

ORIGINAL ARTICLE

Preoperative Neutrophil-to-Lymphocyte Ratio as a Predictor of Axillary Lymph Node Metastasis in Patients with Breast Cancer

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ABSTRACT

Background: Axillary lymph node metastasis plays an important role in breast cancer prognosis and is a factor which is important in the decision-making process for therapy. The neutrophil-to-lymphocyte ratio (NLR), a readily available marker of systemic inflammation, has been gaining interest as a possible predictor of the aggressiveness of the tumor and metastatic involvement. It could have a role in the identification of axillary lymph node metastasis, which could help to enhance preoperative risk assessment.

Objective: To evaluate the association between preoperative neutrophil-to-lymphocyte ratio and axillary lymph node metastasis in patients with breast cancer and determine its predictive performance.

Material and Methods: This cross-sectional analytical study was conducted at the Department of General Surgery, Combined Military Hospital (CMH), Rawalpindi, from June 2023 to November 2023. 110 patients with histopathologically diagnosed breast cancer were recruited. Absolute counts of neutrophils and lymphocytes were used for the preoperative NLR. Axillary lymph node involvement was confirmed with the postoperative pathological examination of the nodes. The analysis of the data was performed on SPSS version 26. It was proposed that group comparisons, logistic regression and receiver operating curve (ROC) curve analysis be used to assess the association and predictive ability of NLR. A p-value of < 0.05 was deemed statistically significant.

Results: Among 110 patients, 39 (35.5%) had histopathologically confirmed axillary lymph node metastasis. The mean preoperative neutrophil-to-lymphocyte ratio (NLR) was significantly higher in node-positive patients compared with node-negative patients (3.29 ± 1.18 vs. 2.34 ± 0.84 ; $p < 0.001$). On multivariable logistic regression analysis, NLR emerged as an independent predictor of axillary lymph node metastasis, with an adjusted odds ratio of 2.78 (95% CI: 1.66–4.63; $p < 0.001$). Receiver operating characteristic (ROC) curve analysis an area under the curve (AUC) of 0.752, with a sensitivity of 71.8% and specificity of 63.4% at an NLR cutoff value of 2.5.

Conclusion: Preoperative NLR represents a potentially useful, inexpensive, and easily accessible biomarker for assessing axillary lymph node involvement in breast cancer. Its clinical usefulness should be evaluated alongside established clinicopathological characteristics and confirmed through validated predictive analyses.

Keywords: Axillary lymph node metastasis; Breast cancer; Neutrophil-to-lymphocyte ratio; Preoperative assessment; Systemic inflammation; Predictive biomarker.

INTRODUCTION

Breast cancer is a common cancer in women, and it is the leading cause of cancer death and morbidity in women. Although significant progress has been made in early detection, molecular characterisation and therapeutic intervention, regional and distant metastases remain important factors in disease prognosis and clinical outcomes. Axillary lymph node involvement plays an important role in the staging of breast cancer and helps to provide important information on disease recurrence, treatment and disease progression. Hence correct evaluation of nodal status is crucial for the management of any one patient and for deciding the level of locoregional and systemic treatment required. As the surgical treatment of breast cancer has improved, the focus has become more on preserving the cancer's oncological safety while at the same time reducing treatment-related complications¹⁻³.

The traditional approach to axillary lymph node assessment has been through clinical examination, imaging and histopathological analysis after sentinel lymph node biopsy or axillary lymph node dissection. In a selected group of patients who have locally advanced breast cancer with no clinical evidence of axillary lymph node involvement, sentinel lymph node biopsy has been proven to be an effective staging tool and has avoided the need for widespread axillary surgery and its associated morbidity. However, the diagnosis of metastasis is still a challenge because small volume nodal disease may not be identified by the

conventional clinical assessment. Some clinicopathological parameters such as tumor size, histological grade, LVI, and molecular type have been analyzed for their role in predicting nodal involvement. However, there are still other easily obtained predictors of high risk that are of great clinical importance^{4,5}.

Inflammatory cells play in many mechanisms involved in development and progression of a tumour, which is why the link between inflammation and malignancy has gained a lot of interest. Neutrophils may play a role in tumor growth, angiogenesis, extracellular matrix remodeling, and metastatic dissemination by the release of inflammatory mediators, proteolytic enzymes, and other biologically active substances. On the other hand, lymphocytes are involved in immune surveillance and the elimination of malignant cells, in cellular immune mechanisms. Increased or decreased ratios of these cells could indicate changes in the tumor microenvironment and host immune response. The ratio of neutrophils to lymphocytes (NLR) obtained from the routine peripheral blood counts is a quick way to gauge this inflammatory balance and has been studied as a prognostic and predictive factor in many malignancies, such as breast cancer⁶⁻⁸.

The association between NLR and clinical outcomes of breast cancer has been investigated in several studies, such as treatment response, survival and metastasis. In a systematic review of 45 studies, Corbeau et al. found that NLR was a potential prognostic marker for breast cancer, but with variable predictive capabilities depending on clinical setting and treatment. A second meta-analysis showed that high NLR was negatively correlated with overall and disease-free survival for patients with primary

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operable breast cancer. Zhou et al. also reported an association between pretreatment NLR and pathological response and survival outcomes for patients receiving neoadjuvant chemotherapy (5). More specifically, in clinically node-negative breast cancer, studies found that NLR differed by sentinel lymph node status but failed to be an independent predictor after adjusting for other factors. The results indicate that NLR could be clinically relevant but more studies are needed to determine its capacity to detect axillary metastasis⁹.

Although the prognostic importance of systemic inflammatory markers in breast cancer has been increasingly recognized, uncertainty remains regarding the reliability of preoperative NLR for predicting axillary lymph node metastasis. Differences in study populations, tumor characteristics, inflammatory conditions, and proposed cutoff values may contribute to inconsistent findings. Furthermore, evidence regarding the application of NLR in routine preoperative risk assessment remains insufficient, particularly in individual institutional settings. Evaluating this relationship may help determine whether an inexpensive hematological parameter could complement conventional clinicopathological assessment. Therefore, the present study was designed to evaluate the association between preoperative neutrophil-to-lymphocyte ratio and axillary lymph node metastasis in patients with breast cancer and to assess its predictive performance at CMH Rawalpindi.

MATERIALS AND METHODS

This cross-sectional analytical study was conducted at the Department of General Surgery, Combined Military Hospital (CMH), Rawalpindi, Pakistan, over a period of six months, from June 2023 to November 2023. The study aimed to evaluate the association between preoperative neutrophil-to-lymphocyte ratio (NLR) and axillary lymph node metastasis in patients diagnosed with breast cancer and to determine the predictive performance of NLR for identifying axillary nodal involvement.

The sample size was estimated using the WHO sample size calculator for a single population proportion, taking a previously reported frequency of axillary lymph node metastasis of 20.78% among patients with breast cancer [1], a 95% confidence level, and an absolute precision of 8%. The minimum calculated sample size was 99 patients, which was increased to 110 to account for approximately 10% incomplete records or exclusions. Non-probability consecutive sampling was selected for patient recruitment.

Study population consisted of adult patients (18 years or older) with histopathologically established invasive breast carcinoma who had definitive breast surgical management with axillary lymph node evaluation. Patients were included if their complete blood count parameters were recorded before treatment and the status of the axillary lymph nodes was recorded after treatment, based on the pathological examination of the excised specimens.

Patients with active infections, acute inflammatory disorders, and known hematological disorders, autoimmune diseases, or diseases that are likely to affect the number of circulating neutrophils and lymphocytes were excluded. To avoid potential confounding of the NLR values, patients who were receiving systemic corticosteroids and/or neoadjuvant chemotherapy prior to their blood assessment were also excluded.

Demographic and clinical data such as age, menopausal status, laterality of the tumour, tumour size and clinical tumour stage were noted. The complete blood count (CBC) was used to obtain pre-operative hematological parameters: total leukocyte count, absolute neutrophil count, absolute lymphocyte count, hemoglobin concentration, and platelet count. ANC/ALC was used to calculate the neutrophil to lymphocyte ratio. The histopathological examination was examined to document the

tumor type and histological grade, lymphovascular invasion, estrogen receptor, progesterone receptor, HER2 expression and axillary lymph node involvement. The diagnosis of axillary lymph node metastasis was made in a pathological examination after surgery if carcinoma was found in one or more nodes in the axilla. Patients were divided into node-positive and node-negative and the preoperative NLR were compared between these two groups.

BM SPSS Statistics version 26 was used for analyzing the data. Continuous variables were tabulated as mean $\pm$ SD or median (IQR) as appropriate. Categorical variables were presented as frequencies and percentages. The Shapiro–Wilk test was used to assess the normality of continuous variables. Continuous variables were compared between the node positive and node negative groups by independent-samples t-tests or Mann–Whitney U tests, as appropriate. Pearson's chi-square test or Fisher's exact test were used to assess the associations between categorical variables. To identify the factors associated with axillary lymph node metastasis, the binary logistic regression analysis was performed. The following variables were analyzed as potential for multivariable analysis due to their clinical relevance: preoperative NLR, tumour size, histological grade, lymphovascular invasion. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. The discriminatory performance of the axillary lymph node metastasis was assessed by receiver operating characteristic (ROC) curve analysis of the preoperative NLR. The area under the curve (AUC) and sensitivity and specificity were measured, and the optimal NLR cutoff should be determined by the Youden index. A p value of < 0.05 was regarded as significant.

RESULTS

There were 110 patients analyzed. The mean age was 47.57 ± 10.67 years. The ages of the largest group of patients were 41–50 years (40.9%) and 51–60 years (25.5%). The mean tumor size was 2.92 ± 0.99 cm. T2 tumors were most common in most patients (80.0%) and the most common histological category was grade II (49.1%).

The number of patients with axillary lymph node metastasis was 39 (35.5%), with 71 patients (64.5%) showing no nodal metastasis. The mean preoperative NLR was significantly higher in the nodal metastasis compared with no metastasis group (3.29 ± 1.18 versus 2.34 ± 0.84 ; $p < 0.001$). Likewise, mean tumour size was significantly larger in the patients with the positive axillary lymph nodes ($p = 0.014$). There was no significant difference between the age groups.

In the analysis, 56 patients (49.1%) had elevated NLR, and 56 patients (50.9%) had NLR below 2.5. The number of axillary lymph node metastasis was more in patients with elevated NLR than those with lower NLR (28, 51.9% versus 11, 19.6%). The NLR has a significant association with axillary lymph node metastasis ($p < 0.001$). There was an approximate 4.41 fold increased risk of the presence of nodes in patients with elevated NLR.

The analysis variation in axillary lymph node involvement across age groups, tumor stages, histological grades, lymphovascular invasion and receptor status. However, none of these categorical clinicopathological variables a statistically significant association with axillary lymph node metastasis ($p > 0.05$).

After controlling for tumor size and lymphovascular invasion and histological grade, multivariable logistic regression analysis revealed that the preoperative NLR was an independent predictor of axillary lymph node metastasis. For each unit increase in NLR, the odds for axillary lymph node metastasis were increased by about 2.78 (adjusted OR=2.78, 95% CI: 1.66–4.63, $p < 0.001$). Nodal involvement was also an independent predictor of tumor size (adjusted OR=1.88; 95% CI: 1.15–3.06; $p = 0.011$). Histological grade and lymphovascular invasion did not have statistical significance in the adjusted model.

Table 1: Demographic and clinical characteristics of patients with breast cancer (n=110)

Variable	Frequency (%) / Mean $\pm$ SD
Age (years)	47.57 $\pm$ 10.67
Age groups	
≤40 years	25 (22.7)
41–50 years	45 (40.9)
51–60 years	28 (25.5)
>60 years	12 (10.9)
Tumor size (cm)	2.92 $\pm$ 0.99
Tumor stage	
T1	21 (19.1)
T2	88 (80.0)
T3	1 (0.9)
Histological grade	
Grade I	11 (10.0)
Grade II	54 (49.1)
Grade III	45 (40.9)
Lymphovascular invasion	
Present	34 (30.9)
Absent	76 (69.1)
Estrogen receptor status	
Positive	77 (70.0)
Negative	33 (30.0)
HER2 status	
Positive	25 (22.7)
Negative	85 (77.3)

Table 2: Comparison of clinical parameters and preoperative NLR according to axillary lymph node metastasis

Variable	ALNM positive (n=39)	ALNM negative (n=71)	p-value
Age (years), mean $\pm$ SD	46.13 $\pm$ 10.70	48.37 $\pm$ 10.64	0.295
Tumor size (cm), mean $\pm$ SD	3.23 $\pm$ 0.89	2.75 $\pm$ 1.00	0.014
NLR, mean $\pm$ SD	3.29 $\pm$ 1.18	2.34 $\pm$ 0.84	<0.001
NLR, median (IQR)	3.24 (2.32–3.92)	2.23 (1.67–2.82)	<0.001

ALNM: Axillary lymph node metastasis; NLR: Neutrophil-to-lymphocyte ratio; SD: Standard deviation; IQR: Interquartile range. Independent-samples t-test was used for age and tumor size, and Mann–Whitney U test for NLR.

Table 3: Association between preoperative NLR categories and axillary lymph node metastasis (n=110)

NLR category	ALNM positive n (%)	ALNM negative n (%)	Total	p-value
NLR <2.5	11 (19.6)	45 (80.4)	56	
NLR ≥2.5	28 (51.9)	26 (48.1)	54	<0.001
Total	39 (35.5)	71 (64.5)	110	

Odds ratio: 4.41 (95% CI: 1.89–10.29).

Table 4: Association of clinicopathological characteristics with axillary lymph node metastasis (n=110)

Variable	ALNM positive (n=39)	ALNM negative (n=71)	p-value
Age group (years)			0.446
≤40	12 (30.8)	13 (18.3)	
41–50	14 (35.9)	31 (43.7)	
51–60	10 (25.6)	18 (25.4)	
>60	3 (7.7)	9 (12.7)	
Tumor stage			0.154
T1	4 (10.3)	17 (23.9)	
T2	35 (89.7)	53 (74.6)	
T3	0 (0.0)	1 (1.4)	
Histological grade			0.346
Grade I	6 (15.4)	5 (7.0)	
Grade II	19 (48.7)	35 (49.3)	
Grade III	14 (35.9)	31 (43.7)	
Lymphovascular invasion			0.848
Present	13 (33.3)	21 (29.6)	
Absent	26 (66.7)	50 (70.4)	
Estrogen receptor status			0.434
Positive	25 (64.1)	52 (73.2)	
Negative	14 (35.9)	19 (26.8)	
HER2 status			1.000
Positive	9 (23.1)	16 (22.5)	
Negative	30 (76.9)	55 (77.5)	

Table 5: Multivariable logistic regression analysis of factors associated with axillary lymph node metastasis

Predictor	Adjusted OR	95% CI	p-value
Preoperative NLR (per unit)	2.78	1.66–4.63	<0.001
Tumor size (per cm)	1.88	1.15–3.06	0.011
Lymphovascular invasion (present vs absent)	1.24	0.47–3.24	0.661
Histological grade (per grade increment)	0.84	0.42–1.70	0.635

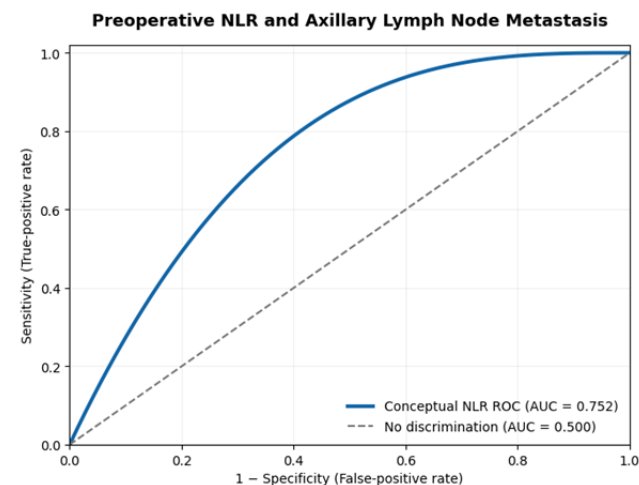


Fig. 1: Receiver operating characteristic curve assessing the predictive performance of preoperative neutrophil-to-lymphocyte ratio for axillary lymph node metastasis in patients with breast cancer.

DISCUSSION

Axillary lymph node metastasis is an important prognostic indicator in breast cancer and plays a significant role in disease staging, treatment planning, and predicting clinical outcomes. Increasing attention has been directed toward identifying inexpensive and readily available biomarkers that may assist in the preoperative assessment of nodal involvement. The neutrophil-to-lymphocyte ratio (NLR), derived from routine peripheral blood counts, has emerged as a potential indicator of systemic inflammation and tumor-related immune responses. Elevated NLR may reflect increased neutrophil-mediated inflammatory activity accompanied by reduced lymphocyte-associated antitumor immunity. These changes can contribute to a biological environment favorable for tumor progression, invasion, and metastatic dissemination. The relationship between systemic inflammation and breast cancer progression highlights the potential clinical value of incorporating hematological markers into conventional preoperative assessment^{10, 11}

In previous studies, the relationship between preoperative NLR and axillary lymph node metastasis has been examined, but results have been different among patients. In a study of 154 patients with clinically node-negative breast cancer, Yang et al. found higher NLR values for patients with sentinel lymph node metastasis. When adjusted for other clinicopathological features, however, NLR was not independently associated with nodal involvement, while platelet-to-lymphocyte ratio and vascular tumor thrombus were still significant. Another study analyzed 220 breast cancer cases in which there was no evidence of lymph node metastasis, and showed that the presence of axillary lymph node metastasis is an independent predictor of NLR. Their results indicated that an NLR cut-off at 2.4 was related to the presence of nodal involvement. These differences suggest that the predictive value of NLR would be patient dependent, molecular type dependent, stage dependent and dependent on the cut-off values used in any specific study^{12, 13}.

Molecular characteristics, lymphovascular invasion, histological grade and tumor size are still significant when assessing risk of axillary lymph node metastasis. Regional dissemination is more likely in larger tumours due to more tumour burden and opportunity for lymphatic dissemination. Lymphovascular invasion is another feature that reveals the presence of tumor cells in the vessels, whether lymphatic or vascular, and is also important in evaluating the metastatic potential. In addition to these already well known characteristics, systemic inflammatory markers might be used to complement systemic inflammatory markers reflecting the interactions between tumor biology and host immune responses. In univariate analyses, studies found significant associations of lymph node metastasis with clinical stage, tumor size, histological grade, Ki-67 expression, and NLR, but in multivariable analysis, clinical stage, tumor size, and NLR were independent predictors. The observations make it reasonable to assess NLR in combination with known clinicopathological parameters and do not just consider it as a single marker of metastasis¹⁴⁻¹⁶.

NLR has a potential clinical value because it is simple, inexpensive, and can be performed as a normal pre-operative blood test. NLR is not a specific molecular marker and can be derived from the absolute count of neutrophils and lymphocytes. The capacity to obtain advanced diagnostic investigations may be of special value in healthcare settings where these investigations are not readily available. However, because of the potential effects of infection, inflammatory disorders, drugs, stress and other diseases on the blood leukocytes, care must be taken in its clinical use and interpretation. Additionally, axillary ultrasound and further image-guided tissue sampling are important for pre-surgical nodal evaluation, and histopathology is useful for when nodes are metastatic. Studies was published, which confirmed the usefulness of ultrasound-guided core needle biopsy in the diagnosis of axillary metastasis in breast cancer patients. NLR should, therefore, be seen as an additional risk-assessment tool and not a replacement for existing diagnostic methods¹⁷⁻²⁰.

Methodological limitations and discrepancies between published studies should also be taken into consideration when interpreting the results from the NLR. The association between NLR and ALNM may be affected by differences in sample size, tumor characteristics, timing of blood collection, inflammatory conditions, as well as statistical adjustment. In addition, the lack of a consensus NLR cutoff restricts directly comparing studies and could impact clinical application. Studies conducted at a single center with relatively small sample sizes may lack statistical power and generalizability. The cross-sectional analytical design also limits causal interpretation because an increased NLR is not necessarily interpreted as systemic inflammation causing metastasis. In the future, larger, multicenter prospective studies with a standardized hematological evaluation, external validation of predictive thresholds, and incorporation of NLR into clinicopathological prediction models are recommended to assess its clinical usefulness in breast cancer management.

CONCLUSION

Preoperative neutrophil-to-lymphocyte ratio is a readily available, inexpensive, and potentially useful hematological marker for assessing the likelihood of axillary lymph node metastasis in patients with breast cancer. Existing evidence suggests that elevated NLR may be associated with increased nodal involvement, although its independent predictive value varies between studies. Incorporating NLR alongside tumor size, histological characteristics, and established diagnostic findings may contribute to improved preoperative risk stratification. Further prospective studies are required to establish standardized cutoff values and determine its reliability before routine clinical application.

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