



## Original Article



## Prognostic Significance of Serum C-Reactive Protein Levels Among Operable Breast Cancer Patients

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## ABSTRACT

Serum C-Reactive Protein (CRP) levels, an indicator of systemic inflammation, are increasingly recognized for their prognostic value in cancer. In operable breast cancer, elevated CRP levels may correlate with tumor progression, treatment outcomes, and survival. **Objective:** To determine the outcome of the raised serum CRP among operable breast cancer patients.**Methods:** This prospective cohort study was conducted on 126 women of 20-60 years of age with a lump in the breast, bloody or serous nipple discharge  $\geq 6$ -week duration and diagnosed as a case of operable breast cancer on histopathology and were selected for modified radical mastectomy. Patients were divided into 2 groups according to CRP levels (Raised; Group A vs normal; Group B). **Results:** In Group A (17.5%) cases had wound infections, 16 cases (25.4%) of seroma, and 10 cases (15.9%) of flap necrosis. In contrast, Group B had a lower incidence of these complications, with 4 cases (6.3%) of wound infections, 8 cases (12.7%) of seroma, and 5 cases (7.9%) of flap necrosis. In terms of pain severity, all 63 patients (100.0%) in Group A reported moderate pain, with no cases of severe pain and in Group B, 48 patients (76.2%) experienced moderate pain, and 15 patients (23.8%) reported severe pain ( $p=0.004$ ). Prolonged Hospital stay was (25.4%) cases of group A and in Group B (49.2%) cases had prolonged hospital stays.**Conclusion:** Patients with elevated CRP levels are more likely to experience postoperative complications, such as wound infection, seroma formation, and flap necrosis, compared to patients with normal CRP levels.

## INTRODUCTION

There is a notable increase in breast cancer cases among Asian women as it occupies 22% of the population as the second most persistent disease [1, 2]. Furthermore, it has also remained the second most lethal form of cancer among women [3]. As advancements go, this means breast cancer is one of the curable diseases, given the fact that it is detected at an early stage. The number of cases of breast cancer is rapidly increasing associated with various factors like sex, age, genetic predisposition, childlessness, breastfeeding, hormones, and lifestyle [4]. The diagnosis of breast cancer is based on a triple assessment including clinical examination along with imaging (ultrasonography is

preferred for younger patients and mammography is for older age group) and is confirmed by the pathological assessment on biopsy with receptor status (ER, PR, Her 2neu) [5]. The mammogram will be done to have Breast Imaging-Reporting and Data System (BIRADS) scoring for both breasts to rule out the status of the contralateral breast as well. An ultrasound / contrast Computed Tomography (CT) scan of the chest, abdominal and bone scan can be considered for the staging of the disease to plan the treatment accordingly [6]. The surgical treatment options are multiple including breast saving procedures and breast scarifying procedures. Simple mastectomy with



or without axillary sampling, radical mastectomy, and Modified Radical Mastectomy (MRM) are the options for breast scarifying procedures. Skin-sparing mastectomy, Breast Conservation Surgery (BCS) with or without sentinel lymph node biopsy is the options of breast conserving procedures. Surgery is concomitant with neoadjuvant or adjuvant chemo-radiotherapy according to the stage of the disease. Cancer antigen 153 (CA153), Cancer antigen 125 (CA-125), and Carcinoembryonic Antigen (CEA) are the most commonly used serum markers in the management of breast cancer but the debate on its specificity is still going on [6]. Inflammation is the seventh hallmark of cancer. Nowadays it is thought that cancer should be considered in patients with raised inflammatory markers. However, inflammatory markers have poor sensitivity for cancer diagnosis but they can lead us towards the path of the prognosis [7]. As the pathogenesis behind the cancer is molecular events include angiogenesis on the top and its association with the inflammatory process, to contribute to its further progression [3, 8]. As systemic inflammatory markers play an important role in cancer progression, they also act as the prognostic indicator including C-Reactive Protein (CRP) [9, 10]. Though CRP is a sensitive, reliable biomarker of systemic inflammation and its prognosis can be measured easily [11]. There is an increased association of CRP with breast cancer among the post-menopausal group due to differences in the site of estrogen production. While serum concentrations of CRP were shown to positively correlate with estrone, total estradiol and free estradiol, SHBG level was negatively correlated. Furthermore, breast density has been shown to correlate with a reduction in CRP levels, whereby lower CRP levels were observed in those with greater breast density [12]. Lowering agents of CRP like COX inhibitors, platelet aggregation inhibitors, lipid lowering agents, angiotensive converting enzymes inhibitors, antioxidants and antibiotics appear to be effective management strategies as accompanying treatments alongside breast cancer chemotherapy, into improving treatment and survival prognosis of such patients. Clinically elevated levels of C-reactive protein suggest that there is more likely to be a deleterious relationship between inflammatory response mechanisms and breast cancer that will more often than not poor patient outcome as well [13]. However, the existing literature on the elevated CRP levels in breast cancer patients in the local setting is scanty and thin. Consequently, this study sought to investigate in what way the elevated biomarkers namely CRP in operable breast cancer patients would lead to accelerated appearance of early postoperative complications as well as prolonged hospital stay in the population.

## METHODS

This Prospective-Cohort study was done from Jan 2023 – June 2023, at the Department of Surgery, Liaquat University Hospital, Hyderabad, on 126 patients, who were divided into two groups. Group A (n=63) with elevated serum CRP (>0.37 mg/dl) and Group B (n=63) with normal serum CRP levels. Women aged 20–60 years with operable breast cancer (stage II or early III), verified by histopathology, with a period of at least 3-months after diagnosis and CT staging, and scheduled for modified radical mastectomy were included. Informed written consent was taken from each participant before enrolment into the study. Exclusion criteria encompassed patients with chronic liver disease, those on immunosuppressive therapy, pregnant or lactating women, stage IV breast cancer patients, and those who previously received non-adjuvant therapy. Patients were chosen via purposive sampling. Sample size was calculated via WHO software with frequency of raised serum CRP level among breast cancer patients as 9% with 5% margin of error and 95% confidence interval [9]. The study was approved by Ethical Review Committee of Liaquat University of Medical and Health Sciences, Jamshoro vide letter no. LUMHS/REC/187. Data collection involved CRP measurement, clinical examination, and a detailed history of each patient. Outcomes assessed included early postoperative complications (e.g., seroma, flap necrosis, wound infection within five days' post-surgery), pain severity, and prolonged hospital stay (defined as >5 days postoperatively). Data analysis was performed using SPSS version 22.0. Chi-square test was used to analyse the association between different qualitative variables.

## RESULTS

Patients in Group A (raised CRP) had a mean age of  $41.60 \pm 10.16$  years, whereas those in Group B (normal CRP) averaged  $45.53 \pm 14.59$  years. Average BMI and lump size were similar between groups, with no significant differences observed in height, weight, or lump dimensions. Group A had a slightly higher proportion of urban residents (49.2%) compared to Group B (25.4%), while rural residency was more common in Group B (74.6%). The right breast was more frequently affected in Group A (74.6%) and left breast in Group B (50.8%). The presence of pain was reported in 38.1% of Group A and 25.4% of Group B patients, with most lumps persisting for 7–12 months in both groups (Table 1).

**Table 1:** Descriptive Statistics (n=126)

Variables	Group A Raised CRP Mean $\pm$ SD / N (%)	Group B Normal CRP Mean $\pm$ SD / N (%)
Age (Years)	41.60 $\pm$ 10.16	45.53 $\pm$ 14.59
Height (cm)	177.49 $\pm$ 5.33	177.67 $\pm$ 6.65

Weight (Kg)	63.84 ± 4.37	65.33 ± 6.76
BMI (Kg/m <sup>2</sup> )	20.48 ± 1.15	20.68 ± 2.22
Lump Size (cm)	3.30 ± 2.13	3.22 ± 2.08
Serum CRP (mg/dL)	0.64 ± 0.21	0.21 ± 0.12
<b>Residence</b>		
Urban	31 (49.2%)	16 (25.4%)
Rural	32 (50.8%)	47 (74.6%)
<b>Site of Lump</b>		
Right	47 (74.6%)	31 (49.2%)
Left	16 (25.4%)	32 (50.8%)
<b>Lump Pain Status</b>		
With Pain	24 (38.1%)	16 (25.4%)
Without Pain	39 (61.9%)	47 (74.6%)
<b>Duration of Lump</b>		
≤ 6 Months	0 (0.0%)	24 (38.1%)
7-12 Months	48 (76.2%)	39 (61.9%)
> 12 Months	15 (23.8%)	0 (0.0%)

Complication rates were higher in Group A, with wound infections occurring in 17.5% compared to 6.3% in Group B ( $p=0.004$ ). Group A also experienced more cases of seroma (25.4% vs. 12.7%) and flap necrosis (15.9% vs. 7.9%). Pain severity was notable, with all Group A patients reporting moderate pain, while 23.8% of Group B reported severe pain ( $p=0.0001$ ). Prolonged hospital stay was required by 25.4% of Group A patients, compared to 49.2% in Group B ( $p=0.006$ )(Table 2).

**Table 2:** Postoperative Outcomes at the Time of Discharge ( $n=126$ )

Variables	Group A Raised CRP N (%)	Group B Normal CRP N (%)	p-Value
<b>Postoperative Complications</b>			
Wound Infection	11 (17.5%)	4 (6.3%)	0.004
Seroma	16 (25.4%)	8 (12.7%)	
Flap Necrosis	10 (15.9%)	5 (7.9%)	
No Complications	26 (41.3%)	46 (73.0%)	
<b>Pain Severity</b>			
Moderate Pain	63 (100.0%)	48 (76.2%)	0.0001
Severe Pain	0 (0.0%)	15 (23.8%)	
<b>Prolonged Hospital Stay</b>			
Yes	16 (25.4%)	31 (49.2%)	0.006
No	47 (74.6%)	32 (50.8%)	

Group A had a higher incidence of postoperative complications (30.2%) than Group B (11.1%), and fewer patients in Group A (66.7%) experienced no complications compared to Group B (87.3%) ( $p=0.006$ ). A small percentage of patients were lost to follow-up in both groups (3.2% in Group A and 1.6% in Group B)(Table 3).

**Table 3:** Postoperative Outcomes at 1-Month Follow Up ( $n=126$ )

Variables	Group A Raised CRP N (%)	Group B Normal CRP N (%)	p-Value
No Complication	42 (66.7%)	55 (87.3%)	0.006
With Complication	19 (30.2%)	7 (11.1%)	
Lost Follow-up	2 (3.2%)	1 (1.6%)	

## DISCUSSION

Breast cancer is one of the most prevalent cancers among women, and its prognosis is determined by various factors, including the stage at diagnosis, tumor characteristics, and response to treatment. In recent years, researchers have been exploring the potential role of C-Reactive Protein (CRP) as a prognostic marker in breast cancer. In Group A, the mean age was 41.60 years with a standard deviation of 10.16, whereas in Group B, the mean age was 45.53 years with a standard deviation of 14.59. Comparatively in the study by Badar F et al, four-thousand, three-hundred and sixty-six female breast malignancies were recorded, their mean age at presentation was  $48.6 \pm 12.2$  years and mean Body Mass Index (BMI) was  $29.0 \pm 5.7$  kg/m<sup>2</sup> [14]. On the other hand, study by Sajid MT et al reported that the mean age of the patients of breast cancer was  $52.90 \pm 9.78$  years [15]. Breast cancer risk generally increases with age, particularly in postmenopausal women. Therefore, when the mean age of breast cancer patients is over 40, it reflects the expected rise in breast cancer cases in this age group. In this study the mean BMI in Group A was 20.48 kg/m<sup>2</sup> and in Group B, it was 20.68 kg/m<sup>2</sup>, p-value for BMI suggested no significant difference between the both groups ( $p=0.541$ ). These findings were supported by the Badar F et al. [14]. In this study group A had more rural resident (50.8%) than Group B (74.6%), while Group A had fewer urban residents (49.2%) compared to Group B (25.4%). In Group A, 74.6% had right-sided lumps, while in Group B, 49.2% had right-sided lumps. For left-sided lumps, 25.4% in Group A had them, compared to 50.8% in Group B. In Group A, no individuals had lumps for over 6 months, 76.2% had lumps for 7-12 months, and 23.8% for more than 12 months. In Group B, 38.1% had lumps for over 6 months, 61.9% for 7-12 months, and none for more than 12 months. These findings regarding residential status were supported by the Moss JL et al., and Sprague BL et al., while findings regarding site of lump not found in their studies [16, 17]. In this study, Group A experienced higher rates of postoperative complications, including wound infections (17.5%), seroma (25.4%), and flap necrosis (15.9%). In contrast, Group B had lower complication rates: wound infections (6.3%), seroma (12.7%), and flap necrosis (7.9%). Pain severity was also higher in Group A, with all patients reporting moderate pain, while Group B had 76.2% with moderate pain and 23.8% with severe pain. The p-value of 0.004 indicates a significant difference in complication rates between the two groups. Additionally, Group B had a larger proportion of patients with prolonged hospital stays (49.2%) compared to Group A (25.4%). The possible explanation of association of elevated CRP levels with prolonged hospital stay lies in development of systemic inflammation, which can compromise wound healing by impairing the immune response, increasing

vascular permeability, and promoting tissue damage. This pro-inflammatory state may predispose patients to complications such as seroma, infection, and necrosis. Chronic inflammation may exacerbate comorbid conditions, contributing to delayed recovery and prolonged hospital stays. Most patients in both groups (87.3%) recovered without complications by the 30th postoperative day. Along the same lines, Dahri FJ *et al.*, reported that seroma formation was the most common complication encountered in 50 (33.3%) of cases, wound infection in 15 (10%) and flap necrosis in 4 (2.6%) cases [18]. Comparatively Shah S *et al.*, reported that the frequency of early postoperative complications [19]. Seroma formation observed in 9 patients (15%) and wound infection seen in 5 cases (8.3%) were the commonest complications [20]. This study uniquely focused on the impact of preoperative CRP levels on early postoperative outcomes, such as seroma formation, wound infection, and hospital stay, among operable breast cancer patients undergoing modified radical mastectomy. Unlike prior studies, the study strengthened lies in context-specific insights for a local population of Pakistan and controls for confounders like prior systemic therapy, ensuring robust and actionable findings.

## CONCLUSIONS

Elevated CRP levels are a valuable predictor of poor outcomes in operable breast cancer patients, linked to higher chances of postoperative-complications like wound infections, and flap necrosis. Enhanced perioperative care and close monitoring are essential for patients with elevated CRP to minimize complications and support recovery. Incorporating preoperative CRP assessments into routine practice could enable clinicians to optimize perioperative care and consider targeted interventions for high-risk patients to improve surgical outcomes.

## Authors Contribution

Conceptualization: NA

Methodology: NA

Formal analysis: ZY, ZK

Writing, review and editing: AIM, SK, AMB, ZY, ZK

All authors have read and agreed to the published version of the manuscript

## Conflicts of Interest

All the authors declare no conflict of interest.

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