The Inflammation Equation: Linking Systemic Markers to Breast Cancer Staging

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KEYWORDS

ABSTRACT

Background: Breast cancer is the most prevalent malignancy among women worldwide, and its prognosis is influenced by a complex interplay of biological factors. Recent studies suggest that systemic inflammatory markers—such as C-reactive protein (CRP), interleukin-6 (IL-6), and the neutrophil-to-lymphocyte ratio (NLR)—may serve as potential prognostic indicators. This study aimed to evaluate the correlation between these markers and breast cancer staging in an Indian cohort.
Methods: In this cross-sectional observational study, 60 patients with histopathologically confirmed breast cancer were enrolled at a tertiary care center in Pune, India. Preoperative blood samples were collected to measure CRP and IL-6 levels, and complete blood counts were used to calculate the NLR. Clinical staging was performed according to standard TNM criteria, and tumor grading was determined histologically. Statistical analyses included Spearman's correlation and Receiver Operating Characteristic (ROC) curve analysis to assess the predictive value of the markers.
Results: The study cohort primarily comprised patients aged 51–60 years (31.7%). The most common clinical stages were T2N0Mx (40.0%) and T2N1Mx (30.0%). Although no statistically significant correlation was found between CRP, IL-6, or NLR and tumor grade ($p > 0.05$), ROC analysis revealed that CRP had a moderate discriminatory ability (AUC: 0.661, $p=0.127$) in predicting breast cancer severity, while IL-6 and NLR showed limited predictive power.
Conclusions: Systemic inflammatory markers, particularly CRP, may have some potential in discriminating between breast cancer stages; however, their standalone predictive value appears limited. Further studies with larger cohorts and longitudinal designs are needed to validate these findings and refine prognostic models.

Introduction

Breast cancer is the leading cause of cancer-related morbidity and mortality among women worldwide[1]. Despite significant advances in early detection and therapeutic strategies, breast cancer remains a highly heterogeneous disease with variable clinical outcomes. Increasingly, chronic systemic inflammation has been recognized as a critical factor in cancer initiation, progression, and metastasis[2,3]. In this context, inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and the neutrophil-to-lymphocyte ratio (NLR) have emerged as potential prognostic indicators in several malignancies, including breast cancer[4,5]. Numerous studies have demonstrated that elevated CRP and IL-6 levels are associated with more advanced tumor stages and poorer survival outcomes[6,7]. Similarly, the NLR, which reflects the balance between pro-tumor inflammatory neutrophils and anti-tumor lymphocytes, has been proposed as a readily measurable marker to predict tumor aggressiveness[8]. However, the existing literature shows conflicting evidence regarding the consistency and strength of

these associations. While some investigations report significant correlations between higher inflammatory marker levels and advanced breast cancer stages[9], others have found no clear relationship[10]. A recent meta-analysis underscored the need for further research to standardize the measurement of these biomarkers and clarify their prognostic utility in breast cancer[11]. Moreover, much of the published data originates from Western populations, leaving a gap in our understanding of these relationships in Asian cohorts[12]. Given this gap, our study aims to evaluate the correlation between preoperative serum levels of CRP, IL-6, and NLR and breast cancer staging in an Indian patient cohort. By elucidating how systemic inflammation relates to tumor progression, we hope to provide additional prognostic insights that can refine risk stratification and guide therapeutic decision-making[13,14]. In summary, although the role of systemic inflammation in breast cancer is acknowledged, the precise prognostic significance of specific inflammatory markers remains uncertain. This thesis addresses that gap through a comprehensive analysis of these biomarkers in relation to tumor stage and grade, potentially enhancing clinical management of breast cancer patients[15].

Materials and Methods

Study Design and Setting: This cross-sectional observational study was conducted at Bharati Hospital and Research Institute, Pune, India, from August 2022 to January 2024. The study protocol received approval from the Institutional Ethics Committee, and all participants provided written informed consent.

Study Population: Sixty female patients with histopathologically confirmed breast cancer were included. Patients with a history of neoadjuvant therapy, concurrent infections, autoimmune disorders, or previous corticosteroid treatment were excluded.

Sample size estimation: 60

Sampling Technique: Convinient sampling.

Inclusion Criteria:
1. Any individual with clinical, radiological and pathological diagnosis of breast cancer.

Exclusion Criteria:
1. Patient diagnosed as benign breast disease in post-operative histopathology report.
2. Any previous history of neoadjuvant therapy.
3. Any blood disorders.
4. Any acute or chronic infection/inflammatory diseases (TB, osteoarthritis, etc)
5. Any autoimmune disorder (rheumatoid arthritis, SLE, etc)
6. History of previous treatment with corticosteroid medications.

Data Collection: Demographic and clinical data—including age, menopausal status, tumor size, lymph node involvement, and clinical stage (as per TNM classification)—were recorded. Tumor grading was performed based on histopathological examination.

Laboratory Analysis: Preoperative blood samples were collected to measure CRP and IL-6 using standard immunoassays. Complete blood counts were performed, and the neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Statistical Analysis: Data analysis was carried out using SPSS version 26. Continuous variables are presented as mean ± standard deviation, and categorical data as percentages. Spearman's correlation was used to assess the relationship between inflammatory markers and tumor grade. ROC curve analysis evaluated the ability of CRP, IL-6, and NLR to discriminate between early and advanced stages of breast cancer. A p-value < 0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics: The mean age of the study cohort was 54.3 ± 10.2 years, with the highest proportion of patients (31.7%) in the 51–60 age group. Most patients presented with intermediate-stage breast cancer, predominantly T2N0Mx (40.0%) and T2N1Mx (30.0%). Tumor grading indicated that 60% of cases were moderately differentiated (Grade 2), 21.7% were poorly differentiated (Grade 3), and 15% were well-differentiated (Grade 1).

Inflammatory Markers:

- **CRP:** Mean level was 4.87 ± 9.32 mg/L; 18.3% of patients had elevated CRP levels.
- **IL-6:** Mean level was 64.28 ± 332.40 pg/mL; 18.3% of patients showed abnormal IL-6 values.
- **NLR:** The average NLR was 2.86 ± 1.49, with 38.3% of patients having an abnormal ratio.

Correlation Analysis: Spearman's correlation analysis did not reveal a statistically significant correlation between CRP, IL-6, or NLR and tumor grade ($p > 0.05$).
ROC Curve Analysis: ROC analysis demonstrated a moderate discriminatory capacity for CRP (AUC: 0.661, p=0.127) in differentiating between early and advanced breast cancer stages, while IL-6 (AUC: 0.533, p=0.755) and NLR (AUC: 0.544, p=0.675) had limited predictive ability.

Figure 1: Correlation of NLR with Tumor Grade

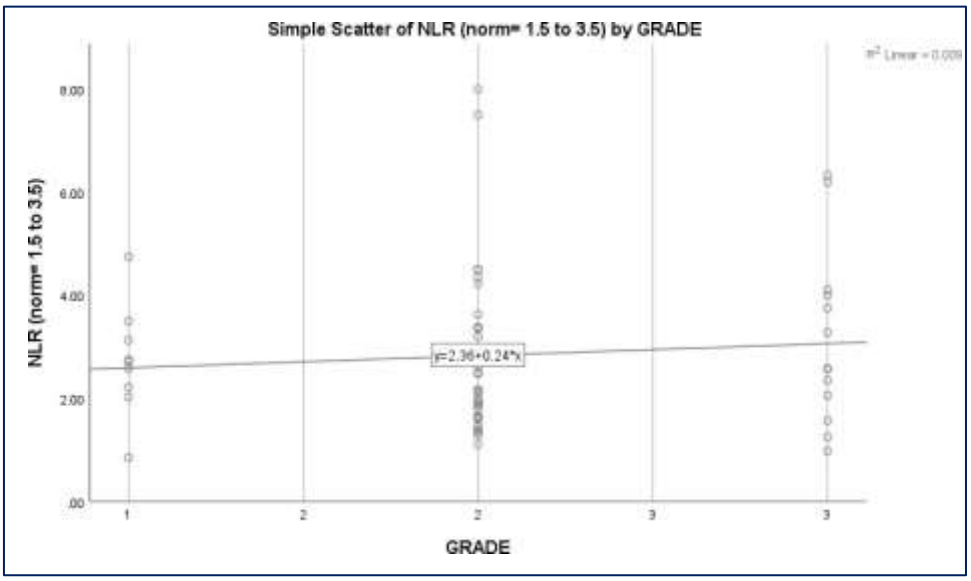


Figure 2: Correlation of CRP with Tumor Grade

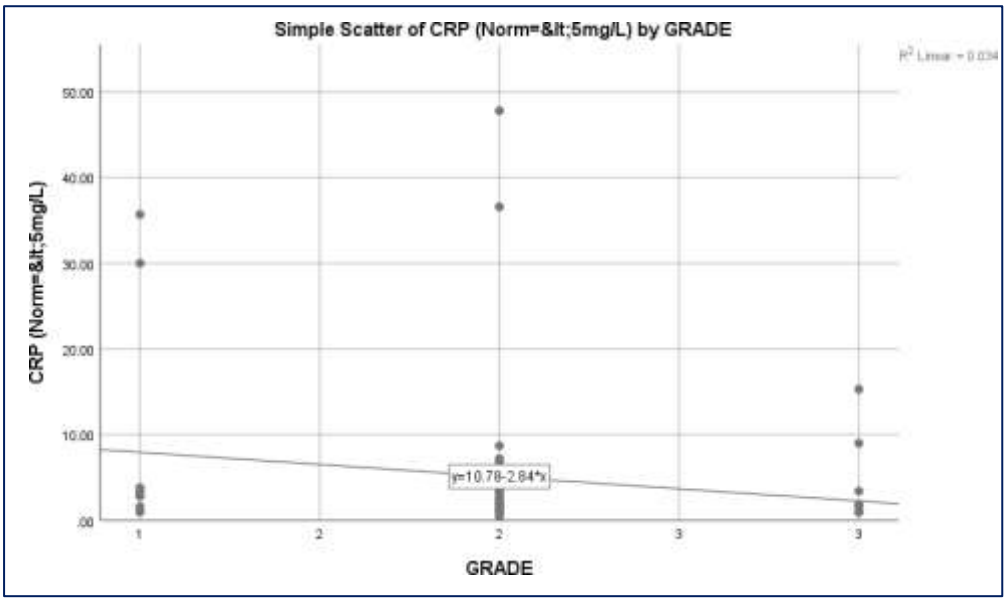


Figure 3: Correlation of IL-6 with Tumor Grade

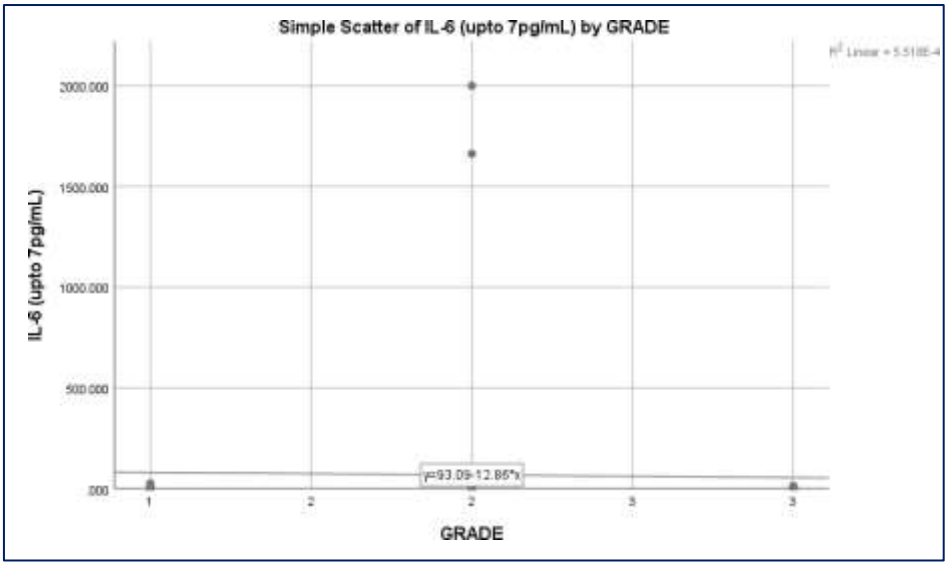
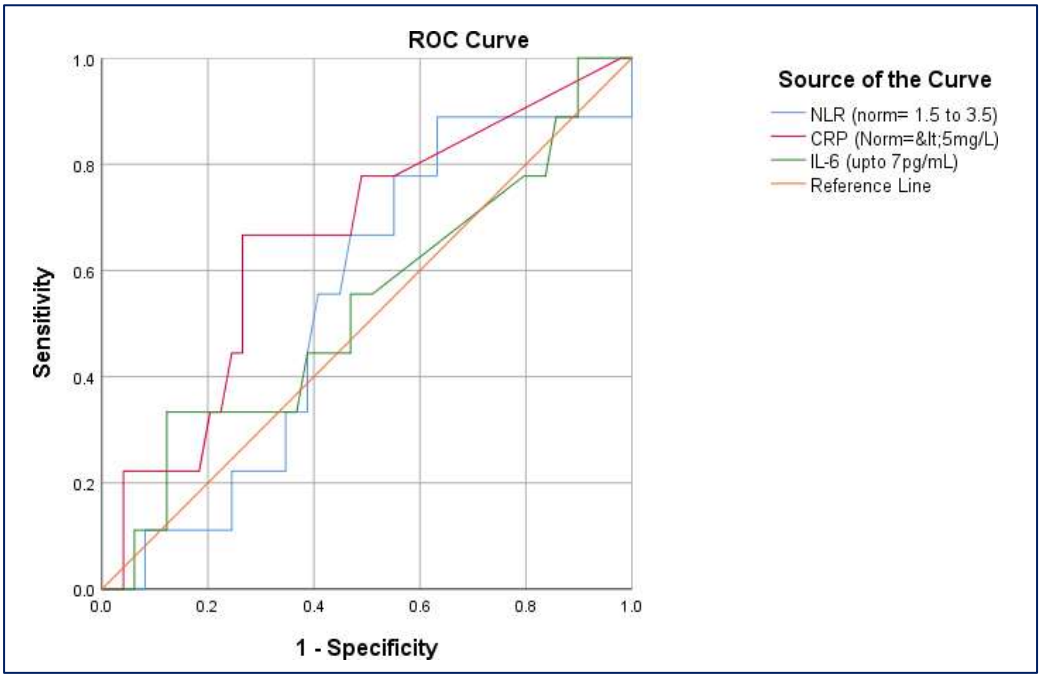


Figure 4: ROC Curve for Inflammatory Markers



Discussion

Our study aimed to investigate the prognostic value of preoperative systemic inflammatory markers in breast cancer staging. Previous research has consistently shown that elevated CRP and IL-6 levels, as well as a higher NLR, are associated with advanced disease and poor outcomes[6,7]. In contrast, other studies have reported no significant correlations between these markers and tumor stage[8,9]. In our cohort, while a trend toward higher inflammatory marker levels was observed in advanced-stage breast cancer, the associations did not reach statistical significance. This discrepancy may be due to factors such as sample size, variability in patient demographics, differences in assay techniques, and tumor heterogeneity.

Our findings align with some recent studies[10,11] that have questioned the standalone prognostic value of these markers. Furthermore, given that much of the previous research is based on Western populations[12], our study contributes valuable data from an Indian cohort, underscoring the need for larger, multicentric studies to further clarify these relationships. In addition, the integration of inflammatory biomarkers into multifactorial prognostic models may enhance their clinical utility.

Conclusion

In summary, our findings suggest that while systemic inflammatory markers such as CRP, IL-6, and NLR are of interest in breast cancer research, their individual predictive value for staging and tumor grading is limited. CRP demonstrated a modest ability to discriminate between stages, but none of the markers showed statistically significant correlations with tumor grade. Further large-scale studies are needed to validate these observations and to explore the combined use of these markers with other clinical parameters for more accurate prognostication.

Declarations

- **Conflict of Interest:** The authors declare that no competing interests exist.
- **Funding:** This study was supported by a research grant from Bharati Vidyapeeth (Deemed to be University), Pune.
- **Ethical Approval:** The study was approved by the Institutional Ethics Committee of Bharati Vidyapeeth (Deemed to be University), Pune.
- **Informed Consent:** Written informed consent was obtained from all participants.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020:GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71:209–49.
2. Kundu JK, Surh YJ. Emerging avenues linking inflammation and cancer. Free Radic Biol Med. 2012 May 1;52(9):2013-37.
3. Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner RN, Neuhouser ML, Wener MH, Baumgartner KB, Gilliland FD, Sorensen BE, McTiernan A, Ulrich CM. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. J Clin Oncol. 2009 Jul 20;27(21):3437-44.
4. Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. *Crit Rev Clin Lab Sci*. 2011;48:155-170.
5. Knüpfer H, Preiss R. Significance of interleukin-6 (IL-6) in breast cancer. *Breast Cancer Res Treat*. 2017;160:145-154.
6. Pierce BL, Ballard-Barbash R, Bernstein L, et al. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol*. 2009;27:3437-3444.
7. Li X, Huang Q, Ding J, et al. Prognostic significance of circulating IL-6 levels in patients with breast cancer: a meta-analysis. *Oncotarget*. 2017;8:82628-82640.
8. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2014;106:dju124.
9. Ethier JL, Desautels D, Templeton AJ, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res*. 2017;19:2.
10. Guthrie GJ, Charles KA, Roxburgh CS, et al. The systemic inflammation-based neutrophil–lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol*. 2013;88:218-230.
11. Gu X, Wang Y, Jiang B, et al. Prognostic significance of the neutrophil-to-lymphocyte ratio in breast cancer: a meta-analysis. *Oncotarget*. 2016;7:8125-8134.
12. Ghoncheh M, Saneei P, Salehiniya H, et al. Worldwide incidence and mortality of breast cancer: Global profile and time trends. *Breast Cancer Res Treat*. 2020;184:249-263.
13. Yu K, Li C, Xu X, et al. Preoperative inflammatory markers as predictors of survival in breast cancer patients. *Cancer Epidemiol*. 2018;55:1-8.
14. Dobrzycka B, Kociemba M, Wieczorek E, et al. Inflammatory markers in breast cancer prognosis. *Clin Chem Lab Med*. 2017;55:177-185.
15. Silva P, Corrêa AP, Amaral J, et al. Systemic inflammation and breast cancer: a comprehensive review. *Clin Transl Oncol*. 2019;21:840-849.