

Prevalence and Risk Factors of Persistent Pain after Treatment among Breast Cancer Patients in King Abdulaziz University Hospital: A Cross-Sectional Study

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ABSTRACT

Breast cancer (BC) presents a unique treatment challenge due to its individual variability. The potential side effects of multiple treatments, such as persistent pain and sensory disturbance, are a significant concern. Despite this, there are few studies on the prevalence of chronic pain in Saudi Arabia. Our study, therefore, holds particular relevance, as we aimed to assess the prevalence of persistent pain after therapy experienced by patients with BC and to investigate its risk factors. We conducted this non-interventional cross-sectional study in June 2021 at a King Abdulaziz University Hospital, Jeddah, Saudi Arabia. All patients with BC who received surgical treatment and adjuvant radiotherapy were included. Data were collected through the hospital's medical records and validated questionnaires during phone calls. Our study included 234 participants, of whom 69.7% reported persistent pain after treatment, predominantly in the breast area. Most patients rated the pain as severe in almost all areas. Neoadjuvant chemotherapy ($p = 0.026$) and adjuvant chemotherapy ($p = 0.010$) were the only identifiable risk factors for chronic pain. A total of 114 patients took analgesics, which managed the pain for 95.6% of them. More than half (139) reported sensory disturbance after treatment, the arm being the most reported area. Persistent pain after treatment was highly prevalent in our study. Therefore, we strongly recommend that physicians enhance the management of this sequela during follow-up visits after treatment.

Keywords: Pain, breast cancer, radiotherapy, chemotherapy

INTRODUCTION

Breast cancer (BC) is the most frequent cancer in females today. About one million new cases are identified each year, accounting for about 25% of all malignancies among women¹⁻³. BC is also the most common cancer among females in Saudi Arabia, with a reported 7,358 patients in 2016⁴. Recent studies showed a tremendous rise in the incidence of BC in the Saudi population, representing a nearly 10-fold increase over reported cases in the past^{5,6}.

BC treatment differs depending on the type, grade, and stage of cancer, as well as on other special situations⁴. It includes a variety of locoregional and systemic treatments. Most patients undergo surgery, which involves either breast-conserving surgery or mastectomy⁷. Some require systemic treatment such as neoadjuvant chemotherapy to downstage bulky tumors or adjuvant radiotherapy to increase the chances of a disease-free recovery and overall survival^{1,8}. As a consequence of the treatment, persistent pain is a possible side effect⁹.

Pain affects between 25% and 60% of all patients and was rated as moderate to severe in 50% of patients¹⁰. Many studies suggested persistent pain contributed to poor quality of life, revealing that women with persistent pain were experiencing high rates of emotional distress, losing hope against illness, and experiencing more sleep disturbances, anxiety, and depression than were women without pain¹¹⁻¹⁴. Other studies showed that persistent pain has a negative effect on patients' social and physical well-being^{15,16} and that it contributes to a higher risk

of unemployment and higher healthcare costs¹⁷⁻²⁰.

Common associated risk factors for chronic pain include type of surgery, axillary lymph node dissection (ALND), radiotherapy, hormonal therapy, and chemotherapy^{10,11,21}. One study published in India concluded that younger age was significantly correlated with higher pain scores¹¹. A prospective observational study conducted in the United States suggested that surgical skills and an increase in operative time were linked with greater severity of pain²². According to a study published in 2017, high body mass index was linked to a higher pain symptom score, a lower degree of function, and relatively lower life quality scores²³. Although many studies suggested that pain may be due to a nerve fiber injury that occurred during surgery or was secondary to adjuvant radiotherapy or chemotherapy²⁴, the exact mechanism is uncertain; however, it is most likely multifactorial²⁵.

Despite improved treatment techniques, persistent pain after BC treatments remains a serious clinical concern, as it affects a noteworthy percentage of patients. In addition, because of the high survivorship, understanding and identifying the risk factors is essential to help manage patient pain and minimize this outcome. To our knowledge, there is a paucity of studies that have reported the prevalence and impact of chronic pain in Saudi Arabia. In our study, we therefore aimed to assess the prevalence of persistent pain after therapy experienced by patients with BC at our institution and to demonstrate the risk factors associated with it.

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METHODS

Study design and setting: This non-interventional cross-sectional study was conducted in June 2021 at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. We included all adult patients with BC who had undergone surgical intervention and adjuvant radiotherapy. Patients with BC recurrence, metastasis, or active cancer and those who had undergone breast reconstruction or were deceased were excluded from the study. The primary objective was to assess the prevalence of persistent pain after therapy experienced by patients with BC. The secondary objective was to investigate the risk factors associated with persistent pain after treatment.

Participants: All adult patients diagnosed with breast cancer (BC) who underwent surgical intervention and adjuvant radiotherapy during the study period were included.

Data collection instruments: Patients' demographic and clinical details regarding the risk factors were obtained from the electronic medical records, which included: nationality, pathological subtypes, type of axillary surgery, type of breast surgery, radiotherapy, adjuvant chemotherapy, neoadjuvant chemotherapy, hormonal treatment, diabetes and smoking.

Questionnaire: Data concerning persistent pain were collected via a validated questionnaire by using Google forms filled out by the research members that were based on phone interviews with participants^{10,26}. We used the standard "forward-backward" translation process to translate the questionnaire from English to Arabic. It consisted of 16 questions divided into three parts. In the first part, we obtained the participant's consent. The second part included questions regarding pain, including the area of pain (breast, side of body, axilla, arm) and pain frequency in each area (every day or almost every day, 1-3 days a week, or rarely). We also asked participants to rate the pain severity in each region by

using a 0–10 numerical rating system, in which zero indicated no pain and 10 indicated the worst pain imaginable^{27,28}. For reporting the results of pain severity, light pain was assigned a score of 1 to 3, moderate pain a score of 4 to 6, and severe pain a score of 7 to 10. Questions about contacting a doctor, taking painkillers, or receiving other kinds of therapy due to pain were also asked. Aside from the questionnaire, we also asked them whether these interventions helped them with the pain. The third part inquired as to whether the patient experienced sensory disturbance or discomfort and to identify the location, if any. The last question asked about feeling pain in other parts of the body.

Statistical analysis: We used Microsoft Excel 2016 for data entry and IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA) for statistical analysis. Prevalence was calculated as a percentage with a 95% confidence level. Categorical variables were represented as frequencies, and the chi-square test was used for categorical variables. A P-value of < 0.05 was considered significant.

Research ethics: The Institutional Review Board of the biomedical ethical committee approved this study (Ref: 301-21). We obtained consent from all participants and notified them about the study objectives and the confidentiality of their responses. All of their information was handled privately and was accessed only by the research team members. Furthermore, names and ID numbers were not recorded in the data collection form.

RESULTS

Participants and Descriptive Data

A total of 234 female patients were included. Half of the patients enrolled in the study were Saudi (52.6%). Only 43 (18.4%) had diabetes, and the majority were nonsmokers (94.9%). All relevant clinical variables of the participants are summarized in Table 1.

Table 1. Clinical Variables

Variable	Frequency (%)
Nationality	
Saudi	123 (52.6%)
Non-Saudi	111 (47.4%)
Pathological subtypes	
DCIS	10 (4.3%)
IDC	201 (85.9%)
ILC	20 (8.5%)
LCIS	1 (0.4%)
Other	2 (0.9%)
Type of axillary surgery	
ALND	146 (62.4%)
SLNB	88 (37.6%)
Type of breast surgery	
BCS	101 (43.2%)
Mastectomy	89 (38.0%)
Mastectomy with immediate reconstruction	44 (18.8%)
Radiotherapy	
Yes	195 (83.3%)
No	39 (16.7%)
Adjuvant chemotherapy	
Yes	125 (53.4%)
No	109 (46.6%)
Neoadjuvant chemotherapy	
Yes	84 (35.9%)
No	150 (64.1%)
Hormonal treatment	
Yes	156 (66.7%)
No	78 (33.3%)

Clinical T	
T1	58 (24.8%)
T2	123 (52.6%)
T3	26 (11.1%)
T4	14 (6.0%)
Tis	4 (1.7%)
No data	9 (3.8%)
Clinical N	
No	78 (33.3%)
N1	118 (50.4%)
N2	26 (11.1%)
N3	4 (1.7%)
No data	8 (3.4%)
Diabetes mellitus	
Yes	43 (18.4%)
No	191 (81.6%)
Smoking	
Yes	12 (5.1%)
No	222 (94.9%)

DCIS: ductal carcinoma in situ; IDC: infiltrating ductal carcinoma; ILC: infiltrating lobular carcinoma; LCIS: lobular carcinoma in situ; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy; BCS: breast-conserving surgery

Table 2. Prevalence of Chronic pain in each area

Location	Frequency (%)
n=163 (69.7%)	
Area of the breast	
Yes	141 (86.5%)
No	22 (13.5%)
Side of the body	
Yes	37 (22.7%)
No	126 (77.3%)
Armpit	
Yes	89 (54.6%)
No	74 (45.4%)
Arm	
Yes	82 (50.3%)
No	81 (49.7%)

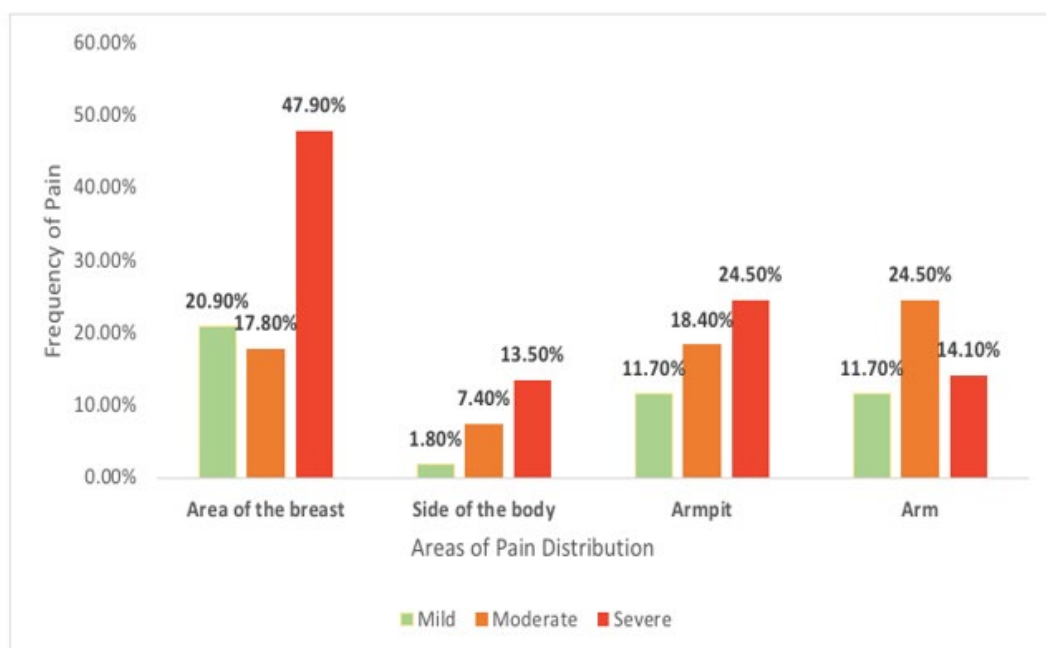


Figure 1. The severity of chronic pain in each area

Main Outcome

Of the 234 participants we contacted and who completed the questionnaire, 163 (69.7%) reported having pain in at least one of the four areas listed in Table 2. The breast area was the most reported area of pain ($n = 141$, 60.3%), followed by the armpit ($n = 89$, 38%), the arm ($n = 82$, 35%), and the side of the body ($n = 37$, 15.8%). Regarding the severity of pain, most patients rated the pain as severe in almost all areas. Among those who reported pain in the breast, 80 patients rated it as severe, whereas only 24 rated the pain as severe in the arm (Figure 1). A total of 53 women experienced pain in the breast every day or almost every day. The frequency of pain in each of the four locations is shown in Figure 2.

Of the 163 patients who reported persistent pain, 63 (38.6%) contacted a doctor in the last 3 months due to persistent pain on the side where the surgery was performed. A total of 114 (69.9%) patients took painkillers; in almost all of these patients, they helped relieve the pain ($n = 109$,

95.6%). In addition, 68 (41.7%) patients received treatments other than medications, such as physical therapy, massage, and chiropractic, which managed the pain for 82.3% of them.

Overall, 139 (59.4%) women reported having sensory disturbances or discomfort after treatment. The most frequent area that they reported to be associated with sensory disturbances was the arm ($n = 95$, 68.3%), followed by the breast ($n = 81$, 58.3%), armpit ($n = 68$, 48.9%), and the side of the body ($n = 28$, 20.1%) (Figure 3).

Risk factors

Eight variables were assessed as potential risk factors for persistent pain. The significance of each variable is summarized in Table 3. A statistically significant association existed between persistent pain after therapy with adjuvant chemotherapy ($p = 0.010$) and neoadjuvant chemotherapy ($p = 0.026$). However, type of breast surgery, type of axillary surgery, hormonal treatment, radiotherapy, diabetes mellitus (DM), and smoking were not found to correlate with persistent pain.

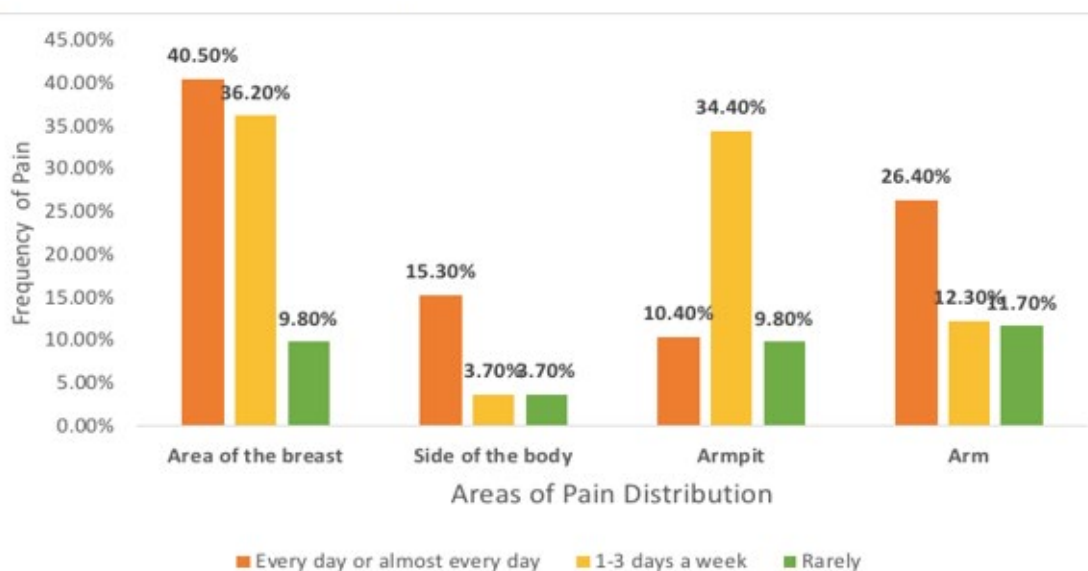


Figure 2. The frequency of chronic pain in each area

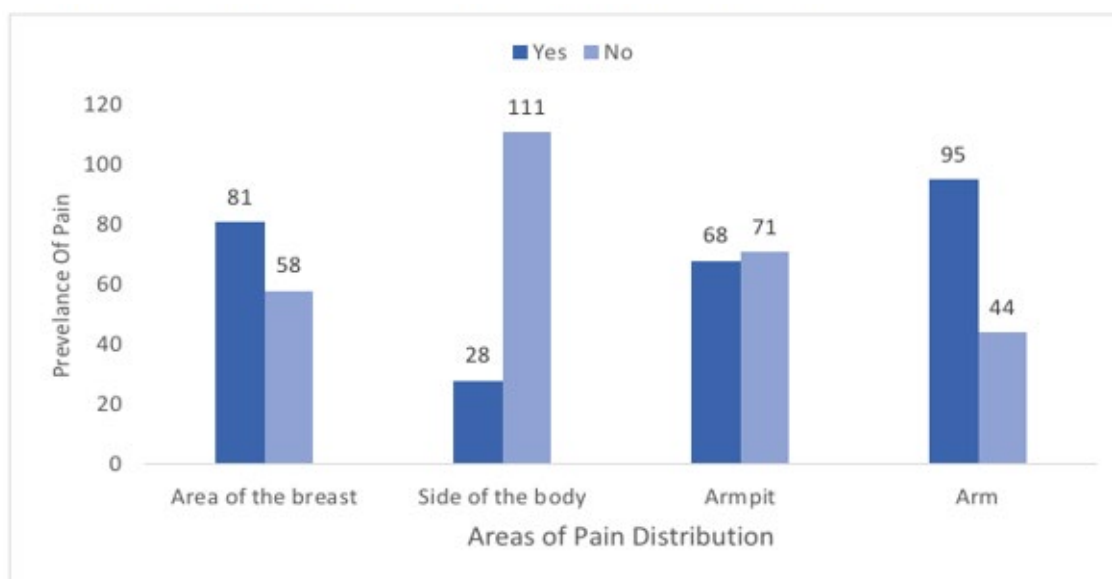


Figure 3. The prevalence of sensory disturbance in each area

Table 3. Risk factors of chronic pain

Variable	Do you have pain in the area of the breast, armpit, side of the body, or arm on the side where you were operated?		P-value
	Yes	No	
Type of breast surgery			
BCS	69 (42.3%)	32 (45.1%)	0.134
Mastectomy	58 (35.6%)	31 (43.7%)	
Mastectomy with immediate reconstruction	36 (22.1%)	8(11.3%)	
Type of axillary surgery			
ALND	101 (62.0%)	45 (63.4%)	0.837
SLNB	62 (38.0%)	26 (36.6%)	
Neoadjuvant chemotherapy			
Yes	66 (40.5%)	18 (25.4%)	0.026*
No	97 (59.5%)	53 (74.6%)	
Radiotherapy			
Yes	137 (84.0%)	58 (81.7%)	0.656
No	26 (16.0%)	13 (18.3%)	
Hormonal treatment			
Yes	111 (68.1%)	45 (63.4%)	0.482
No	52 (31.9%)	26 (36.6%)	
Adjuvant chemotherapy			
Yes	78 (47.9%)	47 (66.2%)	0.010*
No	85 (52.1%)	24 (33.8%)	
Diabetes mellitus			
Yes	27 (16.6%)	16 (22.5%)	0.278
No	136 (83.4%)	55 (77.5%)	
Smoking			
Yes	10 (6.1%)	2 (2.8%)	0.29
No	153 (93.9%)	69 (97.2%)	
BCS: breast-conserving surgery; ALND: axillary lymph node dissection; SLNB: sentinel lymph node biopsy			
*p-value less than or equal to 0.05 was considered significant			

DISCUSSION

Persistent pain

In this study, we aimed to investigate the prevalence and risk factors associated with persistent pain after therapy in patients with BC at our institute. Chronic pain after treatment was found to be highly prevalent in our study, occurring in 69.7% of all participants. The majority of the patients rated their pain as severe. We found a higher percentage of patients with pain in our study than reported in other studies in the literature, where it varied between 27% and 64%^{10,11,13,23,28-36}. The range of chronic pain prevalence and severity reported in the literature can be attributed to the lack of a precise definition for persistent pain, different measurement scales for severity of pain, timing of assessment after surgery, variation in adjuvant treatments received in addition to surgery, a wide age range, and different ethnicities.

In our study, 38.6% of the patients contacted a physician to seek pain management, a higher rate than reported in other studies^{10,33}. We also found that 69.9% of patients took analgesics, and many received nonpharmacological treatments to help ease the pain. Chiang et al.³⁴ observed a correlation between pain severity and the consumption of analgesics when painkillers were more frequently used with moderate to severe pain. In addition, those who reported mild pain were less likely to consult a physician³³. All of these interventions helped significantly with persistent pain, showing a remarkably high percentage of pain relief in our patients. Thus, physicians should discuss and recommend pharmacological and nonpharmacological options to patients during follow-up after treatment for BC.

Sensory disturbance

Sensory disturbance was found in 59.4% of our enrolled participants. A nationwide study conducted in Denmark also reported that 58% of the patients reported sensory disturbances¹⁰. Multiple studies have reported that a large number of patients who experienced sensory disturbance also reported persistent pain, indicating a link between them, as those who reported sensory disturbances had an increased chance of developing chronic pain, which could be attributed to nerve damage due to the invasive nature of surgical procedures^{10,13}. Several studies concluded that there is a significant correlation between sensory disturbance and ALND^{10,37-40}. The invasiveness of the ALND procedure and the proximity of the site to the intercostobrachial and thoracic intercostal nerves makes it more prone to damage, thus causing persistent pain and sensory disturbance^{24,34,41}. Because it is more likely that sensory disturbance is discovered during clinical examination of patients, this issue is likely to be underestimated. Thus, more attention is required from physicians during follow-up visits^{37,42}.

Risk factors

We found no significant relationship between the type of breast surgery and persistent pain in this study, although the occurrence of pain was observed more in breast-conserving surgery than in mastectomy. Many studies have claimed similar outcomes^{10,23,30,34,36,41}. A possible explanation is that the duration of surgery and surgical complications could be influencing factors, which makes it difficult to draw a clear association between the type of breast surgery and persistent pain^{43,44}. On the other hand, several studies have found that radical mastectomies were more of a risk factor for chronic pain than were other surgeries⁴⁵⁻⁴⁷.

Throughout the literature, axillary surgeries have been reported to be inconsistent in terms of chronic pain. Although most studies identified axillary procedures as a risk factor for chronic pain following treatment^{10,23,28,31,32,36,37}, other studies reported a difference in the significance between ALND and sentinel lymph node biopsy (SLNB). ALND was more frequently reported to cause persistent pain than was SLNB, as it carries a higher risk of injury to nearby structures^{11,38,39,41}. Nevertheless, our study did not show that axillary procedures constitute a statistically significant risk factor for persistent pain. Meijuan et al. reported the same result¹³.

In our study, among other variables, we investigated the relationship between chemotherapy and the presence of persistent pain. The correlation between neoadjuvant chemotherapy and chronic pain was statistically significant ($p = 0.026$), as was the link between adjuvant chemotherapy and chronic pain ($p = 0.010$). Thus, patients who received chemotherapy had a higher likelihood of experiencing chronic pain. This outcome is comparable to the results of a systematic review in the literature, which concluded that chemotherapy was substantially linked with an increased risk of chronic pain⁴⁸. Several studies had similar conclusions^{23,28,33}. Contradictory to our findings, however, in a nationwide study, adjuvant chemotherapy had no independent connection with persistent pain and did not raise the likelihood of reporting sensory problems¹⁰. In another study conducted by Juhl et al., chemotherapy was only marginally significant as a risk factor for persistent pain²⁸. Several variables could contribute to these conflicting outcomes. One possibility is that younger women are more likely to receive chemotherapy and are at higher risk of persistent pain³³. Therefore, it is difficult to determine whether chemotherapy itself is the direct cause of the pain, or it is influenced by age. Another explanation is that patients requiring chemotherapy are likely to have a more advanced disease presentation, thus requiring more invasive surgical techniques and a longer course of radiation. In addition, although many chemotherapeutic drugs used in patients with BC have a documented neurotoxic side effect, other drugs may not³⁷.

We did not identify an association between radiotherapy and persistent pain after BC treatment in our study. Several studies have also reported this negative association, in agreement with our finding^{13,28,29,38}. In contrast to our results, however, in multiple studies, radiotherapy was shown to be a potential risk factor for pain, hypothetically explained by damage to the nerve plexus due to radiation itself or fibrosis induced by the radiation^{10,31,32}. A study conducted in Denmark showed a significant relationship between radiotherapy and chronic pain¹⁰. However, in a follow-up to that study, radiation was no longer a risk factor³⁸.

Despite the fact that 66.7% of our participants received hormonal treatment, there was no significant correlation between such treatment and chronic pain. As far as we know, no statistically significant correlation between these factors has been shown in the literature, and authors of various studies have concluded that hormonal therapy is not a risk factor for chronic pain^{10,11,13,23,25,30,33,34,38,49-51}. Although it is known that some hormonal treatment can induce musculoskeletal pain, it has no effect on pain persistence in the breast after therapy⁵².

DM is shown to lower the overall health outcomes in patients with BC, including persistent pain after treatment⁵³. Several studies concluded that DM is a risk factor for persistent pain^{37,53,54}. However, there was no significant correlation between DM and persistent pain in the current study.

Likewise, smoking status was not statistically associated with chronic pain following treatment, although it was reported to be associated with chronic pain in another study³⁶. Van Helmond et al.²³ also did not find a

potential correlation between chronic pain and DM or between smoking and chronic pain, in concordance with our results. One explanation of our results could be the sample size and composition. Our study included a small number of diabetic patients and a predominantly nonsmoking sample. This perhaps makes it difficult to identify subtle differences or draw comprehensive conclusions regarding how smoking and diabetes affect chronic pain in BC survivors. As a result, the findings might not fairly represent the larger patient base, possibly missing complex relationships between these risk variables and the course of chronic pain.

This study's limitations must be addressed. First, its cross-sectional design cannot determine the exact cause of the associated risk factors. Second, the sample size is relatively small, as this study was conducted in a single center. Third, we did not specify the timeline of pain and sensory disturbance precisely.

CONCLUSION

In this study, we aimed to assess the prevalence of chronic pain following treatment in patients with BC and to demonstrate the possible risk factors. Almost 70% of patients experienced persistent pain, with neoadjuvant and adjuvant chemotherapy being potential risk factors. The use of painkillers proved to be effective in alleviating pain for nearly all patients. Our recommendation is for physicians to inform and discuss this matter with patients before treatment and to perform routine follow-ups while offering tailored management to each individual to enhance pain management and improve quality of life. In addition, we recommend that future researchers investigate the pattern of this sequela from a long-term perspective and develop strategies aimed at preventing this problem.

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Potential Conflicts of Interest: None

Competing Interest: None

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