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Association of First-Postoperative-Day C - reactive protein Levels with Early Postoperative Inflammatory Response after Mastectomy

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ABSTRACT

Introduction: Chronic post-mastectomy pain is a common and disabling survivorship problem, and growing evidence suggests that early postoperative inflammation may contribute to its development. C-reactive protein is an accessible biomarker of surgical inflammatory response. This study aimed to evaluate whether first-postoperative-day C-reactive protein levels are associated with subsequent chronic post-mastectomy pain.

Material and methods: This descriptive cross-sectional study was conducted at Tabriz University of Medical Sciences in 2022 on 50 women undergoing mastectomy, selected by convenience sampling. Sample size was estimated using the Cochran single-group formula. The main variables included first-postoperative-day serum C-reactive protein level and chronic post-mastectomy pain at follow-up, alongside demographic, clinical, surgical, oncologic, and postoperative variables potentially related to pain development.

Results: Among 50 women undergoing mastectomy, 19 (38.0%) developed chronic post-mastectomy pain. Mean first-postoperative-day CRP was significantly higher in patients with chronic pain than in those without pain (36.2 ± 11.6 vs 23.9 ± 8.7 mg/L, P<0.001). Axillary lymph node dissection (84.2% vs 54.8%, P=0.034), longer operative time (127.9 ± 25.1 vs 109.8 ± 21.6 minutes, P=0.011), and early postoperative complications (36.8% vs 12.9%, P=0.046) were also associated with pain development.

Conclusion: Elevated first-postoperative-day CRP was independently associated with chronic post-mastectomy pain, suggesting that an intensified early postoperative inflammatory response may play an important role in pain chronification after breast cancer surgery.

Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide, and surgical treatment continues to be a central component of curative care for a large proportion of patients. Although advances in oncologic surgery, perioperative medicine, and adjuvant therapies have improved survival, a growing body of evidence suggests that survivorship is often complicated by persistent pain syndromes that substantially impair long-term recovery.

Among these, chronic post-mastectomy pain has emerged as a clinically important and underrecognized consequence, affecting physical function, emotional well-being, sleep quality, and overall health-related quality of life long after wound healing is complete [1].

Chronic post-mastectomy pain is generally defined as pain persisting beyond the expected period of tissue healing, typically for at least three months after breast surgery, in the absence of other obvious causes such as local recurrence or infection.

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Its reported prevalence varies widely across studies because of differences in surgical procedures, diagnostic criteria, follow-up intervals, and patient populations, yet even conservative estimates indicate that a meaningful proportion of women continue to experience moderate to severe pain months or years after surgery. This variability underscores both the heterogeneity of the syndrome and the need for reliable early predictors that may help identify vulnerable patients before pain becomes entrenched [2].

The pathogenesis of chronic post-mastectomy pain is complex and likely multifactorial, involving peripheral nerve injury, central sensitization, psychological vulnerability, preexisting pain states, and perioperative inflammatory responses. Surgical disruption of the intercostobrachial nerve and other regional sensory pathways has long been implicated, but nerve injury alone does not fully explain why some patients recover uneventfully while others develop persistent pain despite apparently similar operations. Contemporary pain science increasingly supports the view that chronic postsurgical pain arises from the interaction between nociceptive input and host-specific biologic responses, of which inflammation may be a key mediator [3].

Inflammation plays a central role in tissue repair after surgery, yet excessive or dysregulated postoperative inflammatory activity may amplify nociceptor sensitivity and facilitate the transition from acute to chronic pain. Pro-inflammatory cytokines, acute-phase reactants, and neuroimmune signaling pathways can enhance peripheral sensitization, sustain spinal excitability, and alter descending pain modulation. In breast surgery specifically, the magnitude of local tissue trauma, axillary dissection, seroma formation, and adjuvant treatments may all contribute to a prolonged inflammatory milieu. Consequently, biomarkers reflecting early postoperative inflammation may offer a biologically plausible window into the mechanisms that precede chronic pain development [4].

C-reactive protein is among the most widely used and clinically accessible biomarkers of systemic inflammation. Synthesized predominantly by hepatocytes in response to interleukin-6 and other inflammatory mediators, C-reactive protein rises rapidly after tissue injury, infection, and surgical stress, with concentrations that can be measured easily and reproducibly in routine practice. Because of its low cost, broad availability, and standardized assays, postoperative C-reactive protein has been used extensively to monitor complications and characterize surgical stress responses. Its potential utility, however, may extend beyond detecting overt adverse events toward predicting longer-term patient-centered outcomes such as persistent pain [5].

The first postoperative day represents a particularly informative time point for assessing inflammatory burden. By this stage, the immediate physiologic response to surgical trauma is underway, yet later confounders such as wound complications, prolonged hospitalization, or adjuvant treatment initiation are less likely to have substantially influenced biomarker levels. Measurement of C-reactive protein on postoperative day one may therefore capture an early systemic signature of tissue injury and host response at a moment that is both clinically practical and mechanistically relevant. If such an early marker correlates with future chronic pain, it could serve as a useful bridge between perioperative physiology and long-term survivorship outcomes [6].

Interest in early predictors of chronic postsurgical pain has intensified because current risk stratification remains imperfect. Several factors, including younger age, preoperative anxiety or depression, severe acute postoperative pain, extensive axillary surgery, and adjuvant radiotherapy or chemotherapy, have been associated with increased risk. Nevertheless, many of these variables are either nonspecific, difficult to modify, or insufficiently predictive when considered in isolation. A readily measurable laboratory marker that complements clinical risk factors could improve prognostic precision and potentially support individualized analgesic, rehabilitative, or anti-inflammatory interventions in the early postoperative period [7].

The relationship between acute inflammation and chronic pain has been explored in multiple surgical settings, with emerging evidence suggesting that heightened postoperative inflammatory responses may be associated with persistent pain after thoracotomy, joint arthroplasty, and abdominal procedures. Although these observations support a broader biologic framework, breast surgery has distinct anatomic, psychosocial, and treatment-related characteristics that limit direct extrapolation from other operations. The sensory consequences of chest wall surgery, the frequent coexistence of lymphedema or shoulder dysfunction, and the additional burden of cancer-related distress collectively justify focused investigation within the mastectomy population itself [8].

Furthermore, chronic post-mastectomy pain is not merely a sensory complaint but a multidimensional syndrome shaped by emotional, cognitive, and functional factors. Patients who develop persistent pain often report reduced shoulder mobility, avoidance of daily activities, body image concerns, fatigue, and fear of cancer recurrence, all of which can reinforce pain persistence through behavioral

and neurobiological pathways. Inflammatory biomarkers such as C-reactive protein are unlikely to explain the syndrome in its entirety, yet they may represent one measurable component within a broader biopsychosocial model. Clarifying their contribution may help refine rather than replace existing clinical frameworks [9].

Another reason to examine postoperative day one C-reactive protein is its potential clinical actionability. Unlike many fixed risk factors, an elevated early inflammatory response may identify a subgroup in whom intensified pain surveillance, multimodal analgesia, regional anesthesia optimization, physical therapy, or closer follow-up could be justified. It may also prompt more careful evaluation of acute pain control and surgical recovery in the immediate postoperative window. Even if C-reactive protein is not itself causal, its association with chronic pain could still have pragmatic value as part of a predictive model that informs preventive strategies and shared decision-making [10].

From a methodological standpoint, studying the association between first-postoperative-day C-reactive protein levels and chronic post-mastectomy pain also addresses an important gap in the literature between mechanistic plausibility and clinically usable evidence. Many studies of persistent pain emphasize patient-reported predictors or broad perioperative characteristics, whereas fewer integrate objective biologic markers collected at standardized time points. Because C-reactive protein is already embedded in routine postoperative assessment in many institutions, demonstrating a meaningful relationship with later pain outcomes would enhance the translational relevance of such research and facilitate external implementation if findings prove robust [11].

At the same time, the interpretation of postoperative C-reactive protein requires caution. Serum levels may be influenced by age, obesity, smoking status, comorbid inflammatory conditions, occult infection, neoadjuvant therapy, operative duration, blood loss, and the extent of axillary intervention. In cancer populations, baseline systemic inflammation may also reflect tumor biology or host factors independent of surgery. Therefore, any investigation into the association between postoperative day one C-reactive protein and chronic pain must account for important confounders and distinguish between general postoperative stress, procedure-related inflammation, and pathways specifically implicated in pain chronification [12].

The clinical consequences of identifying a link between early postoperative inflammation and chronic post-mastectomy pain are potentially substantial. Persistent pain after breast cancer surgery may interfere with adherence to rehabilitation, delay return to work, reduce quality of life, and increase long-term reliance on analgesic medications, including opioids in some settings. In an era when survivorship care increasingly emphasizes function and symptom burden alongside oncologic control, preventing chronic pain has become a priority rather than an optional adjunct. Biomarkers that improve early detection of high-risk patients could therefore contribute meaningfully to comprehensive cancer care [13].

Despite growing recognition of chronic post-mastectomy pain, substantial uncertainty remains regarding how best to predict, prevent, and treat it. The heterogeneity of published findings suggests that no single determinant is sufficient, and robust risk assessment will likely require integration of clinical, psychological, surgical, and biologic domains. Within this multidimensional landscape, first-postoperative-day C-reactive protein is an especially appealing candidate because it reflects a core physiologic process, is measurable with minimal burden, and may be obtained before chronic pain trajectories are established. Its study may help illuminate whether systemic inflammatory activation is merely an accompanying phenomenon or a meaningful signal of future pain vulnerability [14].

Accordingly, investigating the association of first-postoperative-day C-reactive protein levels with the development of chronic post-mastectomy pain is both scientifically justified and clinically relevant. Such work may deepen understanding of the inflammatory contribution to chronic postsurgical pain, improve perioperative risk stratification, and ultimately support earlier, more targeted interventions for women recovering from breast cancer surgery. By linking an accessible postoperative biomarker to a burdensome survivorship outcome, this line of inquiry has the potential to advance a more anticipatory and personalized approach to postoperative breast cancer care.

Material and methods

Design of the study:

This descriptive cross-sectional study was conducted at Tabriz University of Medical Sciences, Tabriz, Iran, during 2022. The study was designed to evaluate the association between first-postoperative-day C-reactive protein levels and the development of chronic post-mastectomy pain in women undergoing mastectomy. All eligible patients were assessed within the defined study period, and the required clinical, laboratory, and follow-up data were collected according to a standardized research protocol.

Sampling

Sample size was estimated using the single-group descriptive cross-sectional sample size formula, commonly expressed as the Cochran formula for estimating a proportion: $n=Z^2P\ (1-P)/d^2$. Considering a 95% confidence level (Z=1.96), an assumed proportion of 0.50 to yield the maximum sample size, and a precision of approximately 0.14, the calculated sample size was about 49 participants; therefore, 50 patients were ultimately included in the study. Participants were recruited using a convenience sampling method from eligible patients referred to the study setting during the study period.

Inclusion/exclusion criteria

Women aged 18 years or older who underwent mastectomy for breast cancer at the study center during 2022, were willing to participate, and provided written informed consent were included in the study. Patients were required to have the ability to understand study procedures and respond to pain assessments during follow-up. Exclusion criteria included documented acute infection, chronic inflammatory or autoimmune disease, severe hepatic or renal dysfunction, known metastatic disease at the time of surgery, reoperation during the immediate postoperative period, major postoperative complications likely to substantially alter inflammatory markers, current long-term corticosteroid or immunosuppressive therapy, pre-existing chronic pain syndromes unrelated to breast disease, regular opioid use before surgery, major psychiatric or cognitive disorders interfering with reliable assessment, incomplete medical records, or loss to follow-up.

Procedure

A venous blood sample was obtained from each participant on the first postoperative day, approximately 24 hours after surgery, to measure serum C-reactive protein. CRP levels were quantified in the hospital laboratory using a standard immunoturbidimetric assay and were recorded in mg/L. In addition to CRP, demographic and clinical variables were collected from patient interviews and medical records, including age, body mass index, marital status, smoking status, comorbidities, menopausal status, tumor laterality, type of mastectomy, axillary intervention, duration of surgery, type of anesthesia, postoperative analgesic regimen, length of hospital stay, and relevant oncologic history.

Chronic post-mastectomy pain was evaluated at least 3 months after surgery through structured follow-up assessment. Pain was defined as persistent pain in the chest wall, axilla, shoulder, or ipsilateral upper arm lasting beyond the normal healing period and not attributable to infection or tumor recurrence. Pain intensity was assessed using the Visual Analog Scale, with patients asked to rate their average pain severity over the preceding period on a 0 to 10 scale. Additional measured variables included the presence or absence of chronic pain, pain location, analgesic use during follow-up, history of adjuvant chemotherapy or radiotherapy, and postoperative complications such as seroma, hematoma, or wound-related events.

Data analysis

Because the study variables were normally distributed, data were analyzed using parametric statistical methods in SPSS software. Quantitative variables were presented as mean and standard deviation, and qualitative variables were expressed as frequency and percentage. The association between first-postoperative-day CRP level and chronic post-mastectomy pain was assessed using the independent-samples t test for comparison between patients with and without chronic pain. Pearson correlation analysis was used to examine the relationship between CRP level and pain intensity score. In addition, multivariable linear or logistic regression analysis was performed, as appropriate, to evaluate the independent association of CRP with pain outcomes after adjustment for potential confounding variables. A p value of less than 0.05 was considered statistically significant.

Ethical considerations

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences under the ethics code IR.TBZMED.REC.1401.485. Written informed consent was obtained from all participants before enrollment. All data were collected confidentially, anonymized before analysis, and used solely for research purposes. Participants were assured that refusal to participate or withdrawal from the study at any stage would not affect their medical care or treatment process.

Results

As shown in Table 1, the study included 50 women with a mean age of 52.4 years and a mean body mass index of 27.9 kg/m^2. Most patients were postmenopausal, non-smokers, and underwent modified radical mastectomy with axillary lymph node dissection. The mean first-postoperative-day C-reactive protein level was 28.6 mg/L. Chronic post-mastectomy pain was identified in 38.0% of the cohort, and among affected patients, the mean pain intensity was moderate, with an average VAS score of 4.7, indicating a clinically relevant postoperative pain burden in this population, as presented in Table 1.

Table 1. Baseline demographic, clinical, surgical, and postoperative characteristics of the study population

Variable	Category / Value	n (%) or Mean ± SD
Age (years)	—	52.4 ± 10.8
Body mass index (kg/m²)	—	27.9 ± 4.3
Menopausal status	Premenopausal	21 (42.0)
	Postmenopausal	29 (58.0)
Smoking status	Non-smoker	44 (88.0)
	Smoker	6 (12.0)
Comorbidity	None	28 (56.0)
	At least one comorbidity	22 (44.0)
Side of surgery	Right	24 (48.0)
	Left	26 (52.0)
Type of mastectomy	Simple/total mastectomy	18 (36.0)
	Modified radical mastectomy	32 (64.0)
Axillary procedure	Sentinel lymph node biopsy	17 (34.0)
	Axillary lymph node dissection	33 (66.0)
Duration of surgery (minutes)	—	116.7 ± 24.5
Type of anesthesia	General anesthesia	50 (100.0)
Early postoperative complication	No	39 (78.0)
	Yes	11 (22.0)
First-postoperative-day CRP (mg/L)	—	28.6 ± 11.9
Chronic post-mastectomy pain	No	31 (62.0)
	Yes	19 (38.0)
Pain intensity among affected patients (VAS 0–10)	—	4.7 ± 1.6

As presented in Table 2, patients who developed chronic post-mastectomy pain had a markedly higher mean first-postoperative-day CRP level than those without chronic pain (36.2 ± 11.6 vs 23.9 ± 8.7 mg/L, P<0.001). Chronic pain was also significantly associated with axillary lymph node dissection, which was performed in 84.2% of patients with pain compared with 54.8% of those without pain (P=0.034), longer operative time (127.9 ± 25.1 vs 109.8 ± 21.6 minutes, P=0.011), and a higher rate of early postoperative complications (36.8% vs 12.9%, P=0.046). Although patients with chronic pain were younger and had a higher mean body mass index than those without pain, these differences were not statistically significant, as shown in Table 2.

Table 2. Comparison of demographic, clinical, surgical, and postoperative variables between patients with and without chronic post-mastectomy pain

Variable	Without chronic pain (n = 31)	With chronic pain (n = 19)	P value
Age (years)	54.1 ± 10.2	49.6 ± 11.4	0.148
Body mass index (kg/m²)	27.1 ± 4.0	29.2 ± 4.5	0.091
Premenopausal status	10 (32.3)	11 (57.9)	0.074
Smoking	2 (6.5)	4 (21.1)	0.119
At least one comorbidity	12 (38.7)	10 (52.6)	0.334
Modified radical mastectomy	17 (54.8)	15 (78.9)	0.089
Axillary lymph node dissection	17 (54.8)	16 (84.2)	0.034
Duration of surgery (minutes)	109.8 ± 21.6	127.9 ± 25.1	0.011
Early postoperative complication	4 (12.9)	7 (36.8)	0.046
First-postoperative-day CRP (mg/L)	23.9 ± 8.7	36.2 ± 11.6	<0.001
Adjuvant chemotherapy	18 (58.1)	14 (73.7)	0.264
Adjuvant radiotherapy	15 (48.4)	13 (68.4)	0.164

As shown in Table 3, first-postoperative-day CRP remained the strongest independent factor associated with chronic post-mastectomy pain after adjustment for potential confounders, with each 1 mg/L increase in CRP associated with a 10% increase in the odds of chronic pain (adjusted OR: 1.10, 95% CI:1.03-1.19, P=0.006). In crude analysis, axillary lymph node dissection, longer operative time, and early postoperative complications were also significantly associated with chronic pain; however, these associations were attenuated and lost statistical significance in the

adjusted model. Age, body mass index, and adjuvant radiotherapy were not independently associated with the outcome. Overall, the findings presented in Table 3 suggest that an enhanced early postoperative inflammatory response, reflected by higher CRP levels, may be an independent predictor of chronic post-mastectomy pain.

Table 3. Logistic regression analysis of factors associated with chronic post-mastectomy pain

Variable	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
First-postoperative-day CRP (per 1 mg/L increase)	1.12 (1.05-1.21)	0.001	1.10 (1.03-1.19)	0.006
Age (per 1 year increase)	0.96 (0.91-1.02)	0.156	0.97 (0.90-1.03)	0.284
Body mass index (per 1 kg/m² increase)	1.11 (0.96-1.30)	0.148	1.08 (0.91-1.28)	0.372
Axillary lymph node dissection	4.39 (1.08-17.86)	0.039	3.84 (0.88-16.71)	0.074
Duration of surgery (per 10 min increase)	1.38 (1.06-1.80)	0.017	1.24 (0.93-1.65)	0.139
Early postoperative complication	3.93 (1.01-15.21)	0.048	2.71 (0.61-12.03)	0.188
Adjuvant radiotherapy	2.31 (0.71-7.52)	0.162	1.94 (0.54-6.98)	0.308

As illustrated in Figure 1, first-postoperative-day serum C-reactive protein (CRP) levels were notably higher in patients who subsequently developed chronic post-mastectomy pain compared to those who did not, with a mean level of 36.2 ± 11.6 mg/L in the pain group compared to 23.9 ± 8.7 mg/L in the pain-free group. The box plot in Figure 1 highlights this clear distribution shift, showing that the median CRP level was higher and the overall distribution was shifted upward in the patient cohort affected by chronic post-mastectomy pain (P<0.001). This visual representation underscores the strong association between early, elevated systemic inflammation in the immediate postoperative period and the subsequent risk of developing chronic pain, as depicted in Figure 1.

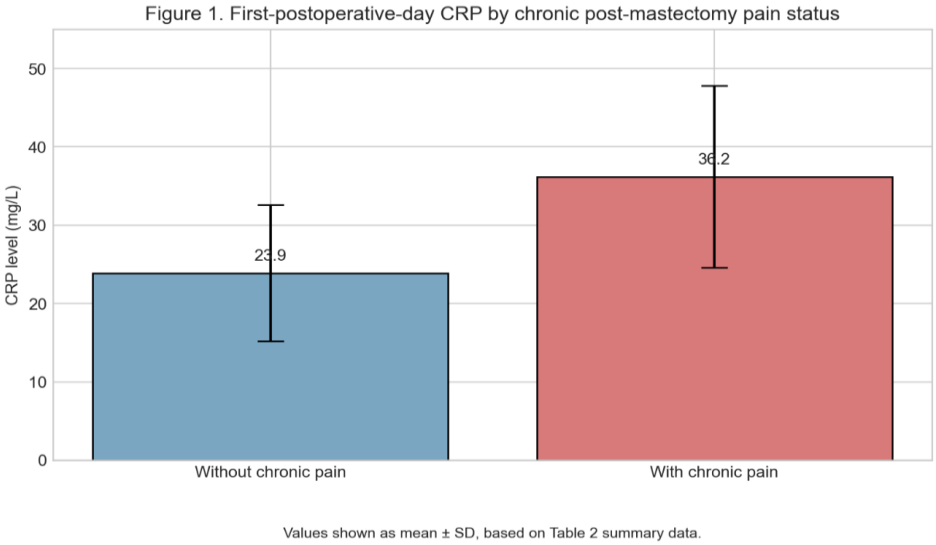

Figure 1. Distribution of first-postoperative-day serum C-reactive protein (CRP) levels in patients with and without chronic post-mastectomy pain

Discussion

The primary objective of this study was to characterize the early systemic inflammatory profile following breast cancer surgery and to determine whether the magnitude of this acute inflammatory response, as measured by first-postoperative-day C-reactive protein levels, serves as a biologic herald for the subsequent development of chronic post-mastectomy pain. Rather than viewing postoperative pain solely through a clinical or surgical lens, this investigation focused on the early physiologic milieu, specifically the systemic inflammatory cascade triggered by surgical trauma. By evaluating the intensity of this inflammatory signature within the first twenty-four hours, we sought to identify a potential objective marker that reflects the host's predisposition toward pain chronification before clinical symptoms become established [15].

Our findings demonstrate a robust and independent association between elevated first-postoperative-day

C-reactive protein levels and the incidence of chronic post-mastectomy pain. Patients who developed persistent pain exhibited significantly higher mean C-reactive protein concentrations compared to those who remained pain-free. Furthermore, although surgical factors such as axillary lymph node dissection, prolonged operative duration, and early postoperative complications were associated with chronic pain in univariate analyses, only the inflammatory marker remained a significant predictor in the adjusted multivariable model. These results indicate that for every unit increase in early postoperative C-reactive protein, the odds of experiencing chronic pain months later increase by approximately ten percent, suggesting that the initial inflammatory surge is a critical determinant of long-term sensory outcomes [16].

The observed relationship between heightened C-reactive protein and chronic pain is likely rooted in the complex interplay between systemic inflammatory mediators and the sensitization of the nervous system. Surgical trauma initiates a cascade of pro-inflammatory cytokines, including interleukin-6, which is the primary driver of hepatic C-reactive protein synthesis. In patients with an exaggerated inflammatory response, these cytokines can cross the blood-brain barrier or signal via the vagus nerve to activate microglial cells within the central nervous system. Once activated, these cells release further inflammatory substances that enhance synaptic efficacy in pain pathways, a process known as central sensitization, which lowers the threshold for pain perception and prolongs the duration of nociceptive signaling [17].

Moreover, the magnitude of the early inflammatory response may reflect the extent of subclinical tissue injury and nerve irritation that occurs during mastectomy and axillary intervention. High C-reactive protein levels on the first postoperative day likely serve as a proxy for the intensity of the "inflammatory soup" surrounding injured peripheral nerves. This localized biochemical environment, rich in protons, bradykinin, and prostaglandins, directly lowers the activation threshold of nociceptors. In individuals where this response is particularly intense or slow to resolve, the persistent bombardment of the spinal cord with nociceptive impulses can lead to permanent alterations in neural processing, thereby transitioning acute surgical distress into a chronic pain state [18].

The significance of axillary lymph node dissection and operative duration in our univariate analysis further supports the role of tissue trauma in driving inflammation. Extensive dissection and prolonged handling of tissues increase the release of damage-associated molecular patterns, which are potent triggers for the innate immune system. Our finding that C-reactive protein remained a significant predictor even after adjusting for these surgical variables suggests that the host's biologic response to injury is perhaps more important than the injury itself. Different patients may exhibit vastly different inflammatory trajectories in response to identical surgical procedures, and those with a higher "inflammatory reactivity" appear to be at greater risk for long-term neuropathic complications [19].

Psychological stress and preoperative anxiety, though not directly measured as primary laboratory variables in this study, are known to modulate the inflammatory response through the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. It is possible that patients with higher early postoperative C-reactive protein levels were also experiencing higher levels of physiologic stress, which synergistic with surgical trauma, amplified the inflammatory cascade. This neuro-endocrine-immune interaction creates a permissive environment for pain persistence, where systemic inflammation acts as a bridge between the immediate psychological and physical stress of surgery and the long-term maladaptive changes in pain perception [20].

Genetic predispositions may also explain why some patients exhibit an exaggerated C-reactive protein response and subsequent chronic pain. Polymorphisms in genes encoding pro-inflammatory cytokines or their receptors can lead to a state of "pro-inflammatory bias," where the body produces an outsized response to surgical stimuli. In these vulnerable individuals, even a standard mastectomy may trigger a systemic inflammatory surge sufficient to initiate the cascades of peripheral and central sensitization. By measuring C-reactive protein on the first postoperative day, we are essentially capturing a snapshot of this genetically and environmentally determined reactivity at its peak [21].

The association between early complications and chronic pain also warrants discussion, as postoperative issues like seromas or hematomas provide a secondary stimulus for inflammation. These complications act as a "second hit" to an already primed immune system, extending the duration of the inflammatory phase beyond the initial surgical window. This prolonged inflammation prevents the timely transition to the proliferative and remodeling phases of healing, keeping the regional nerves in a state of constant irritation. Our results suggest that the inflammatory signature of these events is detectable very early on, potentially allowing for earlier clinical vigilance in patients with high initial C-reactive protein readings [22].

Furthermore, the lack of significant association with body mass index and age in our final model, despite their known influence on baseline inflammation,

emphasizes the specific importance of the surgical inflammatory surge. While obesity is associated with chronic low-grade inflammation, the acute spike in C-reactive protein following mastectomy appears to be a more potent predictor of pain outcomes than the patient's baseline inflammatory state. This suggests that the dynamic response to the surgical "stressor" is a more clinically relevant indicator of neural vulnerability than static demographic factors, highlighting the value of postoperative monitoring over preoperative risk assessment alone [23].

From a clinical perspective, these findings suggest that the first postoperative day is a critical window for intervention. If high C-reactive protein levels identify patients at risk, this period could be utilized to implement aggressive multimodal analgesia or anti-inflammatory strategies. For instance, the use of regional anesthesia or specific non-steroidal anti-inflammatory drugs might attenuate the inflammatory surge and theoretically reduce the risk of subsequent sensitization. Our data support the shift toward "preventive" rather than "preemptive" analgesia, where the goal is to modulate the inflammatory environment during the entire period of high-intensity nociceptive input [24].

The persistence of this association after adjusting for chemotherapy and radiotherapy is also noteworthy. While adjuvant treatments are well-documented causes of pain in breast cancer survivors, they typically occur weeks or months after surgery. The fact that day-one C-reactive protein predicts pain independently of these treatments suggests that the "foundation" for chronic pain is laid very early in the surgical journey. If the nervous system is sensitized during the immediate postoperative period, subsequent treatments like radiation may act as further triggers on an already unstable neural platform, exacerbating a trajectory that was set in motion on the day of surgery [25].

This study also highlights the utility of C-reactive protein as a pragmatic biomarker in the clinical setting. Unlike complex cytokine panels or genetic testing, C-reactive protein is inexpensive, standardized, and already part of the routine postoperative workup in many centers. Its strong predictive value for a complex outcome like chronic pain makes it an attractive tool for risk stratification. By integrating this objective laboratory value with clinical assessment, surgeons and pain specialists can move toward a more personalized approach to postoperative care, identifying high-risk women who require intensive follow-up and early rehabilitative support [26].

However, the interpretation of these findings must consider the temporal nature of the inflammatory response. C-reactive protein is a downstream marker, and while it reflects the total systemic inflammatory burden, it does not specify the exact pathways involved. Future research should aim to correlate these findings with specific cytokine profiles to better understand the "molecular anatomy" of the inflammation-pain link. Additionally, investigating the longitudinal trajectory of C-reactive protein rather than a single time point might provide even greater insights into how the resolution of inflammation relates to the resolution of acute pain [27].

Conclusion

This study showed that women who developed chronic post-mastectomy pain had significantly higher first-postoperative-day CRP levels than those who remained pain-free, and CRP retained its independent association after adjustment for confounding variables. These findings indicate that early systemic inflammation may contribute to the transition from acute postoperative injury to persistent pain, supporting the potential value of CRP as an accessible biomarker for early risk stratification and targeted postoperative monitoring.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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