ORIGINAL ARTICLE

Neutrophil-to-lymphocyte ratio as an independent prognostic factor amongst breast cancer patients – A retrospective observational study

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Received: 12-05-2024
Accepted: 20-05-2024

How to cite this article: Singh H, Rathore A, Malik K. Neutrophil-to-lymphocyte ratio as an independent prognostic factor amongst breast cancer patients – A retrospective observational study. Int J Adv Integ Med Sci 2024; 9(2):9-13.

Source of Support: Nil,
Conflicts of Interest: None declared.

Background: Breast cancer is the most common malignancy in women, contributing to 25% of all cancers globally, with 2.3 million new cases annually. In India, the incidence is 1 in 28 women, and for every two women diagnosed, one succumbs to the disease. Male breast cancer is rare, constituting 0.5% of cases. Despite advancements in diagnostics and treatment, tumor grade, stage, and lymph node status remain critical prognostic factors, requiring tertiary care for assessment. **Aim:** The aim of the study was to determine the Neutrophil-to-lymphocyte ratio (NLR) amongst breast cancer patients and evaluate its prognostic significance as per cancer stage. **Materials and Methods:** The study was conducted at Rohilkhand Medical College and Hospital, Bareilly, with 432 breast cancer patients who were diagnosed, treated, and followed for 5 years. NLR values were measured at diagnosis and post-treatment. Patients were categorized by cancer stage and NLR severity. **Results:** The mean age of participants was 45 years. Most tumors were in the upper outer quadrant (57.4%), with ductal carcinoma being the predominant type (60.6%). Advanced stages (III and IV) accounted for 67.8% of cases. Molecular analysis showed 53% of patients had triple-negative breast cancer, followed by Luminal A (17.4%) and Luminal B/HER2-positive subtypes (13.2%). Elevated NLR (>3.33) was observed in 53.7% of patients, indicating a potential association with tumor aggressiveness. **Conclusion:** Although global studies highlight significant prognostic associations of NLR, this study did not replicate similar results, possibly due to demographic and methodological differences. However, the high prevalence of elevated NLR underscores its potential as a prognostic marker. Larger, multicentric studies are recommended to validate NLR's role in breast cancer management in India.

KEY WORDS: Breast cancer prognosis, Inflammatory markers in cancer, Neutrophil-to-lymphocyte ratio, Prognostic biomarkers, Triple-negative breast cancer, Tumor aggressiveness

INTRODUCTION

Breast cancer is the most frequent malignancy amongst women, with estimated 2.3 million new cases being diagnosed worldwide every year which is about 25% of all the cancer in women. Incidence in India comes to be around 1 in 28 women, and for every 2 women diagnosed with breast cancer, 1 dies of cancer. Carcinoma of the male breast accounts for 0.5% of cases of breast cancer.[1]

Researches over the past 20 years has significantly advanced our understanding of condition, better diagnostic and treatment methods, but even today tumor grade, stage, and lymph node status remain the best and most important prognostic factor for breast cancer patients.[2] However, all of these factors require time and expertise, which only a tertiary care center is capable of

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providing such as histopathological grading, hormone receptor status, measurement of tumor proliferation, such as Ki-67, and oncogene studies.[2]

Various inflammatory markers like C-reactive protein, hypoalbuminemia, circulating leukocytes, Neutrophil-lymphocyte ratio, platelet (PLT)-lymphocyte ratio, lymphocyte-monocyte ratio are being studied for evaluating their role as a prognostic marker for various diseases.[3]

Previous studies suggested Neutrophil-lymphocyte ratio can be considered as an independent prognostic marker in different malignancies like ovarian cancer,[4] Renal cell carcinoma,[5] Colorectal cancers,[6] Carcinoma lung,[7] Nasopharyngeal carcinoma,[8] and many more.

Neutrophil-lymphocyte ratio is a simple ratio between the counts of neutrophils and lymphocytes in peripheral blood. Neutrophils are believed to be promotors of tumor spread, and T-cells being protector against cancer.[9]

The typical neutrophil-to-lymphocyte ratio (NLR) ranges from 0.78 to 3.53.[10]

As only a few studies had been done on Neutrophil-lymphocyte ratio as prognostic factor amongst breast cancer patients in India, thus the need for this study.

METHODOLOGY

Aim

The aim of the study was to determine the NLR amongst breast cancer patients and evaluate its prognostic significance as per cancer stage.

Objectives

The objective of the study was to calculate the NLR in patients of breast cancer, to categorize patient groups based on NLR value in all cancer stages, and to correlate the NLR in the outcome of breast cancer according to stage.

Study Design

This was a retrospective observational study.

Study Settings

The present study was conducted in the Department of Surgery, Rohilkhand Medical College and Hospital, Bareilly.

Study Duration

The study period was one year.

Ethical Aspects

This study was conducted after taking due approval from the Institutional Ethics Committee (Reference number -IEC/RMCH/09/2023/APR dated April 19, 2023).

Participants

All patients were diagnosed with breast cancer.

Inclusion Criteria

Patients admitted, staged, and treated in our hospital, and whose follow-up was available for the past 5 years.

Exclusion Criteria

Male breast cancer patients. Already operated patients. Recurrent breast cancer patients. Patients with concurrent autoimmune diseases. Patients who could not be staged.

Sample Size

A sample size of 432 was calculated using the formula 4 pq/L^2.[11] Where p represents the expected prevalence (assumed from previous studies), q is equal to 1-p, and L is the allowable error.

Statistical Analysis

The data were entered and imported into the Statistical Package for the Social Sciences version 23.0 for statistical analysis. Qualitative data were represented in the form of frequency and percentage. Descriptive analysis was done by calculating proportions, means, and standard deviation. Appropriate statistical tests were applied depending on type and the distribution and type of data. $P < 0.05$ was considered significant.

Methodology

After clearance from the Institutional Ethics Committee, a study was conducted in Rohilkhand Medical College and Hospital, Bareilly. Patients admitted, staged, and treated for breast cancer in our hospital and whose follow-up was available for last 5 years were selected. NLR was calculated at the time of diagnosis, before any treatment initiation. This time point was used for the primary analysis correlating with cancer stage values for total leukocyte count and differential leukocyte count, which were taken, and patients were categorized according to the stage of cancer and severity of NLR. Statistical tests such as the Chi-square test, *t*-test, or analysis of variance were applied based on data distribution and type, with a $P < 0.05$ considered statistically significant.

The six-part Sysmex XN-550 a new, automated, compact hematology analyzer designed to generate a full blood count with a standard six-part white blood cell differential and an immature granulocyte count, as well as an optional reticulocyte and optical PLT counts, was used for analyzing.

RESULTS

The present study evaluates the clinical presentation, histopathological characteristics, and prognostic implications of the NLR in breast cancer patients in Bareilly, India offering insights with greater statistical reliability with a larger sample size as compared to smaller previous studies.

As mentioned in Table 1 – most patients were in the middle-aged group, particularly within the fourth and fifth decades of life. Tumors were generally moderate in size and were most commonly located in the upper outer quadrant of the breast. In terms of histological classification, invasive ductal carcinoma emerged as the most frequently diagnosed type. Among molecular subtypes, triple-negative breast cancer (TNBC) was the most common, followed by the Luminal A and HER2-positive subtypes. When analyzing disease staging, a considerable number of patients presented with locally advanced disease. A smaller portion was diagnosed at metastatic stage. More than half of the patients exhibited elevated NLR levels. Skin involvement and lymphovascular invasion were observed in a notable proportion of cases. However, statistical analysis did not find significant associations between NLR levels and clinicopathological features including age (P = 0.200), tumor location (P = 0.200), histological type (P = 0.391), molecular subtype (P = 0.110), disease stage (P = 0.244), skin involvement (P = 0.733), or lymphovascular invasion (P = 0.423). The association between NLR and cancer stage also failed to reach statistical significance (P = 0.367).

Table 1: Summary of results

Clinical presentation	Findings (%)
Mean age of presentation	45 years
Location of tumor (quadrant involved)	
Upper outer	248 (57.4)
Upper inner	49 (11.3)
Lower outer	63 (14.6)
Lower inner	36 (8.3)
Nipple discharge	27 (6.3)
Ulcer	9 (2.1)
Histological type	
Ductal	262 (60.6)
Others	170 (39.4)
Lymphovascular invasion	
Yes	252 (58.3)
No	180 (41.7)
Perineural invasion	
Yes	9 (2.1)
No	423 (97.9)
Skin involvement	
Yes	144 (33.3)
No	288 (66.8)
Stage	
IIA	46 (10.6)
IIB	93 (21.5)
IIIA	119 (27.5)
IIIB	85 (19.7)
IIIC	22 (5.1)
IV	67 (15.5)
Neutrophil-to-lymphocyte ratio	
Low (<3.33)	200 (46.2)
High (>3.33)	232 (53.7)
Molecular profiling	
Luminal A	75 (17.4)
Luminal B	33 (7.6)
Triple negative	229 (53)
Her-2-neu enriched	37 (8.6)
Luminal B/HER positive	58 (13.2)

DISCUSSION

The findings were compared to previous studies, both national and international, to understand the unique features of this study and the potential role of NLR as a prognostic biomarker.

Age of Presentation

Recent Studies coinciding with the similar results include studies like Lehmann *et al*. (2023)[12] reporting TNBC tends to present in younger women, often under 50 years, aligning with our younger mean age. Jiang *et al*. (2019)[13] also concluded similar trends in Asian populations where younger age at diagnosis is common, especially for TNBC. Nabanita *et al*. (2022)[3]: Conducted on 140 patients in Kolkata, India, with the majority aged 40–49 years (50.7%) coinciding with our results and Varsha *et al*. (2020)[14] in a much smaller study with only 30 patients in Karnataka, India, primarily aged 41–50 years again coinciding with the result of our study. Whereas Ghoncheh *et al*. (2022)[15] found that the global mean age to be higher (55–60 years), suggesting geographical variation.

Tumor Location and Size

Nabanita *et al*. (2022)[3] reported a similar size, that is, 4.7 ± 1.8 cm. Varsha *et al*. (2020)[14] study did not provide this data. Recent Studies like Pernas *et al*. (2023)[16] confirmed that the upper outer quadrant is most frequently affected, often attributed to its dense glandular tissue, and Bareche *et al*. (2022)[17] showing similar findings, with upper outer quadrant involvement exceeding 50% in Western populations.

Histological Type

Recent Studies like Waks and Winer (2022)[18] reported ductal carcinoma as the predominant subtype (70–80%) across most populations same as depicted in our study. Gong *et al*. (2021)[19] noted a slightly lower prevalence in cohorts with higher TNBC rates, comparable to our findings.

Molecular Subtypes

Lehmann *et al*., (2023)[12] in their study suggested TNBC prevalence is globally 15–20%, but higher in certain populations such as African ancestry (up to 50%), matching our data. Burstein *et al*., (2015)[20]: Noted the heterogeneity within TNBC subtypes, emphasizing distinct clinical behaviors, consistent with our molecular subtype data. Jin and Mu[21]: Luminal A remains the most common subtype globally, though its prevalence can be lower in cohorts dominated by TNBC.

Nabanita *et al*. (2022)[3] also identified Luminal A as the predominant subtype (40%).

Staging

Pernas *et al*. (2023)[16] and Bareche *et al*. (2022)[17]: Advanced stages (III-IV) are more common in resource-limited settings due to delayed diagnosis, aligning with our data. Jiang *et al*. (2019)[13] found similar findings in large Asian cohorts.

NLR

Gong *et al*. (2021)[19]: Elevated NLR is associated with advanced disease and aggressive subtypes like TNBC, in contrast to our findings. Jin and Mu[21] also highlighted its prognostic importance in predicting poor outcomes in advanced cancers. Nabanita *et al*. (2022)[3] found higher NLR in Stage IIIB. Varsha *et al*. (2020)[14] observed higher NLR (>3.33) in Stage IIA.

Skin and Lymphovascular Involvement

Waks and Winer (2022)[18] and Pernas *et al*. (2023)[16] report similar rates in advanced cancers and TNBC. Jiang *et al*., (2019)[13] found lymphovascular invasion in approximately 50–60% of advanced cases, mirroring our findings.

Clinical Implications

The high prevalence of elevated NLR (>3.33) in this study highlights its potential as a non-invasive, cost-effective biomarker for breast cancer prognosis. Elevated NLR reflects a pro-inflammatory state, which may facilitate tumor progression through immune suppression, angiogenesis, and metastasis. Despite the lack of statistically significant associations in this study, its utility in global literature suggests the need for further research in Indian studies.

Limitations and Future Directions

Sample size and composition

The relatively small sample size compared to large international studies may have limited the statistical power to detect associations.

Standardization of NLR cutoffs

Variations in NLR cutoffs across studies make comparisons challenging. Standardized thresholds are needed for better clinical applicability.

Longitudinal follow-up

Survival outcomes and recurrence rates were not assessed. Future studies should focus on correlating NLR with long-term prognostic outcomes.

Genetic and socioeconomic factors

Differences in population genetics and healthcare access likely influence NLR's prognostic value in this study. Incorporating these variables in future analyses is crucial.

Key Observations

The Present study had a much larger sample size, providing more robust and generalizable results. While the present study showed no significant associations between NLR and clinical or molecular characteristics, other studies identified correlations with specific tumor stages, molecular subtypes, and nodal involvement. Differences in molecular subtype distribution (e.g., Triple Negative in the Present Study vs. Luminal A in Nabanita *et al*.) may reflect regional or demographic variations. The stark contrast in perineural invasion rates (0.02% vs. 90%) highlights possible methodological or reporting discrepancies.

This detailed comparison highlights both the consistency and variability in findings across these studies, likely influenced by sample size, geographic location, and methodology.

CONCLUSION

This study reveals a notable predominance of advanced-stage breast cancer, aggressive molecular subtypes, and elevated NLR among patients in Bareilly, India – reflecting trends often seen in resource-limited settings. While no statistically significant association was found between NLR and disease stage or subtype possibly due to methodological and demographic differences, the consistently high prevalence of elevated NLR underscores its potential clinical relevance. These findings suggest that NLR, despite limitations in statistical correlation, may still serve as a cost-effective, accessible prognostic marker in regions with limited diagnostic infrastructure. The results also highlight an urgent need for early detection strategies and support the pursuit of larger, prospective, multicentric studies to more definitively establish the prognostic role of NLR in the Indian breast cancer population.

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