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Association between preoperative vitamin D level and postoperative pain in patients undergoing breast cancer surgery: a prospective observational study

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ABSTRACT

Background This study investigated the relationship between preoperative serum vitamin D levels and acute postoperative pain scores in patients undergoing unilateral breast cancer surgery.

Methods The study was conducted at Fayoum University Hospital between September 2024 and April 2025. 184 American Society of Anesthesiologists (ASA) II–III female patients scheduled to undergo elective unilateral modified radical mastectomy were classified into two groups: 92 vitamin D-deficient (<30 nmol/L) and 92 vitamin D-sufficient (≥30 nmol/L). The primary outcome was the occurrence of moderate to severe postoperative pain (Numerical Rating Scale (NRS) >3) at 12 hours. A secondary 24-hour composite outcome (NRS >3 at any time within the first 24 hours) was used for the multivariable logistic regression. Other secondary outcomes included: preoperative serum 25(OH)D level, postoperative NRS, intraoperative fentanyl consumption, postoperative tramadol consumption, sedation scores, intraoperative and postoperative hemodynamics, patient satisfaction, and hospital stay.

Results The baseline characteristics were well balanced between the groups, with small standardized mean differences for all variables. Patients with vitamin D deficiency had a higher occurrence of moderate to severe pain at 12 hours. In multivariable analysis, vitamin D deficiency was independently associated with moderate to severe postoperative pain at any time point during the first 24 hours (adjusted OR 3.12, 95% CI 1.58 to 6.13). Vitamin D-deficient patients had higher intraoperative fentanyl consumption (mean difference 8.04 µg, 95% CI 3.21 to 12.88) and postoperative tramadol consumption (mean difference 112.17 mg, 95% CI 101.44 to 122.91).

Conclusion Vitamin D deficiency is associated with a higher occurrence of moderate to severe postoperative pain and increased opioid consumption in patients undergoing unilateral modified radical mastectomy.

INTRODUCTION

Lower levels of vitamin D have been associated with several pain modalities including musculoskeletal pain, post-traumatic pain, malignancy-associated pain, and postoperative pain. Also, in several studies it has been associated with higher postoperative opioid consumption.¹ A serum concentration of 25-hydroxyvitamin D (25(OH)D) of <30 nmol/L is insufficient to prevent vitamin D deficiency-related bone disorders. Consequently, this threshold is

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Vitamin D has a role in pain modulation and perception through its anti-inflammatory and immune-regulating effects. The link between vitamin D deficiency and postoperative pain is still debated in the literature.

WHAT THIS STUDY ADDS

⇒ In patients undergoing unilateral modified radical mastectomy, vitamin D deficiency is associated with a higher occurrence of moderate to severe postoperative pain and increased opioid consumption.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

⇒ Preoperative vitamin D supplementation in breast cancer patients with vitamin D levels <30 nmol/L may have a role in modulating postoperative pain.

widely accepted for defining vitamin D deficiency in clinical studies.²

Beyond its essential role in calcium and phosphate homeostasis, vitamin D has diverse immunomodulatory and antiproliferative properties.³ Emerging evidence suggests that vitamin D plays a critical role in both pain perception and modulation, likely through its anti-inflammatory effects via its impact on pain-mediated cytokines and immune-regulating effects.⁴ Additionally, vitamin D insufficiency has been linked to other increased risks including respiratory infections, adverse pregnancy outcomes, and various chronic diseases.⁵

Of particular relevance, deficiency of vitamin D is commonly reported among patients with breast cancer. Some studies suggest that a deficiency of vitamin D may contribute to the development or progression of the disease.^{6,7} Although the precise nature of the link between breast cancer and vitamin D remains to be fully elucidated, multiple studies support vitamin D deficiency as a potential risk factor for breast, colorectal, prostate, and pancreatic cancers.^{8–12}

Despite growing interest in the broader physiological functions of vitamin D, the relationship between vitamin D deficiency and acute postoperative pain in patients undergoing breast cancer surgery has not been adequately investigated. Given



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the role of vitamin D in pain modulation, this gap in the literature warrants further exploration. In this study we aimed to investigate the association between preoperative vitamin D levels and acute postoperative pain in patients undergoing unilateral breast cancer surgery (modified radical mastectomy).

METHODS

Patient enrollment

This prospective observational cohort study was conducted at Fayoum University Hospital following approval from the Institutional Ethics Committee and Institutional Review Board (Approval ID: D328). The study was registered on ClinicalTrials.gov under NCT06551688 (Principal Investigator: Mohamed Ahmed Hamed), first submitted on July 3, 2024. Between September 2024 and April 2025, newly diagnosed patients with histopathologically-confirmed breast cancer scheduled for elective surgery were enrolled from the General Surgery Department, with the first patient on September 1, 2024. Written informed consent was obtained from all eligible participants prior to enrollment.

Inclusion and exclusion criteria

Women aged 20–65 years classified as American Society of Anesthesiologists (ASA) physical status II–III who were scheduled to undergo elective unilateral modified radical mastectomy for breast cancer were included.

Exclusion criteria included refusal to participate; chronic opioid use; cognitive impairment; use of medications affecting calcium, phosphorus, or vitamin D metabolism (eg, calcitonin, estrogen, or analogs) within 1 month prior to enrollment; history of hyperparathyroidism or prior parathyroidectomy; disorders affecting vitamin D absorption (eg, chronic diarrhea, pancreatitis, biliary obstruction, colitis, small intestine resection); severe hepatic or renal dysfunction; peripheral or central neuropathy; heart failure; pneumonia; parenteral nutrition; inability to comprehend the Numerical Rating Scale (NRS) or inability to operate a patient-controlled analgesia (PCA) device.

Vitamin D measurement

Preoperatively, serum 25-hydroxyvitamin D (25(OH)D) was measured as it is considered the most reliable marker of vitamin D status due to its longer half-life, higher stability, and repeatability in detection compared with 1,25-dihydroxyvitamin D. Serum 25(OH)D levels were reported in nmol/L. For comparison with guidelines using mass concentration, 1 nmol/L is approximately equivalent to 0.4 ng/mL.

Study design and group designation

Two groups were created depending on preoperative serum 25(OH)D levels: vitamin D-deficient (<30 nmol/L) and vitamin D-sufficient (≥30 nmol/L).

Serum 25(OH)D levels were measured preoperatively using a competitive ELISA kit (Euroimmun, Lübeck, Germany) and recorded by an anesthesiologist not involved in the study. Accordingly, patients were assigned to two pre-defined cohorts based on their natural vitamin D levels until the sample size for each group was met (quota sampling). Patients' preoperative serum 25(OH)D levels were blinded to patients, investigators, attending clinicians, and outcome assessors until the end of the study. The actual vitamin D values were concealed from the surgical and anesthesia teams, and the laboratory reports were omitted from the routine bedside charts until after the 24-hour follow-up.

Anesthesia protocol

In the operating room, standard monitoring was applied. Intravenous (IV) access was established in the hand contralateral to the surgical side. All patients received 4 mg IV ondansetron as premedication. Induction was carried out using IV propofol (2 mg/kg), atracurium (0.5 mg/kg), and fentanyl (1 µg/kg). After intubation, mechanical ventilation was adjusted to maintain normocapnia. Anesthesia maintenance included inhaled isoflurane (1.5%), supplemental atracurium (0.1 mg/kg every 20 min), and fentanyl (0.5 µg/kg) as guided by the Surgical Pleth Index (SPI) (Carestation 650L GE.3.4.2019) to maintain the value below 50. Blood pressure and heart rate were continuously monitored. Hypotension (systolic blood pressure <90 mmHg or ≥20% below baseline) was managed with 5 mg IV ephedrine; bradycardia (heart rate ≤50 bpm) was managed with 0.5 mg IV atropine.

After neuromuscular blockade reversal using neostigmine and atropine, patients were extubated on full recovery and transferred to the post-anesthesia care unit, and subsequently to the general surgery ward when a modified Aldrete score ≥9 was achieved.

During the preoperative consultation, all patients were instructed on the utilization of the PCA device and the 11-point NRS (0=no pain, 10=worst pain). Postoperative pain was assessed by an investigator blinded to group designation. Postoperative analgesia included IV paracetamol 1 g every 8 hours, based on the routine hospital protocol. Additional analgesia was provided using a PCA device delivering IV tramadol (4 mg/mL concentration) with a 20 mg bolus, 10 min lockout interval, and a maximum dose of 50 mg per hour with no background infusion.

Study outcomes

The proportion of patients with moderate to severe postoperative pain (defined as NRS >3) at 12 hours after surgery was the pre-specified primary outcome. Additionally, to provide a statistically robust multivariable analysis without limitations of sparse data bias at a single time point, we defined a secondary composite outcome specifically for the logistic regression model: the occurrence of moderate to severe pain at any postoperative assessment within the first 24 hours (6, 12, 18, or 24 hours).

Other secondary outcomes included preoperative serum level of 25(OH)D (nmol/L), preoperative pain assessment 24 hours before operation by NRS (from 0 to 10 where 0=no pain and 10=most severe pain), intraoperative data, duration of surgery (in minutes), intraoperative fentanyl consumption (in µg) and hemodynamics including non-invasive mean arterial blood pressure and heart rate (baseline, every 30 min intraoperative till the end of operation), postoperative pain scores (NRS) at times: (zero time=immediately in the post-anesthesia care unit, 6 hours, 12 hours, 18 hours, and 24 hours after surgery), postoperative total tramadol consumption (mg) (within first 24 hours postoperative), occurrences of postoperative adverse effects during the first 24 hours including nausea and vomiting (0=no symptoms, 1=only nausea, 2=nausea and vomiting), sedation score (0=awake and alert, 1=quietly awake, 2=asleep but easily arousable, 3=deep sleep, responding to painful stimulus), respiratory depression (respiratory rate <10), hospital stay in days, and patient satisfaction assessed on a 4-point scale (1=excellent, 2=good, 3=fair, 4=poor).

Statistical analysis and sample size estimation

The sample size was calculated using MedCalc Statistical Software version 20 (MedCalc Software, Ostend, Belgium). The calculation was based on the primary outcome and guided by parameters obtained from a study by Zeng *et al* (occurrence of moderate to severe pain of 52.1% in the vitamin D-deficient group and 30.6% in the vitamin D-sufficient group).¹ A minimum sample size of 164 patients, with at least 82 patients in each group, was required to achieve 80% power with an alpha error of 0.05. To compensate for potential loss to follow-up, the sample size was increased by 10% resulting in a total of 184 patients (92 in each group).

Statistical analysis was performed using SPSS version 28 (IBM Corp, Armonk, New York, USA). Numerical data were presented as means and SD and analyzed using the unpaired t-test, or as medians and IQRs and analyzed using the Mann–Whitney U test. Baseline covariate balance between groups was assessed using standardized mean differences (SMDs), with values <0.2 considered indicative of good balance. Categorical data were presented as frequencies and percentages and analyzed using the χ^2 test or Fisher's exact test, as appropriate. Longitudinal pain intensity was summarized as the area under the curve (AUC) of NRS scores over the first 24 hours to reflect the overall pain burden. Mixed-methods ANOVA was used to examine the main effects of group, time, and the interaction effect for variables with repeated measurements. Logistic regression analysis was performed to identify factors associated with the composite

outcome of moderate to severe postoperative pain occurring at any time point during the first 24 hours. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

In this study, 200 women scheduled for elective unilateral modified radical mastectomy were assessed for eligibility. Sixteen patients were excluded: three did not meet the inclusion criteria, two declined to participate, one had a history of intestinal resection, two had cognitive impairment, one had renal dysfunction, and seven eligible patients were not enrolled because the quota for their respective vitamin D group had already been filled. Consequently, 184 patients were enrolled with 92 patients designated to each group, as shown in the STROBE flow diagram (figure 1).

The baseline characteristics were well balanced between the groups. All standardized mean differences were small ($SMD \leq 0.18$), indicating minimal imbalance in age, body mass index, ASA physical status, preoperative pain scores, and duration of surgery (table 1).

The primary endpoint of this study was the occurrence of moderate to severe pain (NRS >3) at 12 hours post-operatively. We observed a statistically significant difference at this time point: 17.4% (16/92) of patients in the vitamin D-deficient group reported moderate to severe pain compared with 2.2% (2/92) in the vitamin D-sufficient

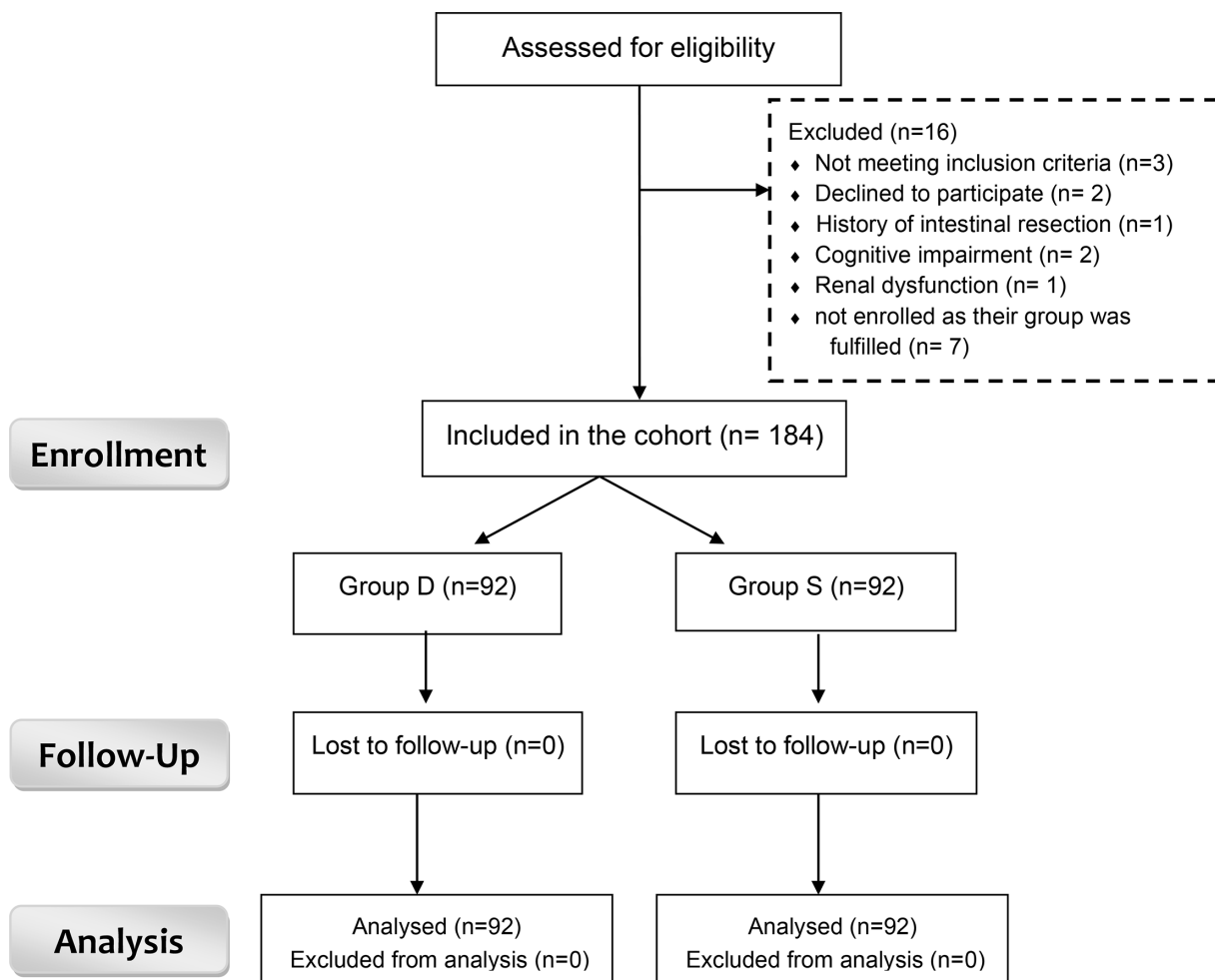


Figure 1 STROBE flow diagram of the study population. Group D, vitamin D-deficient; Group S, vitamin D-sufficient.

Table 1 Baseline characteristics of the studied groups

Item	Vitamin D-deficient group (n=92)	Vitamin D-sufficient group (n=92)	SMD*
Age, mean (SD), years	44.61 (11.69)	42.54 (11)	0.18
BMI, mean (SD), kg/m ²	23.74 (1.78)	23.63 (1.69)	0.06
ASA physical status, n (%)			
ASA II	76 (82.6)	73 (79.3)	0.03
ASA III	16 (17.4)	19 (20.7)	
Preoperative NRS, median (IQR)	0 (0–1)	0 (0–1)	0.01
Duration of surgery, mean (SD), min	126.03 (13.42)	126.4 (13.31)	0.03

*The difference column represents the standardized mean difference for continuous variables and the absolute difference in proportions for categorical variables. ASA, American Society of Anesthesiologists; BMI, body mass index; NRS, numerical rating scale; SMD, standardized mean difference.

group ($p=0.001$). This represents an absolute risk difference of 15.2%.

Analysis of the pain trajectory showed consistent findings at other time points. While pain scores were similar immediately after surgery (median (IQR) NRS 1 (1–2) in both groups), the groups diverged by 6 hours where the occurrence of moderate to severe pain was 32.6% in the vitamin D-deficient group versus 19.6% in the vitamin D-sufficient group ($p=0.044$).

To capture the cumulative pain experience we analyzed the AUC for NRS scores over 24 hours. The overall pain burden was significantly higher in vitamin D-deficient patients (mean difference 7.53, 95% CI 3.97 to 11.09; SMD=0.62), confirming a sustained difference in pain experience throughout the postoperative period (table 2).

Intraoperative fentanyl and postoperative tramadol consumption were higher in the vitamin D-deficient group, with large effect sizes (SMD=0.48 and 3.04, respectively) and clinically meaningful mean differences (table 2). The

Table 2 Perioperative variables

Item	Vitamin D-deficient group (n=92)	Vitamin D-sufficient group (n=92)	Difference* ‡ (95% CI)	SMD
Total intraoperative fentanyl consumption, mean (SD), µg	112.93 (19.7)	104.89 (12.8)	8.04 (3.21 to 12.88)	0.48
Total postoperative tramadol consumption, mean (SD), mg	380.65 (35.26)	268.48 (38.46)	112.17 (101.44 to 122.91)	3.04
NRS AUC, mean (SD)	47.64 (12.71)	40.11 (11.75)	7.53 (3.97 to 11.09)	0.62
Complications, n (%)				
Nausea	19 (20.7)	7 (7.6)	0.13 (0.03 to 0.23)	
Vomiting†	5 (5.4)	0 (0)	0.05 (0.00 to 0.12)	
Respiratory depression	0 (0)	0 (0)	–	
Sedation score, n (%)				
0 hours				
0 (Awake and alert)	89 (96.7)	90 (97.8)	0.01 (–0.04 to 0.06)	
1 (Quietly awake)	3 (3.3)	2 (2.2)		
6 hours				
0 (Awake and alert)	90 (97.8)	90 (97.8)	0.0 (–0.04 to 0.04)	
1 (Quietly awake)	2 (2.2)	2 (2.2)		
12 hours				
0 (Awake and alert)	91 (98.9)	92 (100%)	0.01 (–0.01 to 0.03)	
1 (Quietly awake)	1 (1.1)	0 (0)		
18 hours				
Awake and alert	92 (100)	92 (100)	–	
24 hours				
Awake and alert	92 (100)	92 (100)	–	
Patient satisfaction, n (%)				
Excellent	75 (81.5)	84 (91.3)	–0.10 (–0.2 to 0.00)	
Good	17 (18.5)	8 (8.7)		
Fair	0	0		
Poor	0	0		
Hospital stay, median (IQR), days	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0 p=0.024	

*The difference column represents the absolute mean difference for continuous variables and the absolute difference in proportions for categorical variables. For hospital stay, a 95% CI is not provided due to identical medians and IQRs; therefore, the non-parametric p value is reported.

†For variables with zero events in one group (eg, vomiting), the 95% CI for the difference in proportions was calculated using the Agresti–Caffo method rather than the normal approximation.

‡A Mann–Whitney U test was used to compare median values and a χ^2 test or Fisher's exact test was used to compare proportions.

SMD, standardized mean difference.

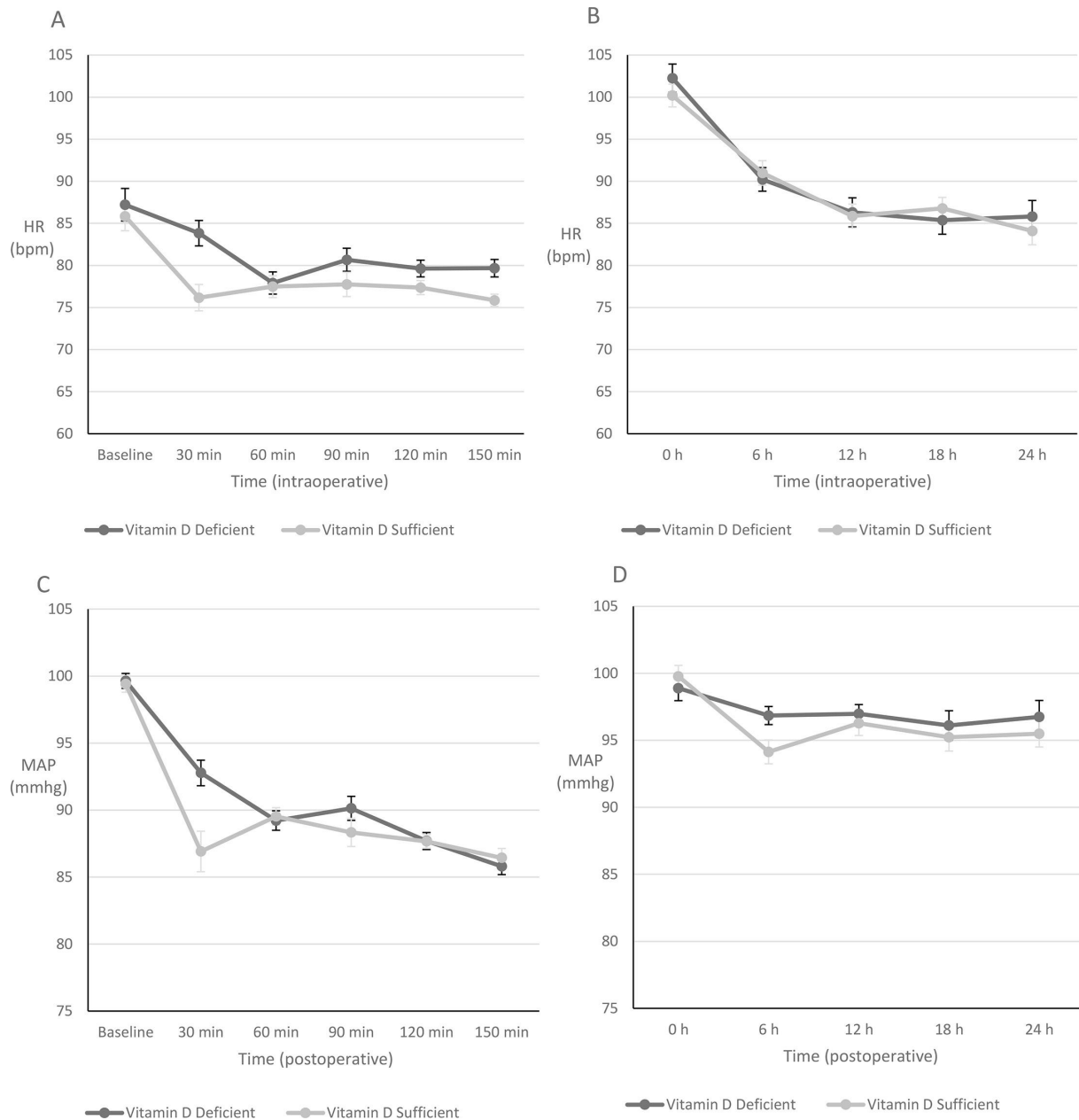


Figure 2 Perioperative hemodynamic trajectories. HR, heart rate; MAP, mean arterial pressure.

trajectories of intraoperative and postoperative hemodynamic parameters (heart rate and mean arterial pressure) over time are shown in [figure 2](#). While mixed-design ANOVA indicated minor statistical variations (see online supplemental table 1), the overall hemodynamic profiles remained largely stable and clinically comparable between the two groups.

The occurrence of nausea was higher in the vitamin D-deficient group, with an absolute risk difference of 13% (95% CI 3% to 23%). Differences in vomiting and sedation scores were small and not significant. No patients experienced respiratory depression. Although patient satisfaction was slightly lower in the vitamin D-deficient group than in the vitamin D-sufficient group, the difference was not statistically significant (81.5% in the vitamin D-deficient group vs 91.3% in the vitamin D-sufficient reported excellent satisfaction, while 18.5% vs 8.7% reported good satisfaction). The hospital stay was significantly more extended

in the vitamin D-deficient group than in the vitamin D-sufficient group (1.05 ± 0.23 days vs 1 ± 0 days, $p=0.024$; [table 2](#)).

Due to the low event count of moderate to severe pain at the strict 12-hour time point, a multivariable model restricted to 12 hours yielded exceptionally wide confidence intervals (sparse data bias). We therefore modeled the 24-hour composite outcome. In multivariable logistic regression adjusted for age, body mass index, ASA physical status, duration of surgery, and fentanyl consumption, vitamin D deficiency remained independently associated with moderate to severe postoperative pain during the first 24 hours (adjusted OR 3.12, 95% CI 1.58 to 6.13; [table 3](#)). The test for overall model fit was statistically significant and collinearity was assessed and was minimal (variance inflation factors (VIFs) 1.02–1.11). Model discrimination was assessed using ROC analysis (AUC=0.69), indicating moderate discriminative ability.

Table 3 Multivariable logistic regression of factors associated with moderate to severe postoperative pain at any time point during the first 24 hours

Item	Univariate analysis		Multivariable analysis	
	Unadjusted OR	95% CI	Adjusted OR	95% CI
Serum 25(OH)D level				
Sufficient	Reference		Reference	
Deficient	3.23	1.68 to 6.18	3.12	1.58 to 6.13
Age, years	1	0.97 to 1.03	0.99	0.96 to 1.02
BMI, kg/m ²	1.09	0.92 to 1.31	1.11	0.92 to 1.34
ASA physical status				
II	Reference		Reference	
III	0.77	0.34 to 1.72	0.82	0.34 to 1.96
Duration of surgery, min	0.98	0.96 to 1.01	0.98	0.96 to 1.01
Total fentanyl consumption, µg	1.01	1 to 1.03	1.01	0.99 to 1.02

ASA, American Society of Anesthesiologists; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D.

DISCUSSION

Our study shows that vitamin D deficiency is associated with a higher occurrence of moderate to severe postoperative pain in patients undergoing unilateral modified radical mastectomy. Additionally, vitamin D deficiency is associated with higher doses of opioid analgesia both intraoperatively and postoperatively. This demonstrates an inverse association between preoperative vitamin D levels and both cumulative opioid use and postoperative pain scores. To our knowledge, this is the first study to discuss the relationship between vitamin D levels and acute postoperative pain following breast cancer surgery.

We found that patients with low vitamin D levels (<30 nmol/L) experienced significantly more moderate to severe pain in the early postoperative period (within 24 hours) compared with those in the vitamin D-sufficient group (adequate vitamin D levels ≥30 nmol/L). It is noteworthy that no patient in either group reported 'severe' pain (NRS ≥7) during the study period, likely due to the efficacy of the standardized PCA protocol. Consequently, the observed difference in analgesic requirements was driven entirely by a reduction in 'moderate' pain (NRS 4–6) in the vitamin D-sufficient group. The relationship between postoperative pain and vitamin D levels has been debated and, while some studies have identified an association, others have not.

Several earlier studies have examined the link between various pain syndromes and vitamin D insufficiency, reporting that individuals with vitamin D levels <30 nmol/L are more likely to benefit from supplementation.^{13–16} Bergman *et al* and Kim *et al* described an association between low 25(OH)D levels and increased opioid consumption.^{17,18} Low vitamin D levels were linked to postoperative pain in patients with palliative cancer and after various major surgeries such as knee arthroplasty,^{19,20} video-assisted thoracoscopic surgery,¹ and laparoscopic cholecystectomy.²¹ These data support our findings of a significant association between serum vitamin D levels and acute postoperative pain.

Conversely, some studies found no correlation between vitamin D levels and postoperative pain intensity or analgesic requirements.^{4,22} This discrepancy may stem from differences in study populations, vitamin D status, types of surgery, and

methodological limitations such as retrospective designs and varied postoperative pain management strategies. Our study, by contrast, benefits from a prospective observational design, a uniform surgical procedure for all patients, and standardized analgesic protocols.

Although a definitive physiological explanation for the connection between vitamin D and pain is lacking, vitamin D is hypothesized to modulate pain processing through anti-inflammatory and neuroprotective pathways. Preclinical evidence suggests that vitamin D may suppress the production of pro-inflammatory cytokines (eg, tumor necrosis factor- α , interleukin-6) and prostaglandin E₂.^{23–25} Furthermore, vitamin D deficiency has been postulated to induce peripheral nerve hypersensitivity and central sensitization, potentially lowering the physiological pain threshold.^{14,16}

In our study, vitamin D deficiency was associated with a higher consumption of both intraoperative fentanyl and postoperative tramadol in the first 24 hours. While the increase in intraoperative fentanyl use was statistically significant, the absolute difference was modest, likely reflecting the standardized nature of intraoperative analgesia. In contrast, postoperative tramadol consumption via PCA showed a substantial and clinically relevant increase in the deficient group during the first 24 hours. This is consistent with Xia *et al*, who reported higher opioid use in vitamin D-deficient patients undergoing colorectal cancer surgery.²⁶

We also observed higher occurrences of postoperative nausea and vomiting in the vitamin D-deficient group, likely due to higher opioid consumption—a known risk factor for postoperative nausea and vomiting. Similar findings were reported by Zeng *et al* following video-assisted thoracoscopic surgery.¹ Although vomiting occurrence was higher in the vitamin D-deficient group, it did not reach significance. Likewise, while patient satisfaction was favorable in the vitamin D-sufficient group, the difference was not significant, possibly due to the multifactorial nature of patient satisfaction. Vitamin D-deficient patients had longer hospital stays, although our study design could not determine the cause; in addition, the clinical importance of such a small difference is questionable.

Limitations

This study has some limitations. It was conducted at a single center and all participants were Egyptian, which may limit the generalizability of the findings. The short follow-up period prevented us from evaluating the association between vitamin D deficiency and chronic postoperative pain. Furthermore, we did not assess inflammatory markers, limiting our ability to explore the mechanisms underlying the relationship between vitamin D and pain. Also, we did not collect data on preoperative anxiety, depression, cancer stage, preoperative neoadjuvant therapy, or sleep disturbance. Because of the potential for residual confounding inherent in an observational design, these observed associations should be interpreted with caution. While our findings demonstrate a strong association between preoperative vitamin D deficiency and increased postoperative pain, the study design precludes us from establishing a direct causal relationship. Future randomized and interventional trials are needed to confirm these findings and better understand the modulatory role of vitamin D in postoperative analgesia.

CONCLUSION

Vitamin D deficiency is associated with a higher occurrence of moderate to severe postoperative pain and increased opioid

consumption in patients undergoing unilateral modified radical mastectomy.

Contributors Conceptualization: MAA, DHM. Methodology: MLB, MHR, SGR. Formal analysis: MAA, MAH, MHR. Investigation: DHM, MLB. Resources: DHM, MHR. Data curation: MAA, MLB. Writing - original draft: DHM, MHR, SGR. Writing - review and editing: MAA, MLB, MAH, SGR, DHM, MHR. Visualization: MAA, SGR. Supervision: MAH, MLB. Project administration: MAA, MAH. MAA is the guarantor of this work.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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