Annals of Medicine and Medical Sciences (AMMS)
Volume 05, 2026, *Page No.: 64 to 68*
Available at: *http://ammspub.com*

Original Article

OPEN ACCESS

Inflammatory Markers in Breast Cancer: A Tertiary Centre Experience

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Abstract

Introduction: Chronic inflammation has shown to have a recognized part in carcinogenesis, influencing tumor initiation, development, and prognosis. In breast carcinoma, systemic inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-8 (IL-8) have been investigated as potential indicators of disease behaviour. This study was intended to evaluate the relationship between these inflammatory markers and key clinicopathological parameters in breast carcinoma patients. ***Methods:*** This study was undertaken at the Pathology department, Government Medical College, Jammu, between August 2023 and July 2024. Serum CRP and IL-6 levels were measured using spectrophotometry and chemiluminescence assays, respectively, while enzyme-linked immunosorbent assay (ELISA) was used to quantify TNF-alpha and interleukin-8. This study aimed to assess the levels of CRP, IL-8, IL-6, and TNF-α in patients with breast carcinoma and to examine their associations with key histopathological parameters. ***Results:*** 56 cases of breast carcinoma were included. The mean age of the patients was 51.15 ± 8.23 years. Elevated levels of CRP, IL-6, IL-8, and TNF-α were observed in 58.2%, 89.1%, 61.8%, and 89.1% of cases, respectively. CRP showed significant associations with lymph node status ($p = 0.005$), tumor stage ($p = 0.002$), tumor grade ($p = 0.001$), lymphovascular invasion ($p = 0.001$), ER/PR status ($p < 0.001$), and HER2neu expression ($p = 0.003$). No significant associations were observed between IL-6, IL-8, or TNF-α and most clinicopathological variables. ***Conclusion:*** Elevated CRP levels demonstrated strong correlations with adverse pathological features in breast carcinoma, proposing its potential as a cost-effective prognostic marker in routine clinical practice. Further prospective studies on a large scale are necessary to corroborate these findings and explore therapeutic interventions targeting inflammatory pathways.

Keywords: ***Breast cancer, CRP, IL-8, TNF-α, lymphovascular invasion.***

Introduction

Breast carcinoma is a common malignancy and one of the leading causes of death due to cancer among women worldwide. In 2020, an estimated 2.3 million new cases were reported [1]. Its development is affected by the interaction between hormonal, genetic, and ecological factors [2]. Chronic inflammation, as suggested by recent findings, plays a crucial role in carcinogenesis by promoting DNA damage, driving tumor growth through cytokine-mediated signalling, and remodelling the tumor microenvironment [3,4].

The platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammation index (SII) are cost-effective inflammatory markers that may be useful prognostic tools for various cancers, including breast carcinoma [5,6]. C-reactive protein (CRP), an acute-phase reactant primarily induced by interleukin-6 (IL-6), is a biochemical marker consistently linked to advanced disease stage, higher tumor grade, and poorer survival in breast cancer patients [7-9].

IL-6, interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) are some of the inflammatory mediators that have well-established roles in tumor biology. IL-6 promotes tumor proliferation and angiogenesis through activation of the JAK/STAT3 signalling pathway [10,11]. IL-8 contributes to angiogenesis, tumor cell migration, and metastatic spread [12]. TNF-α is implicated in tumor progression and the promotion of a pro-metastatic microenvironment [13].

While the prognostic significance of these markers has been widely studied in Western populations, limited data exist from the Indian subcontinent. Evaluating their prevalence and clinicopathological correlations in this regional context may provide valuable prognostic insights and inform therapeutic strategies. This study aimed to assess the levels of CRP, IL-8, IL-6, and TNF-α in patients with breast carcinoma and examine their associations with key histopathological parameters.

Materials and Methods

Received: December 19, 2025; **Revised:** January 09, 2026; **Accepted:** January 13, 2026

Study Design and Setting

This analytical study was conducted at the Department of Pathology along with the Medical Research Unit, Government Medical College, Jammu, India, between August 2023 and July 2024.

Consenting patients with histopathologically confirmed breast carcinoma, both male and female, were included in the study. Demographic information, tumor stage, histologic grade, lymph node status, lymphovascular invasion, and receptor status (ER, PR, HER2neu, TNBC) were extracted from patient records

Inclusion Criteria: Patients aged between 18 and 70 years with histopathologically confirmed breast carcinoma (any stage) and no prior systemic therapy for breast cancer before sample collection were included in the study.

Exclusion Criteria: Patients with a history of major inflammatory or autoimmune disorders, active or chronic infections (e.g., HIV, hepatitis), prior immunosuppressive therapy or corticosteroid use within the last month, pregnancy or breastfeeding, and severe comorbid illness impacting study participation were excluded.

Sample Collection and Biomarker Assays

Histopathological slides were retrieved from the pathology archives. Corresponding patients were contacted for peripheral venous blood collection. The following parameters were analysed.

C-reactive protein (CRP): Quantified via spectrophotometry (Siemens ADVIA Centaur XPT / Abbott ci4100).

Interleukin-6 (IL-6): Measured using chemiluminescence assay (Siemens ADVIA Centaur XPT / Abbott ci4100).

Interleukin-8 (IL-8) and TNF-α: Done by ELISA (enzyme-linked immunosorbent assay).

Statistical Analysis

Mean ± standard deviation (SD) was used for continuous variables, and percentages and frequencies for categorical variables. Chi-square test was used to show affiliations between inflammatory markers and clinicopathological parameters. For statistical significance, a p-value < 0.05 was considered.

Results

Patient Demographics

The study included 55 patients with a mean age of 51.15 ± 8.23 years (range: 31–66 years). The largest proportion (52.7%) was aged 51–60 years, Table 1.

Table 1: Age distribution of study participant

Age group (years)	Frequency (n)	Percentage (%)
31–40	5	9.1
41–50	15	27.3
51–60	29	52.7
61–70	6	10.9
Total	55	100.0

CRP, IL-6, IL-8, and TNF-α were found to be raised in 58.2%, 89.1%, 61.8%, and 89.1% of patients, respectively (Table 2).

Table 2: Proportion of patients with elevated inflammatory markers

Marker	Cut-off value	Raised n (%)	Normal n (%)
CRP	≥10 mg/L	32 (58.2)	23 (41.8)
IL-6	≥5 pg/mL	49 (89.1)	6 (10.9)
IL-8	≥8 pg/mL	34 (61.8)	21 (38.2)
TNF-α	≥8 pg/mL	49 (89.1)	6 (10.9)

Lymphovascular invasion was seen in 26 (47.3%) patients.

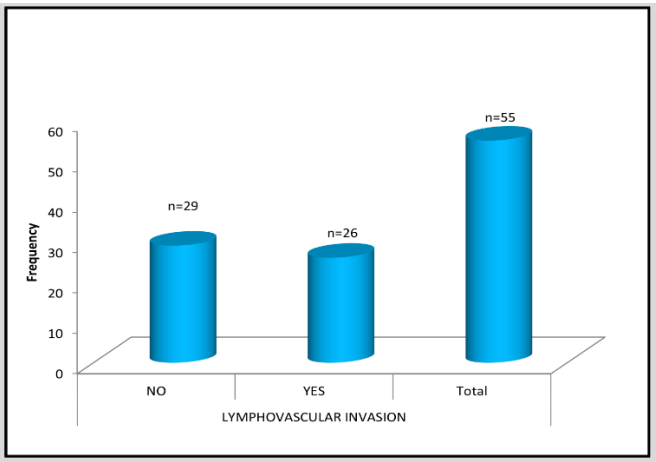

Figure 1: Distribution of lymphovascular invasion

Tumor grading revealed that 43.6% patients had grade 1 tumor followed by 36.4% patients who had grade 2 tumor and 20.0% patients had grade 3 tumor, Figure 2.

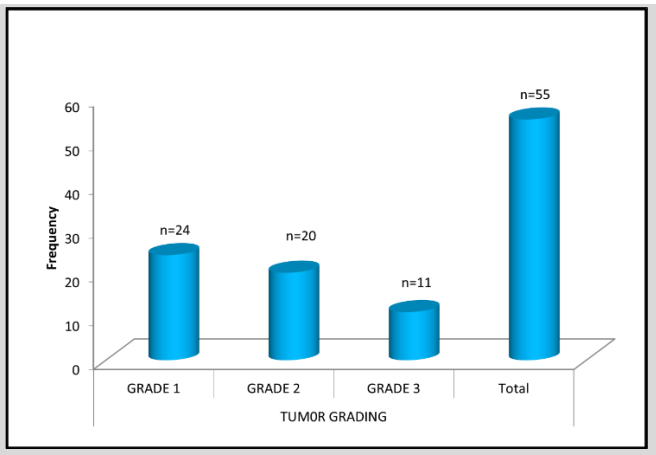

Figure 2: Distribution of tumor grading in the study population

In our study, 29.1% patients had involvement of the left breast, upper outer quadrant, followed by 27.3% patients who had involvement of the right breast, upper outer quadrant, 20.0% patients had left breast lower outer quadrant involvement, followed by 14.6% who had right breast, lower outer quadrant involvement. The right breast, upper inner quadrant, was the least involved (9.1%), Figure 3.

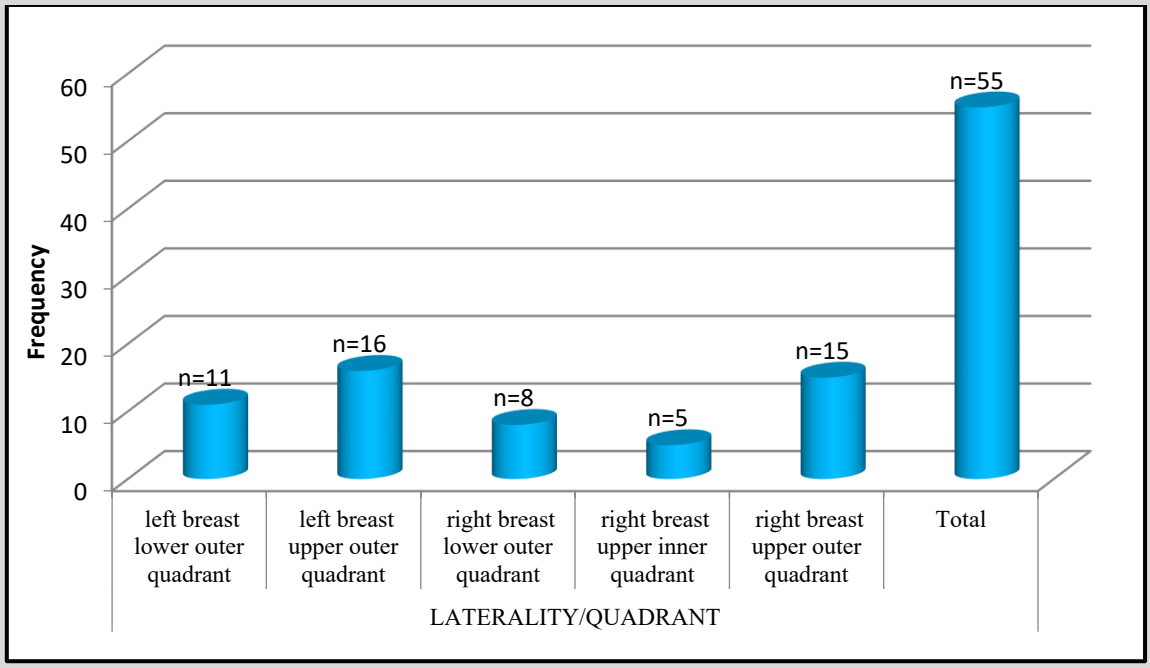

Figure 3: Distribution of laterality/quadrant of the lesions.

The association between CRP and clinicopathological parameters is shown in Table 3. No significant association was observed between CRP and triple-negative breast carcinoma (TNBC) status (p = 0.131).

Table 3: Associations of CRP with clinicopathological parameters

Variable	Category	Normal CRP n (%)	Raised CRP n (%)	p-value
Lymph node status	N0	18 (62.1)	11 (37.9)	0.005
	N1	4 (36.4)	7 (63.6)	
	N2	1 (10.0)	9 (90.0)	
	N3	0 (0.0)	5 (100.0)	
Tumor stage	T1	1 (33.3)	2 (66.7)	0.002
	T2	22 (56.4)	17 (43.6)	
	T3	0 (0.0)	13 (100.0)	
Tumor grade	Grade 1	16 (66.7)	8 (33.3)	0.001
	Grade 2	7 (35.0)	13 (65.0)	
	Grade 3	0 (0.0)	11 (100.0)	
Lymphovascular invasion	No	18 (62.1)	11 (37.9)	0.001
	Yes	5 (19.2)	21 (80.8)	
ER/PR status	Negative	0 (0.0)	13 (100.0)	<0.001
	Positive	23 (54.8)	19 (45.2)	
HER2neu	Negative	23 (51.1)	22 (48.9)	0.003
	Positive	0 (0.0)	10 (100.0)	

Discussion

This study found that among the inflammatory biomarkers evaluated, CRP demonstrated the most consistent and significant associations with adverse clinicopathological parameters, including higher tumor stage and grade, lymph node metastasis, lymphovascular invasion, and negative hormone receptor status. Additionally, TNF-α levels were significantly associated with lymphovascular invasion.

Our findings align with previous large-scale cohort studies and meta-analyses, which have consistently shown that elevated CRP is linked to advanced disease stage, higher tumor grade, and reduced survival in breast carcinoma [14-16]. CRP, primarily induced by IL-6, reflects systemic inflammation and has been implicated in tumor progression through its association with angiogenesis, immune evasion, and metastatic potential [17,18]. The observed correlation between CRP and hormone receptor negativity in our cohort supports prior evidence that inflammatory pathways may influence hormone receptor expression and tumor aggressiveness[19].

The association between elevated TNF-α levels and lymphovascular invasion is biologically plausible, as TNF-α can promote tumor cell intravasation by increasing endothelial permeability and facilitating interaction between cancer cells and the vascular microenvironment [20]. Similar findings have been reported in breast and other epithelial malignancies, supporting TNF-α's role in enhancing metastatic spread [21].

In contrast, IL-6 and IL-8 did not show statistically significant correlations with pathological parameters in our study. Although IL-6 is a key driver of tumor proliferation via JAK/STAT3 activation and has been linked with poor prognosis in several cancers, results in breast carcinoma remain inconsistent across populations [22,23]. Similarly, IL-8 has been implicated in promoting angiogenesis and metastasis, but its association with histopathological features in breast cancer has been variable [24,25].

The lack of significant findings in our analysis may reflect the relatively small sample size, biological variability, or high baseline prevalence of elevation in these cytokines.

Strengths of this study include the use of standardized laboratory methods for biomarker quantification and comprehensive assessment of their relationships with multiple histopathological parameters. Limitations include its single-center, cross-sectional design and absence of survival follow-up, which limit prognostic interpretation. Future large-scale multicenter studies with larger cohorts and survival data are warranted to corroborate these findings and explore the integration of inflammatory biomarkers into prognostic models for breast carcinoma.

Conclusion

Elevated CRP levels showed significant associations with multiple adverse clinicopathological features in breast carcinoma, underscoring its potential as a cost-effective prognostic marker. TNF-α was linked to lymphovascular invasion, suggesting a role in early metastatic spread. Incorporating inflammatory marker assessment into routine pathology reporting could enhance risk stratification in breast cancer.

Abbreviations

CRP: C Reactive protein
ER: Estrogen receptor
HER 2: Human epidermal growth factor receptor 2
IL: Interleukin
NLR: neutrophil-to-lymphocyte ratio
PLR: platelet-to-lymphocyte ratio
PR: Progesterone receptor
SII: systemic immune-inflammation index
TNF-a: Tumor necrosis factor alpha
TNBC: Triple negative breast cancer

Declarations

Ethical Approval and Consent to Participate

The study was approved by the Institutional Ethics Committee of GMC Jammu. Written informed consent was taken from the study participants

Author declarations

All the authors have agreed to send the manuscript for publication.

Availability of supporting data

The data is available and can be produced on reasonable request.

Competing interests

All the authors declare no competing interests.

Funding

No funding

Authors' contributions

Zainab Hashim, Saniya Nisar, and Rabiya Rasheed helped with the conceptualization, collection of data, and manuscript writing. Rajat Gupta and Subhash Bharadwaj helped with the study conceptualization, critical review of the study, and the final manuscript.

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