ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 05 | May - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EVALUATION OF POSITIVE LYMPH NODE RATIO AS PROGNOSTIC TOOL IN INFILTRATING DUCTAL CARCINOMA

Histopathology

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ABSTRACT

Background: Lymph node ratio (LNR) has emerged as a potential prognostic tool in breast cancer. This study evaluated its association with clinicopathological parameters in infiltrating ductal carcinoma. **Methods:** A cross-sectional study analyzed 61 cases of infiltrating ductal carcinoma. LNR was categorized as low (0.01-0.20), intermediate (0.21-0.65), and high (>0.65) risk. Associations with clinicopathological parameters were analyzed using Chi-square or Fischer's exact test. **Results:** The study population showed predominance in the 51-60 years age group (33.3%). Significant associations were observed between LNR and lymphovascular invasion (p=0.037), primary tumor size (p=0.007), nodal status (p<0.001), and disease stage (p<0.001). While 50% of high-risk LNR cases showed lymphovascular invasion, hormone receptor status and molecular subtypes did not demonstrate significant correlations (p>0.05). **Conclusion:** LNR showed significant associations with established prognostic factors, supporting its potential role in risk stratification. The strong correlations with pathological parameters suggest its utility in prognostication and treatment planning.

KEYWORDS

Lymph node ratio, Infiltrating ductal carcinoma, Breast cancer, Prognostic factors, Lymphovascular invasion, Molecular subtypes

INTRODUCTION

Breast cancer remains one of the most prevalent malignancies worldwide, with infiltrating ductal carcinoma (IDC) representing approximately 80% of all diagnosed cases. [1] The accurate staging and prognostication of breast cancer continue to be crucial elements in determining appropriate treatment strategies and predicting patient outcomes. Among the various prognostic factors, lymph node status has consistently emerged as one of the most significant predictors of survival in breast cancer patients. [2]

Traditionally, the absolute number of positive lymph nodes has been used as a key component in the TNM staging system, serving as the primary method for nodal staging in breast cancer. However, this approach has several limitations, particularly in cases where the total number of retrieved lymph nodes varies significantly between patients.[3] This variability can be attributed to multiple factors, including differences in surgical technique, anatomical variations, and the thoroughness of pathological examination.

The concept of lymph node ratio (LNR), defined as the ratio of positive lymph nodes to the total number of retrieved lymph nodes, has emerged as a potentially more refined prognostic tool.[4] This metric aims to address the limitations of absolute lymph node counts by providing a standardized measure that accounts for the extent of lymph node dissection. Recent studies have demonstrated that LNR may offer superior prognostic value compared to the absolute number of positive nodes, particularly in specific subgroups of breast cancer patients.[5]

The biological basis for the prognostic significance of LNR lies in its ability to reflect both the extent of lymphatic invasion by tumor cells and the adequacy of lymph node dissection. A high LNR may indicate not only a greater tumor burden but also a more aggressive disease phenotype with enhanced metastatic potential.[6] Furthermore, research has suggested that LNR might serve as a more reliable indicator of the host immune response against tumor cells, as it considers both positive and negative nodes in its calculation. [7]

Several studies have investigated the correlation between LNR and various clinical outcomes in breast cancer patients. Meta-analyses have demonstrated that elevated LNR is significantly associated with decreased overall survival (OS) and disease-free survival (DFS) in patients with node-positive breast cancer.[8] However, the optimal cutoff values for risk stratification using LNR remain a subject of debate, with different studies proposing varying thresholds.[9]

The integration of LNR into existing prognostic models has shown promise in improving risk stratification and treatment decision-making. When combined with other established prognostic factors such as tumor size, grade, and molecular subtypes, LNR has demonstrated enhanced predictive accuracy for patient outcomes.[10] This suggests that incorporating LNR into clinical practice could potentially lead to more personalized treatment approaches and improved patient care.

Despite these promising findings, several challenges remain in the standardization and widespread implementation of LNR as a prognostic tool. These include the need for validation in larger, prospective studies, the establishment of universally accepted cutoff values, and the development of clear guidelines for its integration into clinical decision-making. Additionally, the role of LNR in the context of modern molecular classification systems and targeted therapies requires further investigation.

Aims And Objectives

The primary objectives of this study were to investigate the association between lymph node ratio and various clinicopathological parameters including age, hormone-receptor status, grade, lymphovascular invasion, pathological tumor stage (pT), and regional lymph node status (pN) in patients with infiltrating ductal carcinoma. Additionally, the study aimed to evaluate the correlation between lymph node ratio and molecular subtypes of breast carcinoma. These objectives were designed to enhance our understanding of lymph node ratio as a prognostic tool in breast cancer management.

MATERIALS AND METHODS

Study Design

This investigation was conducted as a cross-sectional study utilizing retrospective data analysis. The study included a total of 61 cases of infiltrating ductal carcinoma, following predetermined inclusion and exclusion criteria.

Patient Selection

All cases of infiltrating ductal breast carcinoma that met the study criteria were included in the analysis. The study excluded small biopsies without lymph node dissection and specimens received after chemotherapy and radiotherapy to ensure the accuracy of lymph node evaluation and eliminate potential treatment-related changes that could affect the assessment.

Data Collection

Comprehensive demographic and clinical data were retrieved from written archive files. The collected information encompassed patient age, hormone-receptor status, histological features, tumor grade, presence or absence of lymphovascular invasion, pathological tumor stage (pT), total number of lymph nodes resected, and the number of positive lymph nodes identified during pathological examination.

Lymph Node Ratio Calculation And Classification

The lymph node ratio was calculated for each case by dividing the number of positive lymph nodes by the total number of lymph nodes resected. Based on previously established criteria, the lymph node ratios were stratified into three risk categories: low risk (LNR = 0.01–0.20), intermediate risk (LNR = 0.21–0.65), and high risk (LNR > 0.65)[14]. This classification system was adopted from validated research protocols to ensure standardization and comparability with existing literature.

Statistical Analysis

All collected data were systematically entered into Microsoft Excel spreadsheets and subsequently analyzed using SPSS version 22 software (IBM SPSS Statistics, Somers NY, USA). Categorical data were expressed as frequencies and proportions to provide clear representation of the distribution of various parameters within the study population. For analytical statistics, the Chi-square test was employed as the primary test of significance for qualitative data. In instances where 2x2 tables were analyzed, Fischer's exact test was utilized when appropriate. Statistical significance was established at a p-value less than 0.05, following standard statistical conventions. The statistical methodology was designed to ensure robust analysis while maintaining the validity and reliability of the results.

RESULTS

The study analyzed 61 cases of infiltrating ductal carcinoma to evaluate the association between lymph node ratio (LNR) and various clinicopathological parameters. The age distribution of the study population showed a predominance in the 51-60 years age group (33.3%), followed by patients aged >60 years (23.8%). The distribution of LNR across age groups did not show statistical significance (p=0.788).

Lymphovascular invasion (LVI) was present in 7 cases (11.1%) and absent in 54 cases (88.9%). A significant association was observed between LVI and LNR (p=0.037), with 50% of cases in the high-risk LNR group showing lymphovascular invasion compared to only 8.9% in the low-risk group. (Table 1)

Analysis of primary tumor stage revealed that T2 tumors were most common (46.0%), followed by T3 (36.5%). The association between primary tumor stage and LNR was statistically significant (p=0.007). Notably, 64.3% of intermediate-risk LNR cases were T3 tumors, while 50% of high-risk LNR cases were either T2 or T4b. (Table 1)

The regional lymph node status (pN) showed a highly significant correlation with LNR (p<0.001). N1 disease was predominantly associated with low-risk LNR (35 out of 37 cases), while all N3 cases (n=2) fell into the high-risk LNR category. N2 disease showed a more distributed pattern across LNR categories. (Table 1)

Staging analysis demonstrated a significant association with LNR (p<0.001). Stage IIIA was the most common (31.1%), followed by Stage IIB (24.6%). All Stage IIIC cases (n=6) were distributed between intermediate and high-risk LNR categories, with no cases in the low-risk group. Conversely, all Stage IA and IIB cases were exclusively in the low-risk LNR category.

Regarding tumor grade, Grade 1 tumors were most frequent (55.7%), followed by Grade 2 (37.7%). The association between grade and LNR did not reach statistical significance (p=0.118), although 75% of high-risk LNR cases were Grade 1 tumors.

Hormone receptor analysis revealed that 55.6% of cases were ER-positive and 57.1% were PR-positive. HER2 positivity was observed in 41.3% of cases. Ki67 was >14% in 66.7% of cases. The associations between hormone receptor status and LNR were not statistically significant (ER: p=0.128, PR: p=0.753, HER2: p=0.104, Ki67: p=0.47). However, all cases in the high-risk LNR group were ER-positive, and 75% were both PR-positive and HER2-positive. (Table 2) Molecular subtyping showed equal distribution between Luminal A and Luminal B subtypes (33.3% each), followed by Triple-negative breast cancer (TNBC) (22.2%) and HER2+ (11.1%). The association between molecular subtypes and LNR was not statistically significant (p=0.267). However, the high-risk LNR category showed a notable distribution with 50% each of Luminal A and Luminal B cases, with no representation of HER2+ or TNBC subtypes. (Table 2)

The analysis revealed that stage, regional lymph node status (pN), primary tumor size (T), and lymphovascular invasion showed significant associations with LNR (p<0.001, p<0.001, p=0.007, and p=0.037 respectively). In contrast, age, tumor grade, hormone receptor status, and molecular subtypes did not demonstrate statistically significant associations with LNR in this study population.

Table 1: LNR association with LVI, Primary tumor, Regional Lymph node and Stage

Lymphovascular invasion	**Low risk**	**Intermediate risk**	**High risk**	**p Value**
Yes	4	11	2	0.037
No	41	1	2	
Primary Tumor				
T1	2	0	0	0.007
T2	24	2	2	
T3	13	9	0	
T4a	2	2	0	
T4b	2	1	2	
Regional Lymph Node Status				
N1	35	2	0	< 0.001
N2	8	12	2	
N3	0	0	2	
Stage				
IA	2	0	0	< 0.001
IIA	11	1	0	
IIB	15	0	0	
IIIA	11	8	0	
IIIB	4	2	1	
IIIC	0	3	3	

Table 2: LNR association with Grade, ER, PR, Her2Neu and Molecular Type

Grade	**Low risk**	**Intermediate risk**	**High risk**	**p value**
Grade 1	24	7	3	0.118
Grade 2	18	4	1	
Grade 3	1	3	0	
ER				0.128
Negative	20	8	0	
Positive	25	6	4	
PR				0.753
Negative	20	6	1	
Positive	25	8	3	
Her2				0.104
Negative	25	11	1	
Positive	20	3	3	
Ki67				0.47
>14%	32	8	2	
<14%	13	6	2	
Molecular typing				0.267
HER2+	5	2	0	
Luminal A	12	7	2	
Luminal B	17	1	2	
TNBC	10	4	0	

DISCUSSION

The present study evaluated the significance of lymph node ratio (LNR) as a prognostic tool in infiltrating ductal carcinoma by analyzing its association with various clinicopathological parameters. The findings demonstrate significant correlations between LNR and several important prognostic factors.

The age distribution in our study showed a predominance in the 51-60 years age group (33.3%), which aligns with the findings of Wang et al. [11] who reported a median age of 54 years in their analysis of 1589 breast cancer patients. However, unlike their study, which found age to be an independent predictor of LNR (p=0.023), our analysis did not show a significant correlation (p=0.788).

The significant association between lymphovascular invasion (LVI) and LNR (p=0.037) observed in our study corroborates the findings of Ahn et al. [12] who reported a strong correlation (p<0.001) in their analysis of 7741 breast cancer patients. Their study demonstrated that patients with LVI had a significantly higher mean LNR (0.32 vs. 0.18) compared to those without LVI, similar to our observation where 50% of high-risk LNR cases showed LVI presence.

The correlation between tumor size and LNR (p=0.007) in our study is consistent with the results of Solak et al. [13] who analyzed 571 breast cancer cases and found a significant association (p<0.001) between increasing tumor size and higher LNR values. They reported that T3/T4 tumors were associated with a mean LNR of 0.41, compared to 0.23 for T1/T2 tumors.

The highly significant correlation between pN stage and LNR (p<0.001) aligns with the comprehensive analysis by Zhang et al. [8] who studied 4262 node-positive breast cancer patients. They found that LNR was more discriminative than pN staging in predicting overall survival, particularly in patients with 1-3 positive nodes (p<0.001).

Regarding molecular subtypes, while our study did not find a significant association with LNR (p=0.267), Li et al. [15] reported contrasting results in their analysis of 3759 patients, where they found significant differences in LNR across molecular subtypes (p=0.018), particularly between Luminal A and triple-negative subtypes.

The prognostic value of LNR in relation to hormone receptor status has shown varying results across studies. While our analysis found no significant correlation, Matsunaga et al. [16], reported that LNR had stronger prognostic significance in hormone receptor-positive patients (HR=2.8, 95% CI: 1.9-4.1) compared to hormone receptor-negative patients (HR=1.9, 95% CI: 1.2-3.0).

The stage-wise distribution of LNR in our study showed significant correlation (p<0.001), supporting the findings of Chen et al. [17], who analyzed 1068 patients and found that LNR added prognostic value independent of traditional TNM staging (p<0.001). They reported 5-year overall survival rates of 85%, 75%, and 55% for low, intermediate, and high LNR groups, respectively.

CONCLUSION

This study demonstrates that lymph node ratio serves as a valuable prognostic tool in infiltrating ductal carcinoma, showing significant associations with established prognostic factors including lymphovascular invasion, tumor size, nodal status, and disease stage. The findings suggest that LNR could be integrated into existing staging systems to enhance prognostic accuracy and guide treatment decisions. While associations with molecular subtypes and hormone receptor status were not statistically significant in our cohort, the patterns observed warrant further investigation in larger studies. The strong correlation with pathological parameters supports the potential role of LNR in risk stratification and treatment planning for breast cancer patients.

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