

Original Article

Running Title: Post-Treatment Breast Pain in Breast Cancer Patients

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Investigating Post-treatment Breast Pain Severity in Breast Cancer Patients and Its Correlation with Serum Vitamin D and hs-CRP Levels

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Abstract

Background: Current data indicate that serum vitamin D and susceptible C-reactive protein (hs-CRP) levels, both indicative of the inflammatory state, have the potential to predict the onset and severity of chronic pain. Therefore, the objective was to assess the intensity of pain experienced after breast cancer treatment and its relationship with these two parameters.

Method: In this cross-sectional study between 2019 and 2021, 201 patients were enrolled. The McGill Pain Questionnaire was employed to evaluate localized pain intensity at the site six months after the conclusion of cancer treatments. Patients were stratified based on the type of breast surgery, with or without a tissue expander, axillary region surgery, chemotherapy treatment, radiotherapy treatment, serum vitamin D levels, serum hs-CRP levels, and pain intensity. Data analysis was performed using SPSS 21 software with a significance level set at 0.05.

Results: Among the patients, 67.6% (136 individuals) reported mild pain, 31.3% (63 individuals) reported moderate pain, and 1% (2 individuals) reported severe pain. The results of this study demonstrated a positive correlation between high serum hs-CRP levels and increased pain intensity, with serum marker levels being higher in patients experiencing more severe pain compared to those with milder pain. However, no statistically significant association was observed between various serum concentrations of vitamin D and pain intensity ($P = 0.12$).

Conclusion: Elevated levels of inflammatory factors, such as hs-CRP, are linked to a higher likelihood of developing chronic post-surgical pain.

Keywords: Breast neoplasms, Pain, Vitamin D, C - reactive protein, Inflammation

Introduction

Breast cancer is the most common malignancy in women. After the treatment procedures and during the follow-up, most patients complain of chronic pain in the surgical site, the upper limb, and the hemithorax on the affected side. Despite additional investigations to rule out metastasis, no clear cause is often identified for this pain.¹ Studies demonstrate that regardless of the type of surgery (breast-conserving surgery or mastectomy), more than half of the patients suffer from chronic pain.^{2,3}

Among the diverse biological effects of vitamin D that are currently receiving more attention, there are multiple studies about the role of vitamin D deficiency in the occurrence and persistence of pain.⁴ However, due to the many underlying causes affecting chronic pain, the results reported in previous studies are not uniform, and only 25% have reported a significant correlation.⁵ Susceptible C-reactive protein (Hs-CRP) is a more sensitive type of CRP (C-Reactive Protein) test that detects minimal changes within the normal range of the standard CRP testing, demonstrating the presence of low-grade systemic inflammation.⁶ Due to the critical role of inflammation in the occurrence and spread of malignant tumors, this marker has also been proposed and investigated in studies as a tool to estimate the risk of occurrence or spread of cancer.^{7,8} Additionally, it has been suggested as a marker for various complications in breast cancer patients (including skin reactions related to radiotherapy, cardiac complications, and depression), as well as postoperative pain syndromes.⁸⁻¹⁰ The notable importance of demonstrating this association is linking pain to inflammatory processes and highlighting the role of anti-inflammatory medications in prevention and treatment.¹¹ Cohort studies of patients with post-surgical neuropathic pain have

demonstrated a direct relationship between this complication and the hs-CRP levels.¹²

The objective was to evaluate pain intensity after breast cancer treatment and its relationship with the serum vitamin D and Hs CRP levels in patients presenting to the oncology clinic.

Methods

Study design

The McGill Pain Questionnaire was used to assess pain.^{13,14} It is the most frequently used questionnaire for the multidimensional assessment of pain, and its Persian translation is culturally appropriate and reliable enough for use in epidemiological studies. It has been effectively used in research related to breast cancer.¹⁵ The questionnaire contains 20 questions along 4 dimensions. A <25 (out of 75) score was considered mild pain, 25 to 45 moderate pain, and >45 severe pain.

For each patient, a questionnaire was completed during pain, and blood samples were taken simultaneously to check the serum vitamin D and CRP levels. High-performance liquid chromatography (HPLC) was used to measure serum vitamin D concentrations, and a particle enhancement immunoturbidimetric assay was used to measure hs-CRP concentrations. Vitamin D levels below 10 nanograms/ml were considered deficient, between 11 and 29 were considered disproportionate, between 30 and 150 were normal, and above 150 were considered toxic. Serum hs-CRP levels were reported as usual (Less than 0.3 mg/dL) and high risk (≥ 0.3 mg/dL). This is because a high-risk value represents a high risk of inflammation. Patients were further classified according to the type of breast surgery (breast-conserving surgery (BCS) or modified radical mastectomy (MRM), lymph node surgery, axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB), chemotherapy treatment, type of radiotherapy, and the presence or absence of

comorbidities (diabetes and blood pressure). Chronic pain severity was also compared between different subgroups.

Participants

In this cross-sectional study, 201 patients were examined at two prominent tertiary referral cancer centers in Mashhad, Iran: the Imam Reza Cancer Clinic and Omid Educational Hospital. Both institutions are affiliated with the Mashhad University of Medical Sciences. The study spanned from August 2019 to February 2022.

The study's inclusion criteria required patients to have non-metastatic breast cancer and to present with complaints of breast pain. Additionally, participants were expected to have no orthopedic issues in the study area. Eligible participants must have completed their oncology treatment, which included surgery, radiotherapy, and chemotherapy, at least 6 months and up to 5 years prior. Exclusion criteria comprised the presence of cancer recurrence, metastasis, and the absence of informed consent to participate in the study.

Ethical approval

The research protocol received approval from the Ethics Committee of Mashhad University of Medical Sciences under approval code IR.MUMS.fm.REC.1399.024. Informed written consent was obtained from all patients before their participation.

Sample size

The sample size was determined using the following formula to estimate the mean of total pain scores based on the McGill questionnaire. With alpha set at 0.05, beta at 0.2, $d = 0.30$, and $s = 2.10$, as per Johanssen et al.'s¹, a sample size of 200 people was estimated.

$$n = \frac{z^2_{1-\frac{\alpha}{2}} s^2}{d^2}$$

Statistical analysis

Qualitative data were compared using the chi-square test, whereas the independent t-

test was employed for comparing quantitative data between two groups. The ANOVA test was applied for comparisons involving three or more groups, with a significance level 0.05. (SPSS Inc., Chicago, IL).

Results

Participants

A total of 201 breast cancer patients, with a mean age of 51 ± 10.6 years, were examined, comprising 198 women and 3 men. The general characteristics of the patients are detailed in Table 1. Postoperative complications included 2 cases of abscess, 30 cases of seroma formation, 11 cases of surgical site infection, and 10 cases of acute postoperative pain, as illustrated in figure 1.

Main results

The mean score on the McGill Pain Questionnaire was 16.6 ± 10.4 . Mild, moderate, and severe pain were reported by 67.6% (136), 31.3% (63), and 1% (2) of participants, respectively. Table 2 elucidates the relationship between pain intensity and other variables. Diabetes ($P = 0.30$) or hypertension ($P = 0.74$), type of mastectomy ($P = 0.20$), type of axillary surgery ($P = 0.30$), use of taxane-based chemotherapy (88, $P = 0.00$), and the presence of adjuvant radiotherapy ($P = 0.76$) did not exhibit significant associations with pain intensity. Marginally significant associations were observed between breast-conserving surgery ($P = 0.8$), sentinel lymph node biopsy ($P = 0.08$), and pain intensity.

An exploration of the relationship between elevated hs-CRP levels and pain intensity revealed that concentrations of this serum marker were higher in patients with severe pain compared with those with mild pain intensity. The rate of increased hs-CRP in patients with severe, moderate, and mild pain was 100%, 68.2%, and 7.3%, respectively ($P = 0.001$). Conversely, no significant association was found between different

serum vitamin D levels and pain intensity ($P = 0.12$), as detailed in tables 3 and 4.

Discussion

The present study showed that the frequency of mild, moderate, and severe pain was 67.6% (136), 31.3% (63) and 1% (2) respectively. Pain intensity was significantly related to CRP levels but not vitamin D levels.

In various studies, the incidence of pain after completion of treatment in breast cancer patients has been measured in different populations (considering racial and socioeconomic differences), with different research methods (including tools and questionnaires), as well as also different assessment intervals (postoperative, pre-radiation or post-radiation), demonstrating the eminence of this disturbing complication. Edmond et al. (2018) reported that the frequency and severity of chronic pain (6 months or more) were significantly higher in breast cancer patients compared to healthy individuals (in terms of frequency, 46.5% and 12.7%, respectively, with $P = 0.05$).³ The authors appear to have reported only the presence or absence of pain. The choice of this method may be due to the subjective nature of pain, which makes comparisons between studies difficult.^{13, 16} In contrast, in the studies reviewed by Wang et al.,¹⁷ various questionnaires were used to measure pain intensity, including the VAS, which is considered a fast and valid measurement tool for self-assessment of pain in patients aged 8 and above.¹⁶ In the present study, the McGill Pain Questionnaire was preferred, as a more detailed test was favored, and a specialized interview was used to record the results.

The systematic review by Wang et al. investigated and analyzed data from 187 studies, including 297,612 breast cancer patients, and demonstrated that the overall incidence of persistent pain after breast cancer surgery varies from 2% to 78% (with

an average of 37%). The prevalence of pain reported by the patients, of any intensity and in any area, was reported as 46%. About half of the patients had constant pain, and 1 in 4 patients experienced moderate to severe pain.¹⁷

In another study by Meretoja et al. on the incidence of chronic pain 12 months after breast cancer treatment, 16% of patients reported severe pain complications, and 50% reported mild to moderate pain.¹⁸ As the above studies show, a significant proportion of breast cancer patients will complain of chronic pain after completing treatment, which severely impacts their quality of life and mental health, as shown by Sipila et al. in a study regarding the role of chronic pain in psychological status and feeling well.¹⁹ Additionally, new research shows a link between this chronic pain and movement-related complaints and movement disorders in the upper extremities.^{20, 21} That said. However, according to the results of the study, patients' pain was only rated as severe in 1% of cases; any chronic pain reduces the quality of life of patients in many psychological and physical aspects.

The present study indicated that patients with chronic postoperative pain have higher hs-CRP levels. Consistent with the results of this study, Hashimoto et al. (2018) also showed that serum hs-CRP levels on the day of surgery are associated with chronic postoperative pain in breast cancer patients.²² Because serum hs-CRP levels were measured at least 6 months after completing the entire treatment process, further research is needed to determine the optimal timing for evaluating this serum marker. In a study by Lee et al. (2019), authors retrospectively assessed CRP before and after adjuvant radiotherapy in 366 women with breast cancer.

They reported that the pain rate was 17% before the start of radiation therapy and increased to 30% in the post-radiation survey.

Pre-irradiation evaluation also showed that the higher the CRP value, the more intense the pain. The presence of pre-RT serum CRP concentration ≥ 10 mg/L was found to be associated with a twofold risk of post-treatment pain. This association was more pronounced in obese women with breast cancer.²³ Starkweather et al. evaluated the relationship between serum levels of pro-inflammatory and anti-inflammatory cytokines and chronic pain and fatigue in women with early-stage breast cancer. Patients complaining of chronic pain after surgery had higher serum CRP levels ($P < 0.01$).²⁴

Previous studies revealed that oncologic treatments such as chemotherapy, especially radiotherapy, are associated with the induction of immune/inflammatory responses.^{25, 26} On the other hand, animal and human²⁷ studies have shown a significant positive correlation between increased inflammatory cytokines and pain intensity. In addition to the association of pain with inflammatory factors such as CRP, increased pro-inflammatory cytokines after cancer treatment are associated with other disorders such as persistent fatigue and sleep disturbances in breast cancer patients.^{10, 28} These findings may point to a common cause of symptoms and complications associated with cancer treatment. Since the immune/inflammatory system influences the symptoms and complications associated with cancer treatment, anti-inflammatory agents can be considered preventive.

Further evidence, in line with the study, is the prospective research by Perry et al., reporting that caspase-1 p17 and hs-CRP levels were increased in patients with higher scores concerning chronic fatigue and breast pain.²⁹ Considering the risk factors for postoperative pain in breast cancer patients, including young age, degree of axillary lymph node dissection, chronic preoperative pain, preoperative breast pain, surgery, high body

mass index, use of adjuvant radiation therapy, severe acute postoperative pain, and psychosocial factors (e.g., anxiety, depression, catastrophizing, somatization),^{30, 31} testing of serologic parameters such as hs-CRP levels can identify subgroups of patients with risk of post-surgical pain. Therefore, providing preoperative counseling can help align physician and patient expectations.

In the present study, there was no significant association between serum vitamin D levels and the development of chronic pain after completion of tumor treatment in breast cancer patients.

Serum level of vitamin D affects breast cancer patients in different aspects. Various studies have shown its impact on disease occurrence, progression, and prognosis, along with influences on fatigue levels, chronic musculoskeletal pain, mental health, and quality of life.³²

Recently, in a review study, Habib et al. explained the various mechanisms of the effect of vitamin D and its receptor (VDR) on the pathways of pain sensation.⁴ Among these pathways are the posterior horn ganglia and the pathways of nerve growth factor, glial-derived neurotrophic factor, epidermal growth factor receptor, and opioid receptors (Figure 2). Vitamin D also affects the production and secretion of cytokines.³³ Although the above biological effects suggest a general association, in a review of 81 articles (50,834 patients in total), Wu et al. inferred that the relationship between mean serum levels of 25(OH) D and the occurrence of chronic pain is not the same for different organs, suggesting that widespread pain and chronic headaches were not related to vitamin D levels, but localized pain such as that caused by arthritis or muscle pain were aggravated due to lower levels of vitamin D.³⁴

So far, the relationship between serum vitamin D levels and postoperative pain in breast cancer survivors has not been studied.

However, in some studies, its relationship with chronic pain in metastatic patients,³⁵ and pain related to certain medications such as hormone therapies,^{35, 36} was observed. In a systematic review by Zarrati et al., of nine studies evaluating the outcomes of vitamin D supplementation in patients with various cancers, six studies reported a significant decrease in treatment-related pain.³⁷ Andersen et al. investigated the effect of vitamin D supplementation on the quality of life of 553 breast cancer patients/survivors. The researchers used the SF-36 (the 36-item Short Form Health Survey questionnaire), which includes physical functioning, physical role, pain, general health, vitality, social functioning, and emotional and mental health measures. This form was filled at baseline and 6 months after completing treatment. Although there were no significant changes in pain factors at baseline, consumers of vitamin D supplements reported less pain, improved general well-being, and more energy after six months of follow-up. ($P < 0.05$ for all cases).³²

In the present study, serum hs-CRP and vitamin D levels were assessed during the chronic pain evaluation of the patients. This approach stands as the primary strength of this investigation. Regrettably, elucidating variations occurring during these diverse treatments was impossible due to the absence of baseline assessments of serum hs-CRP and vitamin D levels prior to surgical, chemotherapeutic, and radiotherapeutic interventions. This constitutes the principal constraint of the current research. The concurrence of this project with the COVID-19 pandemic and the heightened, indiscriminate utilization of vitamin D-containing supplements could be considered another constraining factor affecting the interpretation of the findings. Moreover, considering the substantial prevalence of vitamin D deficiency in the general populace, particularly amongst breast cancer patients,³⁸

there arises a necessity for comprehensive large-scale investigations to draw conclusive inferences.

Conclusion

According to the results of this study, mild, moderate, and severe pain were reported by 67.6% (136), 31.3% (63), and 1% (2), respectively. The results of this study showed that the presence of high levels of inflammatory factors such as hs-CRP is associated with a higher likelihood of being diagnosed with chronic pain, highlighting the role of anti-inflammatory medications in prevention and treatment. Vitamin D levels in breast cancer patients were not related to pain levels.

Data availability statement

All data generated during this study can be accessed through direct communication with the corresponding author and the agreement of all research team members.

Acknowledgment

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Conflict of Interest

None declared.

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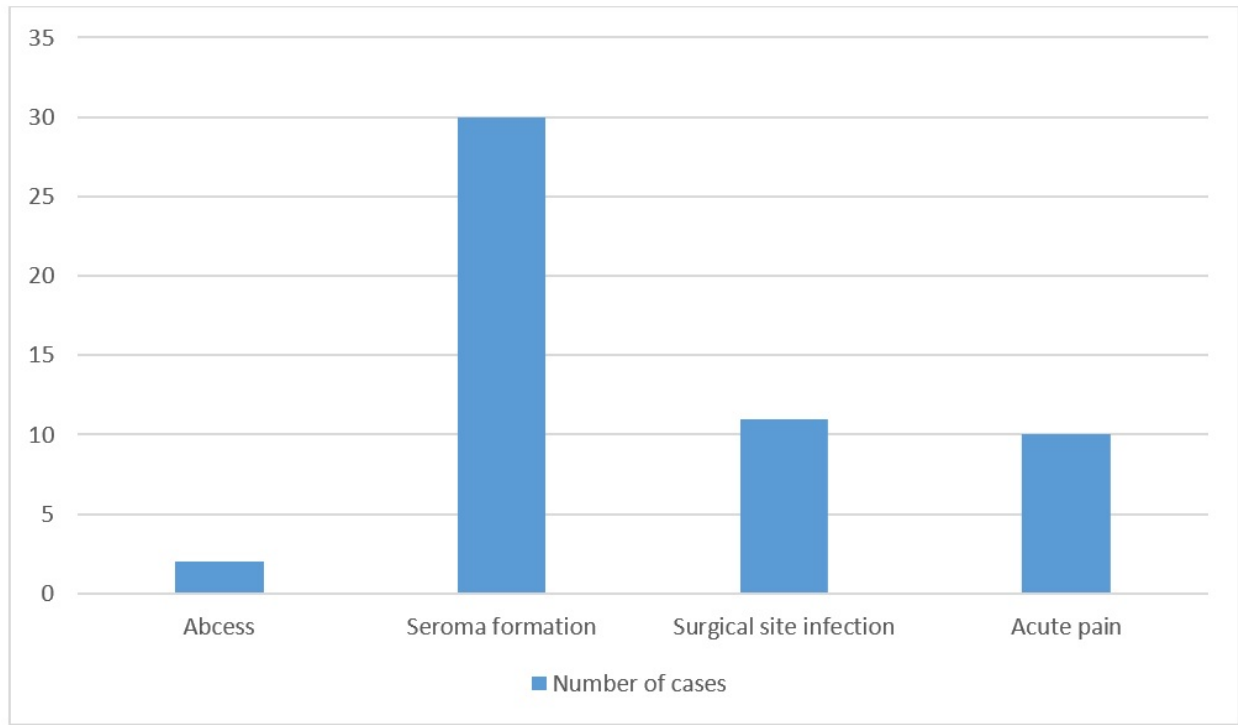


Figure 1. The frequency of postoperative complications in 201 breast cancer patients is demonstrated in a chart. After surgery, seroma formation was the most commonly reported complication, with 30 cases.

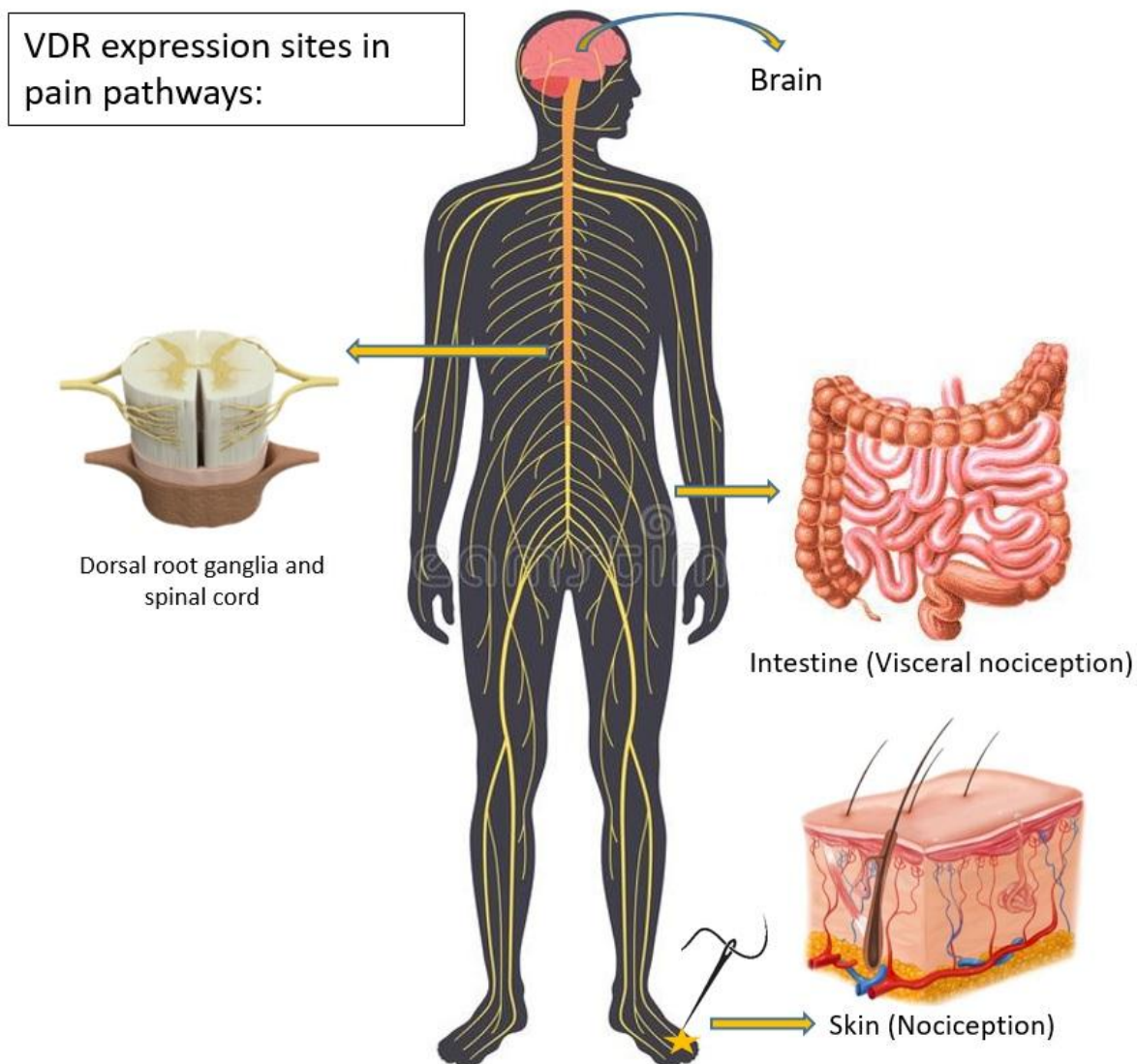


Figure 2. VDR expression sites in pain pathways. VDR is expressed through nociceptive pathways in the central nervous system and at receptors in dermal and intestinal structures. (The present figure is an illustrated summary based on the study's findings by Habib et al.⁴ For a more comprehensive illustration, refer to the images and content provided by the reference.)

VDR: Vitamin D receptor

Table 1. Overall patient characteristics

		Number of patients	Percent
Male		3	1.5
Female		198	98.5
Premenopausal		97	49
Perimenopause		16	8
Postmenopausal		85	43
Molecular subtype	Hr + Her 2 –	132	65.6
	Hr + Her 2 +	25	12.4
	Hr – Her 2 +	18	8.9
	TNBC	26	13.1
Stage T	In situ	4	2
	1	52	26.2
	2	111	56
	3	29	14.6
	4	1	1
Stage N	0	95	48
	1	72	36.3
	2	22	11.1
	3	9	4.5
Time since operation	1 year	25	12.4
	2 years	55	27.3
	3 years	31	15.4
	4 years	28	13.9
	5 years	62	30.8
Type of breast surgery	Modified radical mastectomy	120	59.7
	Partial mastectomy	81	40.3
	Reconstructive surgery	10	4.5
Type of axillary surgery	SLNB	56	27.9
	ALND	145	72.1

Hr: Hormone receptor; TNBC: Triple-negative breast cancer; SLNB: Sentinel lymph node biopsy; ALND: Axillary lymph node dissection

Table 2. Patients' conditions and treatments in the three groups of severe pain, moderate pain, and minimal pain; Number of patients (percent)

Variables	All	Severe pain	Moderate pain	Minimal pain	P-value
DM					
+	29(14.40)	0(0.00)	11(37.90)	18(62.00)	0.30
-	172(85.60)	2(01.10)	43(25.00)	127(73.80)	
HTN					
+	33(16.40)	0(0.00)	10(30.30)	23(69.70)	0.74
-	168(83.60)	2(01.10)	44(26.10)	122(74.10)	
Sx of breast					
BCS	120(59.70)	1(01.20)	15(18.50)	65(80.20)	0.08
MRM	81(40.30)	1(0.80)	39(32.50)	80(66.60)	
ALND					
+	145(72.10)	1(0.60)	44(29.30)	105(70.00)	0.30
-	56(27.90)	1(01.90)	10(19.60)	40(78.40)	
SLNB					
+	56(27.90)	1(01.70)	9(16.00)	46(82.10)	0.08
-	145(72.10)	1(0.60)	45(31.00)	99(68.20)	
Chemotherapy					
Taxan Based	168(91.30)	2(01.10)	46(270)	120(71.40)	0.88
Other	16(08.70)	0(0.00)	4(25.00)	12(75.00)	
Hypofx RT					
+	11(4.80)	0(0.00)	2(18.10)	9(81.80)	0.76
-	190(95.20)	2(1.20)	43(26.30)	118(72.30)	
IORT					
+	3(1.70)	0(0.00)	1(33.00)	2(66.60)	0.94
-	198(98.30)	2(01.10)	44(25.70)	125(73.00)	

DM: Diabetes mellitus; HTN: Hypertension; Sx: Surgery; BCS: Breast conserving surgery; MRM: Modified radical mastectomy; ALND: Axillary lymph node dissection; SLNB: Sentinel lymph node biopsy; Hypofx RT: Hypo-fractionated radiotherapy; IORT: Intra operative radiotherapy

Table 3. The relationship between elevated hs-CRP levels and pain intensity: Number of patients (percent)

	Severe pain	Moderate pain	Minimal pain	P-value
Elevated hs-CRP (≥ 0.3 mg/dL)	2(100.00)	43(68.20)	10(7.30)	0.001
Normal hs-CRP (< 0.3 mg/dL)	0(0.00)	20(31.70)	126(92.60)	

hs-CRP: highly-sensitive C-reactive protein

Table 4. The relationship between serum vitamin D levels and pain intensity: Number of patients (percent)

Vitamin D serum levels	Severe pain	Moderate pain	Minimal pain	P-value
Deficient (<10 ng/ml)	(6/30) 5	(5/9) 6	(0)0	0.12
Insufficient (11-29 ng/ml)	(3/46) 63	(4/44) 28	(100.00) 2	
Sufficient (30-150 ng/ml)	(50) 68	(8/42) 27	(0)0	
Toxic (>150 ng/ml)	(0)0	(1/3) 2	(0)0	