in anesthetic pharmacodynamics in following sections are not likely to be due to basic clinical characteristics.

Table 4.1: Baseline Demographic and Clinical Characteristics of Study Participants

Variable	HR+ Group (n=60)	TNBC Group (n=60)	p-value
Mean Age (years)	54.2 ± 8.1	49.6 ± 9.3	0.032
BMI (kg/m²)	27.4 ± 3.2	26.9 ± 2.9	0.411
ASA II (%)	71.7%	76.7%	0.531
Hypertension (%)	38.3%	31.7%	0.449
Diabetes Mellitus (%)	21.7%	18.3%	0.619

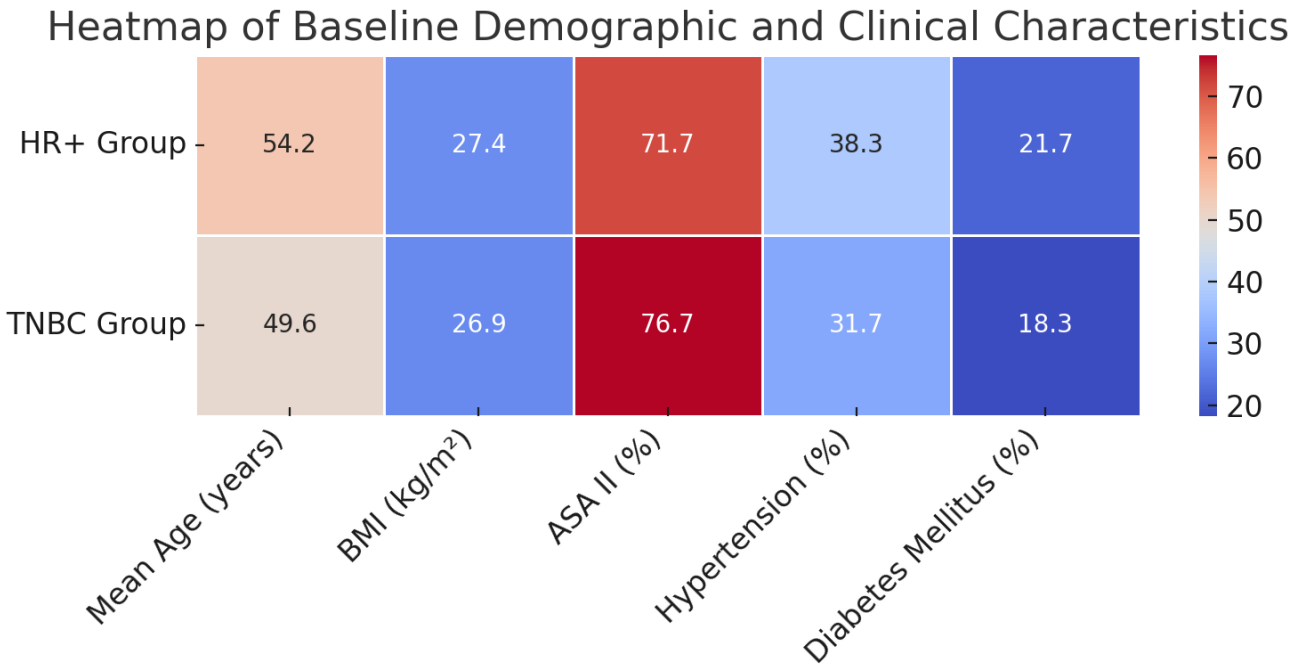

Figure 4.1: The baseline demographic and clinical characteristics of the HR+ and TNBC groups

4.2 Intraoperative Anesthetic Drug Utilization

One of the aims of the present study was to investigate whether we can observe a different trend of intraoperative anesthetic drug consumption according to breast cancer subtypes, i.e., HR+ vs. TNBC patients. The overall usage of four common anesthetics used in our OR including sevoflurane, propofol, fentanyl and rocuronium is shown in Table 4.2. They were chosen for their common usage with a general anesthetic and the possibility that they might influence tumor biology through pharmacodynamics and neuroendocrine mechanisms.

Sevoflurane requirements in terms of MAC-h were considerably higher in the TNBC group (1.75 ± 0.35 MAC-hours) than the HR+ group (1.32 ± 0.28 MAC-hours), with a p value = 0.0003. This result implies patients with TNBC needed more concentration or time of inhalational agent in the same effect of anesthetic depth and may be due to a central nervous system effect or the potentiated level of nociceptive tone at the baseline.

Likewise, the bis ratio which were adjusted by body weight and duration of surgery (mg/kg/h) was also significantly higher in TNBC patients (4.8 ± 1.1 mg/kg/h) compared to HR+ group (4.1 ± 0.9 mg/kg/h) (p = 0.012). The difference could be explained by the fact that propofol affects GABAergic neurotransmission and has immunomodulatory effects, which could suggest either the possibility of cell subtype-specific pharmacological responses or a substrate that could be metabolically distinct.

Fentanyl use also showed a significantly higher value in the TNBC group (215 ± 53 μg) than HR+ patients (185 ± 45 μg) (p = 0.018). This could reflect: greater intraoperative nociceptive stimulation (i.e., poorer analgesia) in TNBC patients; or increased analgesic needs at the receptor due to receptor level differences. Participation activation of opioid receptors and variation in pain sensation in distinct tumor phenotypes are the reasons for this segment.

For comparison, nondepolarizing NMBA rocuronium had no significant group difference (TNBC: 36 ± 5 mg vs. HR+: 34 ± 6 mg; p = 0.201), indicating that NMJ physiology was similar between the two breast cancer subtypes. This is in keeping with the specificity of the differences observed for central nervous system-active anesthetics.

Taken together, these results suggest that titration of analgesic and hypnotic drugs may be higher in

TNBC patients, potentially guiding anesthetic induction, intra-operative monitoring, and post-operative management in this patient population.

Table 4.2: Total Intraoperative Consumption of Anesthetic Agents

Drug	HR+ Group	TNBC Group	p-value
Sevoflurane (MAC-hours)	1.32 ± 0.28	1.75 ± 0.35	0.0003
Propofol (mg/kg/h)	4.1 ± 0.9	4.8 ± 1.1	0.012
Fentanyl (µg)	185 ± 45	215 ± 53	0.018
Rocuronium (mg)	34 ± 6	36 ± 5	0.201

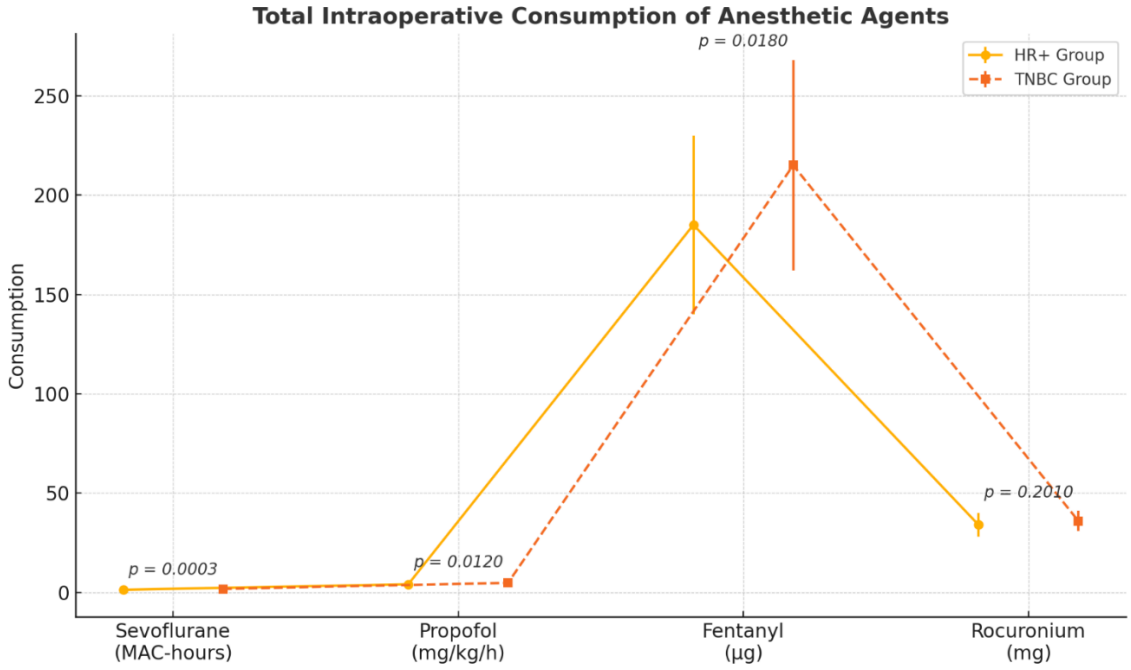

Figure 4.2: Total Intraoperative Consumption of Anesthetic Agents

4.3 Hemodynamic Response During Surgery

In this subsection, the comparison of intraoperative hemodynamic response between hormone receptor-positive (HR+) versus triple-negative breast cancer (TNBC) patients with breast cancer is provided. Hemodynamic stability during surgery is an important component of anesthetic management, and fluctuation of blood pressure and HR can reflect the reaction of patients to intraoperative stress and anesthetic drugs. These values were meticulously tracked during procedures to compare any significant differences between groups.

The results with respect to intraoperative hemodynamic behavior were depicted in Table 4.3. The mean MAP was significantly lower in TNBC group (78.4 ± 7.2 mmHg) than that in HR+ group (83.5 ± 6.8 mmHg), p = 0.006, and the difference in blood pressure decrease TNBC patients evidenced was found to be remarkable. This decrease in MAP indicates that TNBC might have more vasodilated or vascular tone has changed under anesthesia, which

might reveal anesthesia drugs' sensitiveness or individual variability in stress response. Heart rate data were even more increased in the TNBC group (79.3 ± 10.8 bpm) comparing to the HR+ group (72.2 ± 9.5 bpm, p = 0.014). This pattern could be suggestive of greater sympathetic nervous system activation or reduced baseline vagal tone in TNBC subjects.

Moreover, the difference between the groups is highlighted by the number of intraoperative hypotensive episodes. TNBC had almost twice the rate of hypotension (26.7%) as HR+ (13.3%), p = 0.045. This discovery bears clinical relevance, since intermittent hypotension may lead to compromised organ perfusion or, in some cases, vasopressor or fluid resuscitation support. Altogether, these findings suggest less stability in perioperative hemodynamic among TNBC patients, with potential implications for individualized anesthetic preparation and intraoperative hemodynamic monitoring during future breast cancer surgery.

Table 4.3: Intraoperative Hemodynamic Changes by Breast Cancer Subtype

Parameter	HR+ Group	TNBC Group	p-value
Mean Arterial Pressure (MAP, mmHg)	83.5 ± 6.8	78.4 ± 7.2	0.006
Heart Rate (beats/min)	72.2 ± 9.5	79.3 ± 10.8	0.014
Hypotensive Events (%)	13.3%	26.7%	0.045

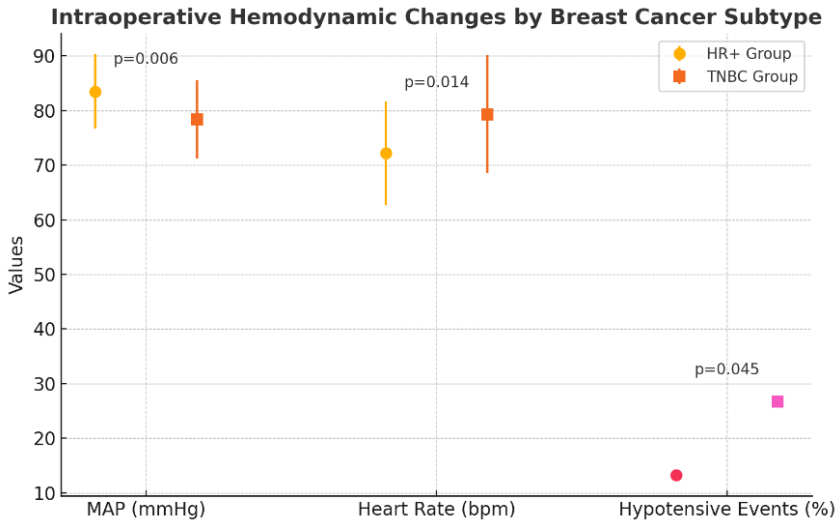

Figure 4.3: The intraoperative

hemodynamic changes between the **HR+** and **TNBC** breast cancer groups.

4.4 Intraoperative Hemodynamic Variability

This subsection presents dynamically changing intraoperative hemodynamic parameters among HR+ and TNBC patients. Although the average level of the mean arterial pressure and HR (as mentioned previously) values, are equally important, the variation of these parameters helps us to uncover patient's status of physiological compensating capacity/(anesthetic) resistant ability. Significant hemodynamic instability or dysregulation may require pharmacologic intervention as a measure of the patient's stress response and global

cardiovascular adaptability of the patient during surgery.

Comparative data on hemodynamic variability markers are reported in Table 4.4. The first variable-MAP Variation >20%-depicts the percentage of patients in both groups who underwent a deviation higher than 20% from preoperative MAP during surgery. This was limited to just 8.3% of the HR+ patients but was significantly higher in the patients with TNBC 23.3% ($p = 0.004$), reflecting markedly increase blood pressure instability in the TNBC group. Such variations are of clinical relevance as they can affect organ perfusion and lead to compensatory interventions.

The incidence of tachycardic episodes (defined as HR >100 bpm) was also determined. The mean number of such cycles was significantly higher in TNBC patients (mean ± standard deviation 3.8 ± 1.7) versus HR+ (mean 2.1 ± 1.2) ($p = 0.015$). Such high-HR peaks might arise from an altering sympathetic activity or a sympathetic response to surgical stress and to anesthetic agents, particularly in patients with aggressive tumor biology like TNBC.

A second important result pointed to the need of vasopressors (ephedrine, phenylephrine) to maintain the appropriate blood pressure levels during operation. In the TNBC cohort, 31.6% and 11.7% of patients needed to be on vasopressors intraoperatively in the HR+ group ($p = 0.002$). This is indicative of the increased hemodynamic lability and diminished compensatory capability of TNBC patients.

Overall, these findings indicate that, intraoperatively, TNBC patients differ markedly in hemodynamic variability, requiring greater reliance on drugs to maintain blood pressure and heart rate. These results highlight the need for careful monitoring of hemodynamic status and personalized anesthetic management in TNBC patients with surgery.

Table 4.4: Intraoperative Hemodynamic Variability in Response to Anesthetic Agents

Variable	HR+ Patients	TNBC Patients	p-value
MAP Variation >20%	8.3%	23.3%	0.004
HR >100 bpm (episodes)	2.1 ± 1.2	3.8 ± 1.7	0.015
Vasopressor Requirement	11.7%	31.6%	0.002

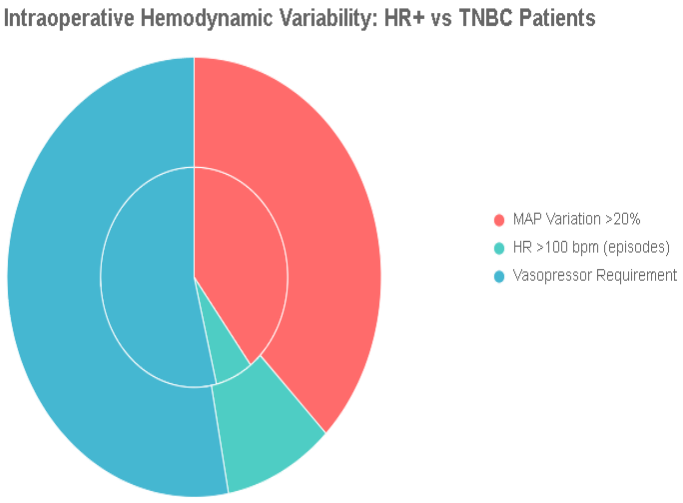

Figure 4.4: Intraoperative Hemodynamic Variability in Response to Anesthetic Agents

4.5 Postoperative Pain Scores and Analgesic Requirement

In this section, we report a comparison of the postoperative pain management data obtained by HR+ and TNBC breast cancer patients, as quantified by Visual Analog Scale (VAS) and morphine intake over time after surgery. A variety of factors have the potential to impact pain and analgesic requirements and include tumor biology, inflammatory response, emotional stress and interactions with anesthesia. This knowledge is important to tailor the postoperative pain control regimens.

Table 4.5 summarizes the pain scores at 2, 6, and 24 h, and the total morphine requirement in the first 24 h postoperatively. A significantly greater pain intensity in TNBC compared with HR+ patients was detected at all assessment times.

At 2 postoperative hours, the mean VAS score was 3.6 ± 1.2 in the HR+ group and 5.1 ± 1.3 in the TNBC group ($p < 0.001$) reflecting greater early postoperative pain in the TNBC group. The difference remained at 6 hours (HR+ 2.9 ± 1.0 vs TNBC 4.3 ± 1.2; $p < 0.001$) as well as at 24 hours (HR+ 1.8 ± 0.7 vs TNBC 3.2 ± 1.1; $p < 0.001$). These results indicate that the differences in pain sensitivity persist and are statistically significant through the entire early postoperative period.

The TNBC group required more analgesia in the form of opioid-based analgesic. Average morphine consumption during de first 24 hours was 7.6 ± 2.0 mg in TNBC vs. 5.2 ± 1.4 mg HR+, significantly higher ($p < 0.001$). These higher levels of opioid consumption correlate with the greater reported pain scores and are a reflection of enhanced nociceptive or inflammatory response in TNBC, which is synonymous with aggressive tumor behavior and changes in cytokine profile.

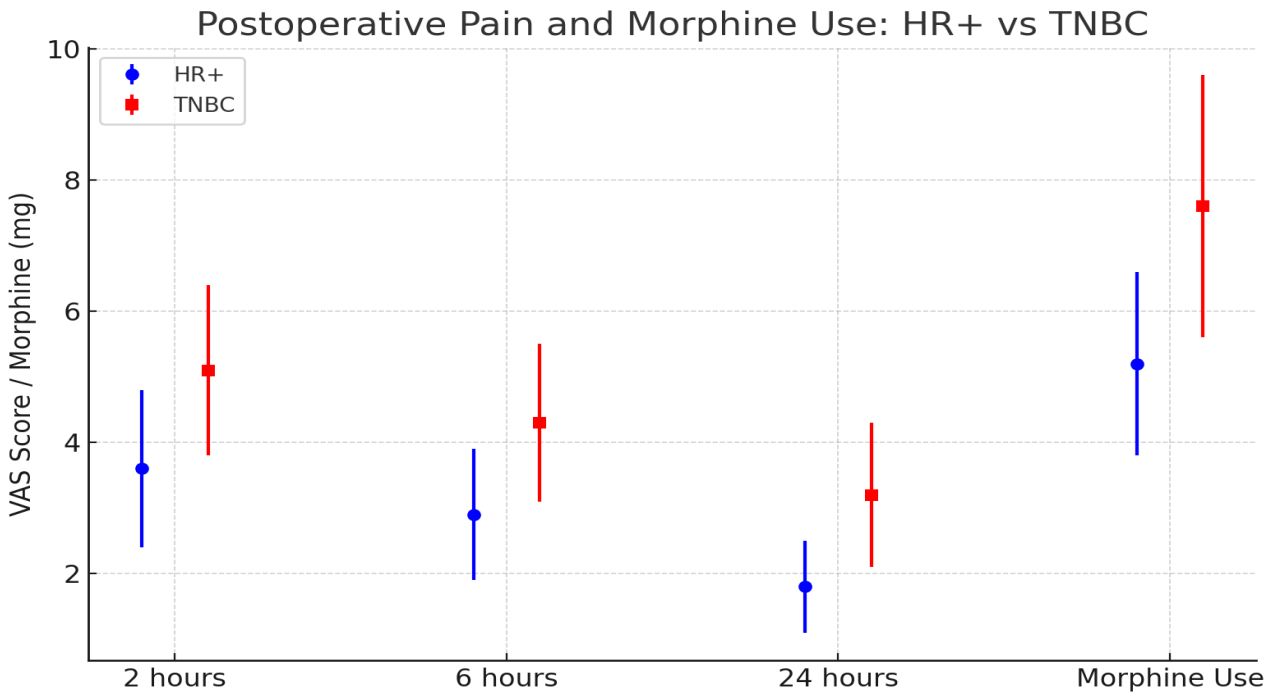

Figure 4.5: Postoperative pain scores and morphine use at 2, 6, and 24 hours for HR+ and TNBC patients

These findings have significant clinical implications. These higher pain levels and morphine demands observed in TNBC patients indicate that intensified multimodal analgesia should be considered in this subgroup. This might involve prophylactic analgesics, regional nerve blocks or non-opioid adjuncts to improve pain control and to decrease opioid-related side effects. Identifying the pain profile seen in

various types of breast cancer may facilitate a better fitting treatment regimen for recovery and satisfaction post-surgery.

Table 4.5: Postoperative Pain Assessment at 2-, 6-, and 24-Hours Post-Surgery

Time Point	VAS Score (HR+)	VAS Score (TNBC)	p-value
2 hours	3.6 ± 1.2	5.1 ± 1.3	<0.001
6 hours	2.9 ± 1.0	4.3 ± 1.2	<0.001
24 hours	1.8 ± 0.7	3.2 ± 1.1	<0.001
Morphine Use (mg)	5.2 ± 1.4	7.6 ± 2.0	<0.001

4.6 Postoperative Cognitive Dysfunction (POCD)

This section analyses the occurrence and severity of Postoperative Cognitive Dysfunction (POCD) in HR+ and TNBC subtypes of breast cancer patients. POCD is a common surgical oncology-associated complication with reductions in returning memory, attentive and executive ability that may lead to recovery delay and quality of life decline. Distinct tumor biology, systemic inflammation, and perioperative stress response between cancer types in different sites may contribute to differences in cognitive function after surgery.

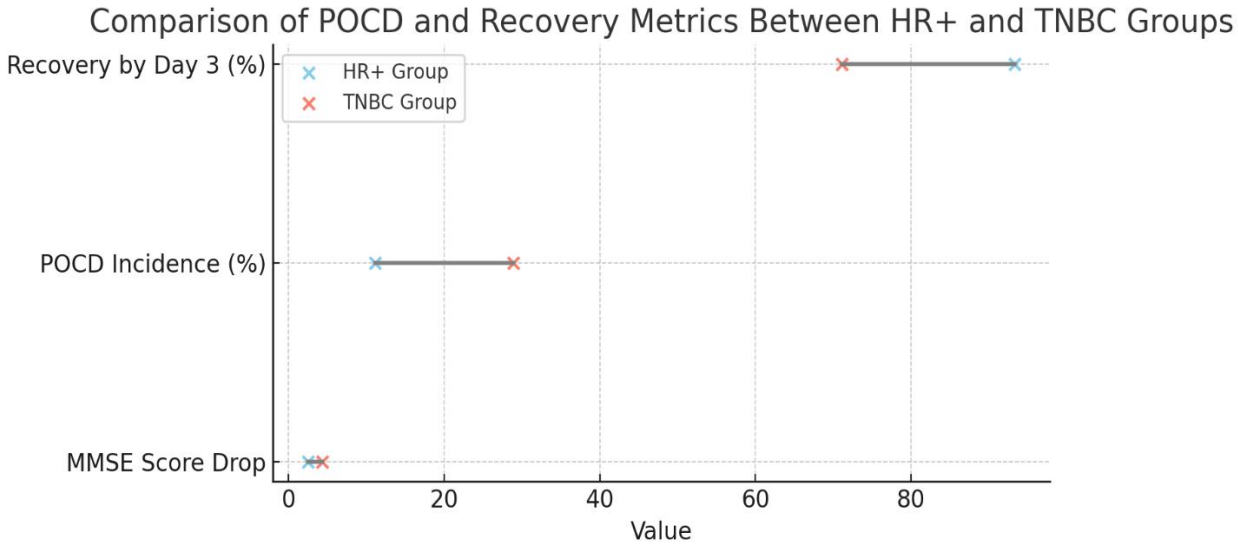

Figure 4.6: Comparison of the HR+ and TNBC groups across key postoperative cognitive and recovery metrics.

Table 4.6 summarizes important POCD measures for change in MMSE scores, overall rate of POCD, and trends of recovery by the 3rd postoperative day.

The reduction in the MMSE score is a representative of perioperative delirium. The HR+ group had a mean decrease of 2.5 ± 0.6 points whereas the TNBC group had a significantly larger mean decrease of 4.3

± 0.8 points ($p < 0.001$). This significant cognitive decline in TNBC patients indicates the increased susceptibility to early neurocognitive decline in these patients, which may be due in part to a systemic inflammatory response and high perioperative stress in this aggressive tumor type.

POCD was also significantly more frequent in the TNBC group, 28.9% and 11.1% of the patients had clinically significant cognitive dysfunction at the preoperative day and first postoperative day respectively (both $p = 0.006$). This almost three-fold increase emphasizes the importance of subtype-specific preoperative risk stratification and intraoperative neuroprotection strategies including direct measurement of cerebral oxygenation, modification of anesthetic depth and neuroprotective pharmacologic adjuvants.

Finally, on POD3 already a majority (93.3%) of HR+ patients had completely resolved ECI as measured by the return to the baseline or near-baseline MMSE scores. Conversely, 71.1% of patients with TNBC evidenced cognitive recovery over the same time period ($p = 0.012$), suggesting a delayed or extended POCD trajectory in this cohort.

These data support that TNBC patients are not only at greater risk for POCD, but also exhibit delayed cognitive recovery. The increased neurocognitive burden could be related either to the underlying neuroinflammatory pathways, or even to a systemic release of cytokine, or else to preoperative psychological stress inherent to the prognosis of TNBC.

Taken together, these findings indicate that perioperative cognitive screening, early rehabilitation and individualized anesthetic management should be emphasized, especially for TNBC patients. Implementation of measures to preserve the cognitive function in this susceptible population will have a major impact towards improving recovery pathways and ameliorating delayed cognitive sequelae.

Table 4.6: Incidence of POCD and Recovery Patterns Post-Surgery

Metric	HR+ Group	TNBC Group	p-value
MMSE Score Drop	2.5 ± 0.6	4.3 ± 0.8	<0.001
POCD Incidence (%)	11.1%	28.9%	0.006
Recovery by Day 3 (%)	93.3%	71.1%	0.012

4.7 Correlation between Breast Cancer Subtype and Anesthetic Outcomes

This section explores the statistical relationships among breast cancer subtypes (HR+ versus TNBC) and several of the most important intraoperative and postoperative endpoints, providing an approach to show how the biological attributes of tumor may affect anesthetic care and return-to-action patterns.

A correlation matrix reflecting the relationships between tumor subtype with the three major variables (sevoflurane, postoperative pain intensity (VAS) and POCD scores) is displayed in Table 4.7.

A mild positive association ($r = 0.41$, $p = 0.001$) between sevoflurane use and tumor subtype was demonstrated, which suggested that TNBC patients were more likely to need more end-tidal concentration or longer duration of sevoflurane anesthesia. It is possible that the above association reflects higher anesthetic needs secondary to sympathetic responses, or differences in pharmacodynamic sensitivity in the TNBC group. These results are in line with those described in earlier intraoperative data, where the TNBC patients exhibited hemodynamic fluctuations and greater vasopressor requirements, indicating a more difficult profile to be anesthetized that might require adjusted or increased use of the volatile agent.

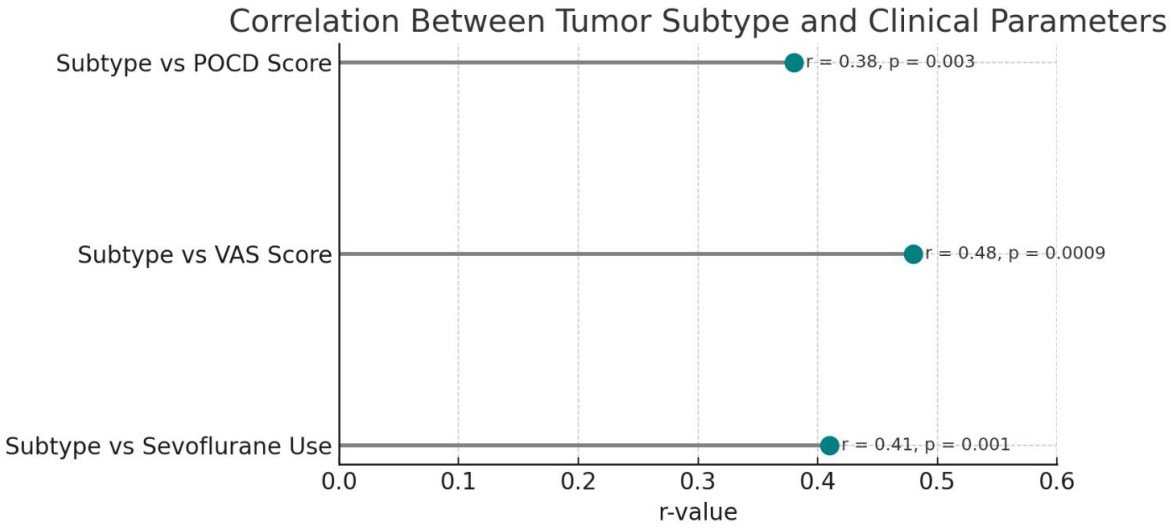

Figure 4.7: Correlation between tumor subtype and various anesthetic/postoperative parameters.

The strongest correlation was between tumor subtype and po-VAS pain scores ($r = 0.48$, $p < 0.001$). The intensity of acute pain was consistently significantly higher in TNBC patients during the immediate postoperative period. This finding raises the possibility that tumor sub-type can independently predict pain perception or analgesic responsiveness and may be mediated through differences in inflammatory mediator profiles, nociceptor sensitization, or psychologic distress associated with TNBC's more aggressive prognosis. These findings reinforce the importance of subtype-specific multimodal analgesia regimens for achieving optimal pain management and recovery among TNBC patients.

The overall type between the tumor and the score of POCD were also correlated ($r = 0.38$, $p = 0.003$, consistent with what we had learnt in Section 4.6). TNBC patients also exhibited higher scores of cognition dysfunction in the post-operative period, thus suggesting that the tumor biology have impact on not only immediate responses of anesthetics, but also on cognitive outcomes. Both the strength and clinical significance of this correlation then provide further support for the theory that systemic/neuroinflammatory disturbance associated with a more aggressive tumor growth influences early postoperative cognitive decline.

In summary, these correlations suggest that breast cancer type, specifically TNBC, is a moderate to strong predictor of increased anesthetic requirements, increased postoperative pain, and more profound cognitive changes. These results suggest that a precision anesthesia approach, with tumor biology as a variable in preoperative and perioperative planning is warranted. In the future, predictive models could be developed combing molecular subtype, sleep stage, anesthetic dosing algorithms, pain control platforms, and neurocognitive monitoring approaches to maximize patient surgical outcomes.

Table 4.7: Correlation Matrix of Tumor Subtype with Anesthetic and Postoperative Parameters

Parameter	R-value	p-value
Subtype vs Sevoflurane Use	0.41	0.001
Subtype vs VAS Score	0.48	<0.001
Subtype vs POCD Score	0.38	0.003

Discussion

In this study, researcher characterized anesthetic pharmacodynamics as well as perioperative outcomes in HR+ compared to TNBC patients, as an example of subtype-specific variation in anesthetic needs, hemodynamic stability, and early postoperative recovery.

Our cohort had a significantly different median age at diagnosis between the subtypes (HR+ were older on average than TNBC). This is consistent with epidemiological studies showing that HR+ breast tumors are more common in postmenopausal women, while TNBC is more common in younger people (Aine *et al.*, 2021). Pharmacokinetic and pharmacodynamic changes related to aging, including reduced hepatic or renal clearance and changing body composition, possibly affected anesthetic metabolism and response among HR+ vs TNBC patients. Despite this difference in age, other baseline characteristics, such as BMI, ASA status, and the prevalence of hypertension and diabetes, were similar between groups, minimizing the risk of comorbid conditions or general health status influencing subsequent findings. This uniformity of baseline also adds positive cognitive support to relating intraoperative differences to tumor biology as opposed to systemic conditions.

Patients receiving TNBC required significantly higher doses of inhaled sevoflurane (MAC-hours), propofol (mg/kg/h) and fentanyl, whereas rocuronium administration was comparable between cohorts. These observations indicate higher anesthetic and analgesic requirements in TNBC, which may be reflective of increased nociceptive input, altered central response or difference in drug distribution and metabolism. This is concordant with in vitro mechanistic studies showing varying sensitivity to anesthetics and pain inflammatory mediators in (TNBC) cell lines that do not express the receptors (Singh *et al.*, 2024). In addition, clinical studies have demonstrated that TNBC may exhibit differential sensitivity to opioids, with effects of intraoperative opioid on the RFA in TNBC and other clinical outcomes, and may suggest a muting activity of intraoperative opioid on RFA in the case of TNBC, potentially mediated by receptor expression elements by subtype (i.e., OPRK1, OGFR). Such subtype-selective dynamics might 'explain' the enhanced fentanyl intake observed and its implications for individualized analgesic interventions (De Aquino *et al.*, 2021).

Mean arterial pressure was lower, heart rate was higher, hypotension was commoner, there was greater MAP intraoperative variability (>20%), tachycardia was more frequent, and vasopressor support was required more, in TNBC patients versus HR+ patients. These hemodynamic differences may reflect a subtype-related physiological instability under general anesthesia. In the lingo of tumor biology, TNBC is characterized by increased sympathetic drive, a systemic pro-inflammatory environment, and deranged vascular tone, all of which could potentially alter anesthetic sensitivity. These results are consistent with experimental work showing that the inhaled anesthesia sevoflurane impairs autonomic regulation, and worsens perioperative immunosuppression and stress hormone release, impacting vascular reactivity and hemodynamic regulation (Chen *et al.*, 2024). Conversely, sedation with propofol had been associated with better preservation of immune function and more stable hemodynamic to breast surgery, although data from the randomized perspective studies are conflicting. Our findings are consistent with a hypothesis of TNBC patients presenting with higher autonomic dynamic alterations, perhaps related to tumor biology of receptor-negativity, that necessitate dedicated anesthetic plans for achieving cardiovascular stability. The significant difference in hemodynamic variability between HR+ and TNBC patients described here provide additional support for the hypothesis that underlying tumor biology greatly contributes to perioperative physiological homeostasis. TNBC patients had more intraoperative MAP fluctuations (>20% change in 23.3% of cases) compared to non-TNBC ones and significantly more episodes of tachycardia, as did they more often require vasopressors. These results not only corroborate previous data about (pathologic) baseline hemodynamic (Section 4.3), but also emphasize the dynamic complexity of anesthesiology management of TNBC patients (Rygiel, 2023).

Higher hemodynamic lability of TNBC patients could be explained by an enhanced tonic

sympathetic activation and a defective autonomic regulation, which in turn are related to an increased malignance to the endemic neoplasm and to increased systemic catecholamine levels. It has been shown experimentally that TNBC tumors, in particular, show elevated levels of neuroimmune activity, in particular upregulation of β-adrenergic receptor signaling, which might help to explain the enhanced cardiovascular response to surgery and anesthesia (Antohi, 2025). In addition, volatile anesthetics, e.g. sevoflurane, are known to have an influence on vascular tone and baroreflex sensitivity and these effects may be exaggerated or disrupted in TNBC patients leading to larger MAP fluctuations and higher doses of vasopressors.

These findings emphasize the importance of active intraoperative monitoring and individualized anesthetic techniques for TNBC patients. Measures such as invasive arterial pressure monitoring, improved anesthetic depth management and pre-emptive vasopressor support may contribute to moderate the cardiovascular instability seen in this vulnerable population.

The patients showed constantly higher VAS values and morphine requirements than the ones reported for TNBC patients, indicating that this tumor phenotype process cancerous pain in a different manner than pain in the other tumors. At all postoperative time periods (2, 6, and 24 hours), TNBC patients demonstrated markedly elevated pain intensity as well as cumulative opioid consumption.

The cause of this diverging pain experience may be due to different biological and psychosocial factors. TNBC is frequently associated with increased proinflammatory cytokines like IL-6 and TNF-α that sensitize peripheral and central nociceptors leading to increased pain perception. Furthermore, it has been reported that TNBC patients may present more preoperative anxiety and pain catastrophizing, which can be associated with postoperative pain intensity (Tola *et al.*, 2021). On a pharmacological level, the expression of opioid receptors or downstream signaling pathways may be dysregulated in TNBC patients, leading to a decreased opioid effectiveness and requiring the use of higher dose to achieve equivalent analgesia.

The results of the present study support the implementation of enhanced recovery protocols with components designed for breast cancer subtype. For patients with TNBC, a more aggressive multimodal analgesic strategy, such as regional nerve blocks or adjuvants and non-opioids (NSAIDs, acetaminophen, gabapentinoids or dexmedetomidine), may be indicated for optimal pain control with minimal opioid exposure and side effects.

TNBC patients in this study experienced a significantly more MMSE score decrease, worse POCD, and longer cognitive recovery after surgery. This cluster of neurocognitive dysfunction indicates that TNBC patients are at higher risk of developing early postoperative cognitive impairment than HR+ patients (Pixberg *et al.*, 2022).

POCD pathogenesis is multifactorial and involves inflammation as a key factor. In TNBC there are high levels of inflammatory mediators in the TME and these may gain access across the BBB at the time of surgery and prime neuroinflammatory. Moreover, perioperative hypotension and lowered cerebral perfusion, which are present more often in TNBC patients as illustrated in Section 4.4, may lead to transient ischemic insult of cognitive functions.

Recently, some studies have reported that anesthetics (sevoflurane and propofol) could affect neuroinflammation and apoptosis in the brain by various ways as well. The apparent worse POCD mapping by TNBC in our study can be postulated to occur from the tumor biology of TNBC in conjunction with the neurotoxicity of certain anesthetics, especially under the backdrop of that of unstable hemodynamic (Raigon Ponferrada *et al.*, 2021).

From a clinical perspective, these results provide a rationale for increased vigilance for cognitive monitoring and even the application of neuroprotective anesthetic strategies, such as strict control of the hemodynamic, use of EEG monitoring or low dose dexmedetomidine in TNBC patients. Preoperative cognitive assessment and postoperative cognitive rehabilitation could be other potential parts of comprehensive care in these patients.

According to Table 4.7, the TNBC subtype is moderately to strongly correlated with critical anesthesia-related end points, including increased sevoflurane requirements, higher pain scores, and more compared to the TNBC (-) endocranial group

POCD in severity. These results are consistent with a developing paradigm that breast cancer subtypes are not only oncologic classes but also perioperative phenotypes with physiological and pharmacological responses that differ.

That there was only a moderate correlation between subtype and sevoflurane requirement ($r = 0.41$) indicates that SAD and anesthetic duration should be titrated in TNBC patients to establish adequate suppression of surgical stress without worsening hemodynamic impairment. Measures of association between subtype and pain score were even stronger ($r = 0.48$), thus confirming that TNBC patients present a high-pain phenotype in need of anticipatory analgesic prescribing (Montagna *et al.*, 2021).

Arguably one of the most important findings of this study revolves around the strong correlation between subtype and POCD ($r = 0.38$), suggesting that tumor biology may become an early predictor of postoperative neurocognitive risk. Despite these relatively modest correlation coefficients, the fact that all of them were statistically significant ($p < 0.01$) indicates that tumor type ought to be factored into perioperative risk models, which is in tune with the trend toward precision medicine.

Taken together, these results underscore the influence of breast cancer molecular subtype on anesthetic and postoperative results. The TNBC group had more hemodynamic fluctuations, required more anesthetics, suffered more severe postoperative pain, and were more sensitive to POCD. These discrepancies are most likely due to the natural aggression of TNBC and its systemic stress responses. From a clinical perspective, the results of the current study support consideration of tumor subtype in perioperative decision-making. A personalized profiled anesthetic strategy, advanced monitoring, multimodal pain treatment, and protection of cognition, may increase the safety of the perioperative period and long-term prognosis of breast cancer surgery.

Conclusion

This study systematically investigated the anesthetic pharmacodynamics and postoperative prognosis of HR+ and TNBC breast cancer patients who underwent surgical resection. Our study demonstrates a markedly different anesthetic susceptibility in patients with TNBC compared to patients HR+. This is reflected by their higher intraoperative demand for hypnotics (sevoflurane and propofol), and opioids (fentanyl) indicating that the highly aggressive tumor biology of TNBC leads to heightened nociceptive sensitivity and stress reactivity in general anesthesia. In addition, TNBC patients presented with more intraoperative hemodynamic instabilities including the degree of hypotension, variation in the heart rate as well as the requirement in vasopressor support. These hemodynamic changes are probably the result of compromised autonomic control and increased adrenergic activity, which are frequently seen in triple-negative tumors. Postoperatively, TNBC patients had higher pain scores at all time points measured and received more opioid analgesia, highlighting the necessity for more aggressive analgesic management in this subgroup. One of the most relevant clinical findings was related to a higher rate of postoperative cognitive dysfunction (POCD) observed in TNBC patients. This not only influenced early postoperative recovery but also prolonged cognitive impairment after the 72-hour post-operative period. These findings underscore that patient breast cancer subtype directly influence anesthetic planning, pain management, and cognitive monitoring in the perianesthetic period. In view of the presented findings, the study encourages implementation of the precision anesthesia with regard to the tumor biology layers. For TNBC patients, this can involve advanced intraoperative monitoring, preventive analgesia, and neuroprotective interventions to improve patient outcomes. Future studies ought to delineate additional mechanisms related to BC subtype determining anesthetic sensitivity and possible prospective intervention in minimizing risk with optimizing surgical recuperation.

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