Clinical Pain Research

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The association of hemodynamic parameters and clinical demographic variables with acute postoperative pain in female oncological breast surgery patients: A retrospective cohort study

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Abstract

Objectives – Appropriate administration of intraoperative analgesia is an essential factor in care and reasonable recovery times. Inappropriate intraoperative analgesia puts the patient at risk of acute postoperative pain (APOP). The absence of an objective standard for intraoperative nociceptive monitoring complicates pain care. Heart rate (HR) and mean arterial blood pressure (MABP) have been suggested as useful parameters during general anesthesia for nociceptive monitoring. However, studies focusing on whether intraoperative heart rate variability (HRv) and mean arterial blood pressure variability (MABPv) during general anesthesia can accurately monitor nociception in patients have remained inconclusive. The current study aimed to (1) identify the association of intraoperative heart rate and blood pressure variability in patients undergoing low-risk surgery with the incidence of APOP in the immediate postoperative setting and (2) evaluate the associations of clinical demographic factors with the incidence of APOP.

Methods – A retrospective observational cohort study was conducted. The outcome was moderate-to-severe APOP, defined as a numeric rating scale score of ≥4. HRv, MABPv, and potential confounders, such as age, body mass index, duration of surgery, smoking, depression, preoperative use of analgesics, and type of surgery, were used as independent variables.

Results – Data from 764 female oncological breast surgery patients were analyzed. No statistically significant association of HRv and MABPv with APOP was found. Lower age was associated with higher odds of APOP (odds ratio [OR] 0.978, $p = 0.001$). Increased length of surgery (OR 1.013, $p = 0.022$) and a history of depression were associated with increased odds of APOP (OR 2.327, $p = 0.010$). The subtype of surgery was statistically significantly associated with APOP ($p = 0.006$).

Conclusions – Our results suggest that heart rate and blood pressure variability intraoperatively, in female patients undergoing low-risk surgery, are not associated with, and thus not predictive of, APOP in the immediate postoperative setting.

Keywords: acute pain, pain management, postoperative pain, Cohort study, retrospective study

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1 Introduction

Adequate analgesia is an integral part of general anesthesia, along with the induction of a hypnotic state and potentially neuromuscular blockade. Analgesics are essential to prevent and manage the activation of the central nervous system by surgery-induced noxious stimuli [1]. This is called nociception: the physical or autonomic sensation of noxious stimuli. Modern techniques enable anesthesia care providers to assess the depth of neuromuscular blockade and to a lesser degree the depth of hypnosis; however, there is no

standardized measurement instrument to effectively monitor nociception [2].

The absence of an objective standard to monitor nociception complicates intraoperative pain care [2–4], as well as postoperative pain management. A balance between Nociception and Anti-Nociception (NAN) is essential to prevent hemodynamic instability and increased recovery times due to under or overdosing of analgesics. NAN dysbalance also puts the patient at risk for acute postoperative pain (APOP) [5]. APOP occurs in 55% of all surgical patients and is therefore considered a major health burden [6]. Moreover, APOP is associated with a higher incidence of postoperative nausea and vomiting, increased cardiac stress, delayed wound healing, and increased odds of postoperative complications within the first 30 days after surgery [6,7]. Several demographic factors have been described as being predictive of APOP such as age, body mass index (BMI), duration of surgery, smoking, history of depression, American Society of Anesthesiologists (ASA) classification, preoperative use of analgesics, and type of surgery [8–10]. The risk of APOP can be reduced by appropriately managing surgery-induced noxious stimuli intraoperatively through adequate anesthetic management [11–13].

While attempts have been made to build objective assessment tools to assess the NAN balance during anesthesia, those suggested have not been widely implemented due to a lack of validation [2]. Practically, increased heart rate (HR) and mean arterial blood pressure (MABP) are often the only parameters available during general anesthesia that might indicate an inadequate NAN balance [14]. Unfortunately, these autonomic variables are not specifically associated with nociception as other factors may also affect them [15]. Studies focusing on whether heart rate variability (HRv) and mean arterial blood pressure variability (MABPv) during anesthesia can accurately monitor nociception have, as yet, remained inconclusive [14,16–22].

Therefore, this study aims to (1) identify the association of intraoperative heart rate and blood pressure variability, in patients undergoing low-risk surgery, with the incidence of moderate to severe APOP in the immediate postoperative setting, and (2) evaluate the associations of clinical demographic factors, in patients undergoing low-risk surgery, with the incidence of moderate to severe APOP in this population.

2 Methods

2.1 Study design

We conducted a single-center, retrospective observational cohort study. The Research Ethics Committee determined that this study was not subject to the Medical Research Involving Human Subjects Act. The requirement for written informed consent was waived. All data were pseudo-anonymized. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline [23].

2.2 Participants and setting

Participants were women aged ≥18 years old, who underwent oncological breast surgery between March 2018 and May 2022 in a tertiary-level teaching hospital in the Netherlands. Selected data from the electronic medical record (EMR) were requested from the hospital Datawarehouse for all female patients who underwent oncological breast surgery within the study period.

This patient category was chosen because the hemodynamic parameters HRv and MABPv were expected to be minimally influenced by volume shifts and this type of operation is classified as low risk [24,25]. In this population, approximately 28–57.7% of patients suffer from APOP [26,27].

EMRs were excluded if the patient underwent oncoplastic or reconstructive surgery, received local anesthesia, received total intravenous anesthesia, or was assigned an ASA classification of ≥3. EMRs were also excluded if vasoactive or vasoconstrictive drugs were given as continuous infusion during the procedure. If the refusal of permission for the use of data for study purposes was explicitly mentioned in the EMR, that patient was also excluded. Analysis was limited to complete cases. Cases were considered incomplete if values of at least one study data point were not documented within the EMR.

2.3 Study parameters

2.3.1 Outcome parameter

APOP was measured in the Post Anesthesia Care Unit (PACU) through the numeric rating scale (NRS), which is a unidimensional measure of pain intensity in adults based on an 11-point scale ranging from 0 (“no pain”) to 10 (“worst pain imaginable”) [28]. The highest NRS score at rest registered during their stay in the PACU, regardless of time frame, was used for the analysis.

2.3.2 Independent variables

Both HR and MABP measurements were carried out non-invasively. The baseline value for the independent

variables HRv and MABPv was the average of all HRs or MABPs measured during the first 10 min after incision. The reason for the waiting period was to avoid hemodynamic changes and reactions to airway management associated with induction. The count of intraoperative HR and MABP values exceeding baseline values by at least 20% was scored as the incidence of HRv or MABPv and expressed as "events." These events were categorized. The cutoff of 20% was based on generally accepted good clinical practice policy and has been used in studies we refer to [21,22]. If a vasoactive or vasoconstrictive medication were bolus-dosed, HR and MABP measurements in the subsequent 5 min were excluded from analysis.

2.3.3 Other variables

Other factors have been suggested as being predictive of APOP [8–10] and could therefore potentially confound the relationship of HRv and MABPv with APOP. Therefore, the following eight clinical and demographic factors were collected as variables: age in years at the time of surgery, BMI at the time of surgery in kg/m^2, duration of surgery in minutes, current smoking status (yes/no), history of depression (yes/no), ASA Classification (ASA 1/ASA 2), preoperative use of analgesics (yes/no), and type of surgery (five categories: [1] unilateral lumpectomy, [2] bilateral lumpectomy, [3] unilateral mastectomy without axillary lymph node dissection, [4] bilateral mastectomy without axillary lymph node dissection, and [5] unilateral mastectomy with axillary lymph node dissection).

2.4 Study size

A sample size calculation for binary outcomes was performed [29], for which, an expected outcome proportion of 0.3 was used, as 28–57.7% of the women undergoing breast surgery experience moderate to severe postoperative pain [26,27]. Furthermore, the sample size calculation assumed a mean absolute prediction error of 0.05 and considered 15 predictor parameter coefficients, which led to a minimum required sample size of

$$n = \exp\left(\frac{-0.508 + 0.259\mathrm{In}(0.3) + 0.504\mathrm{In}(15) - \mathrm{In}(0.050)}{0.544}\right)$$

$$\approx 670.99 = 671 \text{ patients.}$$

2.5 Data collection

The data source for this study was the EMR. A data abstraction guideline was developed and strategies for locating data within the EMR were documented. The preliminary study cohort was identified using the standardized Dutch Diagnosis Treatment Combination codes (33911, 33920, 33930) and the inclusion criteria identified.

Next, patients in the preliminary study cohort were checked for exclusion criteria by the principal investigator and a business intelligence specialist and removed from the cohort if ineligible. Extracted data were randomly checked against the actual EMR data. The data were then imported into SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 28.0; IBM Corporation, Armonk, NY, USA) for further analysis [30].

2.6 Statistical analysis

Continuous variables are presented with mean and standard deviation (SD), and categorical variables are presented as absolute numbers and percentages. Differences between groups within continuous variables were tested using the independent Student's *t*-Test and differences within categorical variables were tested with the Pearson chi-square or Fisher Freeman Halton exact test. The incidence of the primary outcome parameter APOP was calculated as a dichotomized variable: an NRS score of ≥4 indicated the presence of moderate to severe APOP (1) and an NRS score of <4 indicated its absence (0) [31–34]. HRv and MABPv were divided into three categories: HRv was categorized as 0 events (1), 1–2 events (2), and ≥3 events and MABPv was categorized as 0 events (1), 1 event (2), and ≥2 events (3). Outliers (Zresidual >3 or interquartile range >1.5) were thoroughly examined and subgroup analysis was used to prevent inappropriate removal or acceptance of data points. Univariate and multivariable logistic regressions were used for analysis, and for both univariate and multivariable logistic regressions, the dependent binary variable was the presence of moderate-to-severe APOP. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). Multivariable statistical modeling was used to control for confounding by the predictive clinical and demographic variables. The absence of multicollinearity was checked by estimating Pearson's correlation coefficient for all pairs of independent interval and ratio parameters with a cutoff value of <0.7 and if the variation inflation factor (VIF) was <2.5. The logistic regression

model was built using backward elimination. To determine the significance of the final logistic regression model compared to the classification table in block 0, The omnibus tests of model coefficients and the Hosmer–Lemeshow goodness-of-fit test were executed [35]. Statistical analysis was performed using SPSS. Significance levels were set at p <0.05.

3 Results

3.1 Participants

In the study period, 1,643 EMRs of patients who underwent oncological breast surgery under general anesthesia were found and enrolled in the study. Following a check against exclusion criteria, 785 patients were excluded. Thus, 858 patients were eligible for inclusion. Missing value exploration led to the exclusion of a further 94 patients. Therefore, 764 patients were included in the analysis (Figure 1).

3.2 Clinical demographic characteristics

All included patients were female and their mean age (years) was 58.5 ± 13.1 (19–88 years old). The type of surgery varied and 163 patients (21.3%) experienced moderate-to-severe APOP during their stay in the PACU. The clinical demographic characteristics are presented in Table 1. An overview of the incidence of HRv and MABPv in relation to APOP is presented in Table 2. No variability in HR (n = 621, 81.3%) or BP (n = 610, 79.8%) was most common in the study population.

3.3 Univariate analysis

Table 3 shows the results of the univariate logistic regression analysis of an association of HRv and MABPv with APOP; no statistically significant association was found.

3.4 Multivariable analysis

The absence of multicollinearity was confirmed as Pearson's correlation coefficient was <0.7 and all VIFs were <2.5 for all pairs of independent interval and ratio parameters (Table 4). A longer duration of surgery, per additional minute, was statistically significantly associated with increased odds of APOP (OR 1.013, 95% CI 1.002–1.024, p = 0.022). Older age

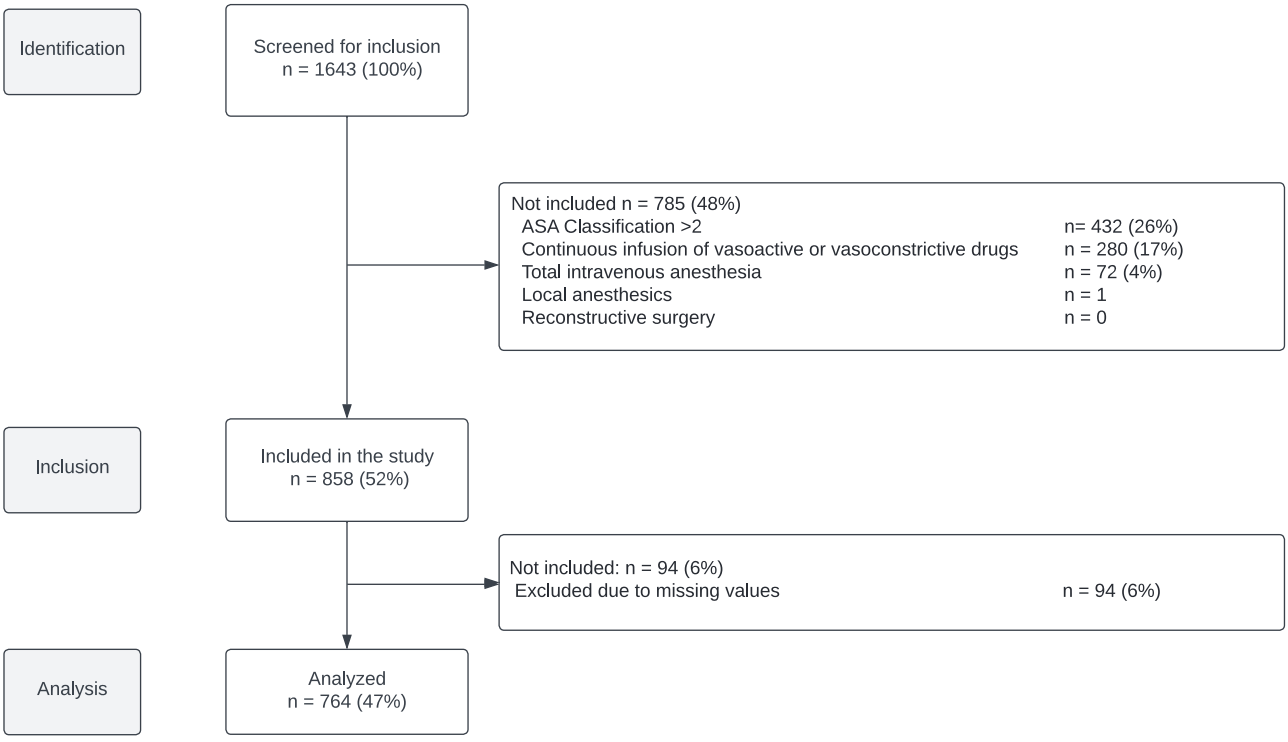

Figure 1: STROBE Flow diagram of the recruitment process.

Table 1: Clinical demographic characteristics of the study population

	Variable		All participants, *n* (%)	APOP, *n* (%)	No APOP, *n* (%)	*p*-value[a]
			764 (100%)	163 (21.3%)	601 (78.7%)	
Continuous variables	Age (years)		58.5 ± 13.1	55.7 ± 13.9	59.3 ± 12.8	0.002[b]
mean ± SD	Duration of surgery (minutes)		47.2 ± 19.5	49.1 ± 19.8	46.7 ± 19.4	0.160[b]
	Body mass index (kg/m^2)		26.7 ± 4.6	26.6 ± 4.4	26.7 ± 4.6	0.786[b]
Categorical, *n* (%)	ASA classification	ASA1	209 (27.4%)	43 (20.5%)	167 (79.5%)	0.753[c]
		ASA2	555 (72.6%)	120 (21.7%)	434 (78.3%)	
	Type of surgery					0.019[d]
		Unilateral lumpectomy	294 (38.5%)	54 (18.4%)	240 (81.6%)	
		Bilateral lumpectomy	7 (0.9%)	2 (28.6%)	5 (71.4%)	
		Unilateral mastectomy without axillary lymph node dissection	405 (53.0%)	96 (23.7%)	309 (76.3%)	
		Bilateral mastectomy without axillary lymph node dissection	9 (1.2%)	5 (55.6%)	4 (44.4%)	
		Unilateral mastectomy with axillary lymph node dissection	49 (6.4%)	6 (12.2%)	43 (87.8%)	
	Smoking	No	649 (84.9%)	138 (21.3%)	511 (78.7%)	0.909[c]
		Yes	115 (15.1%)	25 (21.7%)	90 (78.3%)	
	Depression	No	716 (93.7%)	146 (20.4%)	570 (79.6%)	0.014[c]
		Yes	48 (6.3%)	17 (35.4%)	31 (64.6%)	
	Preoperative use of analgesics	No	611 (80.0%)	123 (20.1%)	488 (79.9%)	0.104[c]
		Yes	153 (20.0%)	40 (26.1%)	113 (73.9%)	

Abbreviations: APOP, acute postoperative pain defined as an numeric rating scale score of ≥ 4 measured in the postoperative care unit; CI, confidence interval; SD, standard deviation; ASA, American society of anesthesiologists classification. [a]*P*-values were considered statistically significant if $p < 0.05$. [b]Independent *T*-Test for Equality of Means. [c]Pearson Chi-Square. [d]Fisher Freeman Halton Exact Test.

had protective properties as an increase in age, per additional year, was statistically significantly associated with decreased odds of APOP (OR 0.978, 95% CI 0.965–0.992, $p = 0.001$). Women who underwent a unilateral mastectomy with axillary lymph node dissection had statistically significantly decreased odds to experience APOP compared to the women in the reference categories unilateral lumpectomy (OR 0.311, 95% CI 0.106–0.909, $p = 0.033$), unilateral mastectomy without axillary lymph node dissection (OR 0.217, 95% CI 0.076–0.617, $p = 0.004$), and bilateral mastectomy without axillary lymph node dissection (OR 0.078, 95% CI 0.015–0.391, $p = 0.002$). The presence of depression in the medical history statistically significantly increased the odds of APOP (OR 2.327, 95% CI 1.227–4.414, $p = 0.010$). No statistically significant association was found between the clinical demographic variables BMI, smoking status, ASA classification, and preoperative use of analgesics and APOP. The omnibus test of model coefficients was statistically significant ($p < 0.001$). The

Table 2: Number and incidence of HRv and MABPv, expressed as percentages of the total number of participants

	Variable		Incidence of variability,[a] *n* (%)	APOP	No APOP	*p*-value[b]
Categorical, *n* (%)	Categorized HRv	0 events	621 (81.3%)	131	490	0.644[c]
		1–2 events	81 (10.6%)	16	65	
		≥3 events	62 (8.1%)	16	46	
	Categorized MABPv	0 events	610 (79.8%)	130	480	0.616[c]
		1 event	77 (10.1%)	19	58	
		≥2 events	77 (10.1%)	14	63	

Abbreviations: APOP, acute postoperative pain defined as a numeric rating scale score of ≥4 measured in the postoperative care unit; HRv, heart rate variability; MABPv, mean arterial blood pressure variability. [a]Expressed as a percentage of the 764 participants. [b]*p*-values were considered statistically significant if $p < 0.05$. [c]Pearson chi-square.

Table 3: ORs obtained from univariate binary logistic regression estimating the association of HRv and MABPv with acute postoperative pain

Independent variable[a]	Category	OR	95% CI	*p*-value[b]
HRv	0 events			0.645
	1–2 events	0.921	0.516–1.644	0.780
	≥3 events	1.301	0.714–2.372	0.390
MABPv	0 events			0.617
	1 event	1.210	0.696–2.103	0.500
	≥2 events	0.821	0.446–1.511	0.525

Abbreviations: OR, odds ratio; CI, confidence interval. [a]Variables entered in the model: HRv and MABPv. [b]*P*-values were considered statistically significant if $p \leq 0.05$.

Hosmer–Lemeshow goodness-of-fit test indicated that poor prediction of the final model was not statistically significant ($p = 0.394$).

4 Discussion

Our results suggest that the use of heart rate and blood pressure variability intraoperatively as nociceptive parameters, in patients undergoing low-risk surgery, is not associated with, and thus not predictive of, moderate-to-severe APOP in the immediate postoperative setting. From the clinical demographic variables, lower age, longer duration of surgery, and history of depression were statistically significantly associated with increased odds of APOP. The results indicate that type of surgery may be associated with increased odds of APOP as women undergoing unilateral mastectomy with axillary lymph node dissection had statistically significant lower odds of experiencing APOP than women who underwent a unilateral lumpectomy with axillary lymph node dissection or bilateral mastectomy with axillary lymph node dissection, despite the later operations involving far more extensive incisions and tissue damage. However, with our small sample size, these results should be interpreted with caution.

The incidence of APOP in our study (21.3%) was similar to that described by Schreiber et al. [26], as 28% in their study experienced moderate-to-severe APOP after carefully described oncological breast surgery types. That no statistically significant relation was found for HRv and MABPv with APOP incidence is consistent with Ledowski et al. [36], when they investigated the relationship between hemodynamic parameters and APOP in conscious patients of both sexes in the PACU who had undergone minor elective orthopedic or plastic surgery. No correlation, or one doubtfully clinically relevant, was found between APOP measured with the NRS and hemodynamic changes. However, in their study, continuously conscious patients were participating, which was different in our study.

In relation to the nociceptive predictive properties of HRv and MABPv, a review article by Martinez-Vazquez and Jensen [37] reports that autonomic signs, such as HRv and MABPv, have low sensitivity and specificity. They state that these parameters can be affected by anesthetics and other factors related to the surgical procedure and conclude that an expectation that prediction of APOP in the PACU from a single dimension parameter, such as HRv or MABPv, seems unrealistic.

The clinical relevance of our findings relates to a common approach by medical professionals during intraoperative care to use hemodynamic parameters as an indicator for the quality of pain management. Our study implies that this approach appears inappropriate for anesthetized female patients undergoing low-risk surgery.

In relation to the multivariable analysis, an increase in the duration of surgery was associated with increased odds

Table 4: ORs obtained from multivariable binary logistic regression estimating the association of HRv and MABPv with APOP

Independent variable[a]	OR	95% CI	*p*-value[b]
Duration of surgery (in minutes)	1.013	1.002–1.024	0.022
Age (years)	0.978	0.965–0.992	0.001
Type of surgery (reference category: unilateral lumpectomy)			0.006
Bilateral lumpectomy	1.230	0.219–6.919	0.814
Unilateral mastectomy without axillary lymph node dissection	1.435	0.979–2.103	0.064
Bilateral mastectomy without axillary lymph node dissection	3.994	0.989–16.124	0.052
Unilateral mastectomy with axillary lymph node dissection	0.311	0.106–0.909	0.033
Presence of depression at the time of surgery	2.327	1.227–4.414	0.010

Abbreviations: OR, odds ratio; CI, confidence interval. [a]Variables initially entered in the model: body mass index, duration of surgery, age, type of surgery, American Society of Anesthesiologists classification, presence of depression, smoking status at the time of surgery, preoperative use of analgesics, MABPv, HRv. [b]*p*-values were considered statistically significant if $p \leq 0.05$.

of APOP. Our results are aligned with those obtained by Habib et al., who found in their prospective study among women undergoing elective breast cancer surgery that every additional 30 min of surgery was a statistically significant predictor for increased severity of APOP [10]. Moreover, Habib et al. also found that older age had protective properties, in line with the current study [10]. A possible explanation for this is that pain may be considered more common in older age and that coping strategies change with age [38]. Contrary to expectations, our study found that women who underwent a unilateral mastectomy with axillary lymph node dissection had decreased odds of APOP compared to the less extensive procedures. This outcome is not in line with Schreiber et al. [39]. A possible explanation for this result is that the incision size and extent of loose tissue trauma are not directly related to APOP incidence and intensity [40]. Observationally, we extrapolate that underestimation of the need to manage nociception caused by less extensive procedures amplified by caregiver focus on timely spontaneous breathing might lead to underdosing analgesics in the intraoperative setting, leading to APOP. That history of depression increased the odds of APOP was also reported by Schreiber et al. [39], who investigated preoperative psychosocial predictors of APOP in female breast surgery patients. This relationship was also reported in studies investigating predictors of APOP among other surgical specialties [8], which also corresponds with current insights on pain and coping, suggesting that psychological state influences pain sensation [41]. No statistically significant association of BMI, smoking status, ASA classification, and preoperative use of analgesics with APOP was found.

One of the strengths of this study's methodology is that the data collection was standardized through a data abstraction guideline and that extracted data were randomly checked against the actual EMR context. This increased reliability and validity. Strategies for locating data within the EMR were documented to strengthen consistency. Males were not included in this study as breast cancer is rarely diagnosed in men and pain perception has been shown to differ between sexes [25].

A limitation of this study is the lack of data concerning anesthesia depth and analgesic management. Due to its retrospective, database nature, this study could not objectify anesthesia depth, i.e., with bispectral index monitoring. Although an increase in HR and BP is described as nociceptive parameters, they can also be indicators of insufficient anesthesia depth [42]. In addition, intraoperative analgesic management was not standardized, which complicates the interpretation of our study results, and the number of patients in the different types of surgery varied strongly. This may have caused statistical testing to fail in identifying relationships within the data set. As oncological breast surgery is designated as a low-risk procedure, extrapolating our results to moderate and high-risk procedures seems inappropriate, with volume shifts and more invasive procedures potentially complicating such an analysis further.

In conclusion, this study suggests that intraoperative HR and blood pressure variability as nociceptive parameters, in female patients undergoing low-risk surgery, are not associated with moderate to severe APOP in the immediate postoperative setting. This study has also shown that lower age, increased length of surgery, and history of depression, in female patients undergoing low-risk surgery, are associated with higher odds of moderate-to-severe APOP in the immediate postoperative setting. This study indicates that subtype of surgery is associated with APOP; yet, this finding should be interpreted with caution. Further research is needed to identify sensitive and specific intraoperative nociceptive indicators, preferably with a prospective design and a uniform procedure including anesthesia depth monitoring, to improve perioperative pain care.

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Research ethics: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the authors' Institutional Review Board (METC Brabant #NW2022-07).

Informed consent: In accordance with the Code of Conduct for Medical Research, the requirement for written informed consent was waived by the Ethical Committee as obtaining this consent from all eligible participants would have required a disproportionate effort.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission. Lieselotte van Rijbroek: This author helped develop the study's concept and design. She collected and analyzed the data, and wrote the manuscript. Gerrit J. Noordergraaf: This author helped through collaboration on the study design and the strategy for data collection, assisted with the statistical approach, and reviewed the manuscript. Janneke de Man-van Ginkel: This author helped through collaboration on the study design and reviewing and supervising the writing of the manuscript. Regina van Boekel: This author helped through collaboration on the study design, conducted the study, collected the data,

analyzed the data, and reviewed and supervised the writing of the article.

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