Lymph Node Ratio as an Independent Prognostic Factor in Breast Cancer: A Retrospective Study of 4060 Patients Undergoing Axillary Lymph Node Dissection

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Abstract

In 4060 breast cancer patients undergoing ALND, lymph node ratio (LNR) outperformed pN staging as an independent predictor of DFS and OS. Higher LNR significantly correlated with worse survival, with optimal cutoffs of 0.2 and 0.5. LNR-based stratification demonstrated clear prognostic separation, supporting its role in refining risk assessment beyond conventional nodal staging.

Background: Pathological nodal (pN) staging in breast cancer is based on the number of positive nodes but may be influenced by surgical extent and technique. Lymph node ratio (LNR)—the ratio of positive to total nodes—accounts for both tumor burden and nodal yield, potentially improving prognostic accuracy. **Methods:** We retrospectively analyzed data from 4060 breast cancer patients who underwent axillary lymph node dissection (ALND) between 1995 and 2021 at a tertiary cancer center in India. Disease-free survival (DFS) and overall survival (OS) were assessed using Kaplan–Meier curves and log-rank tests. Correlation analysis and multivariate analysis were used to compare prognostic utility of LNR versus pN stage. Optimal LNR cutoffs were identified using Youden's index. **Results:** The median follow-up was 93.8 months. On multivariate analysis, LNR retained a strong independent prognostic value for both DFS (HR = 2.00 for LNR 0.2-0.5; HR = 3.29 for LNR > 0.5; $P < .001$) and OS (HR = 1.77 for LNR 0.2 to 0.5; HR = 2.77 for LNR > 0.5; $P < .001$). LNR cutoffs of 0.24 (DFS) and 0.21 (OS) were identified. Stratification into 3 LNR groups (≤ 0.20, 0.21-0.50, > 0.50) showed significantly different survival outcomes (log-rank $P < 0.001$). **Conclusions:** LNR is a superior and independent prognostic marker compared to pN stage in breast cancer patients undergoing ALND. Incorporating LNR into prognostic models may enhance risk stratification and guide adjuvant treatment decisions.

Clinical Breast Cancer, Vol. 26, No.xxx, 67–72

Keywords: Axilla, Axillary lymph nodes, Breast cancer, LNR, Staging

Introduction

Breast cancer is the most common cancer in females and the second most common cancer overall according to GLOBOCAN 2022 data. It is the most common cancer in India accounting for 13.6% of the cancer burden in 2022, and also the most common cause of cancer related mortality in India, accounting for 10.6% of cancer associated deaths.[1]

Axillary lymph node status is the most important prognostic factor for breast cancer.[2] NCCN has long recommended removal of at least 10 lymph nodes for adequate axillary staging in patients undergoing axillary lymph node dissection (ALND).[3,4] AJCC eighth edition defines nodal staging based on number of positive nodes.[5] However, since it relies on absolute nodal counts, it fails to account for variation in surgical extent, expertise and pathologi-

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Submitted: Jan 11, 2026; Revised: Feb 19, 2026; Accepted: Feb 21, 2026; Epub: 24 February 2026

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1526-8209/$ - see front matter
https://doi.org/10.1016/j.clbc.2026.02.014

cal processing—a limitation that may compromise staging accuracy and therapeutic planning.[6]

With current protocols including neoadjuvant chemotherapy for most node positive cases and reports of lower lymph node yields in post NACT patients, there may be a need for alternative prognostic parameters.[7] Lymph node ratio (LNR), defined as the proportion of pathologically positive nodes to the number of examined nodes, integrates both tumor burden and surgical effort. Recent studies have shown a prognostic relationship between LNR and survival but neither a consensus, nor a cutoff value have been established due to heterogenous and disordered data.[8]

In this study, we evaluate the prognostic value of lymph node ratio on survival in patients who have undergone axillary lymph node dissection for breast cancer at our center.

Methods

The study has been conducted in a tertiary care oncology center in North India. It involves retrospective analysis of data from a prospectively maintained database at the Department of Surgical Oncology at our center. 4060 breast cancer patients (cT1-T4, cN0-N3) who underwent axillary lymph node dissection are included in this study from 1995 to 2021 with most of the patients being operated after 2010.

All patients who present with diagnosed breast cancer or a breast lump undergo a complete triple assessment as needed with clinical history and examination followed by bilateral mammography/sonography and tissue diagnosis when needed. For early breast cancers (Stage I and II), staging workup included chest x-ray and ultrasound abdomen and pelvis. For locally advanced cancers, a CECT of chest, abdomen and pelvis along with a bone scan or a PET-CT scan was done for staging. Tissue diagnosis was obtained by means of core biopsy using 14G needles (image guidance used, if needed). All patients underwent ER, PR testing. Her 2 neu testing was included after it became available in 2008 at our center.

Initially (1995 -2010) all patients underwent upfront surgery with ALND at our center. SLNB was slow to pick up due to availability and logistic issues, even after the validation of SLNB by NSABP B-32 trial in 2004. Since 2010, most patients who have undergone ALND had locally advanced or node positive disease at presentation. Neoadjuvant chemotherapy is now routinely given for TNBC > 1 cm and Her 2 positive tumors > 2 cm. For hormone receptor positive cases, NACT is reserved for locally advanced cases and patients with poor tumor breast ratios who want breast conservation, after careful discussion with patients. Adjuvant chemotherapy and radiation has been given according to time-specific standardized protocols with inclusion of genomic testing like Oncotype Dx and Can-assist for decision making in the recent times.

Statistics

Data was collected regarding demographics, clinical, stage, histopathology, surgical procedure, recurrences. Disease free survival (DFS) was taken from time of treatment completion to recurrence or last follow-up. Overall survival (OS) was taken from registration to mortality or last follow-up. Lymph node positivity ratio (LNR) was defined as the ratio of number of positive nodes divided by the number of total nodes harvested. Analysis was performed using JASP version 0.19.3. Youden's index was used to analyze the node positivity ratio and survival after adjusting for zero spiked data. Pearson's test was used to determine correlation. Univariate and multivariate analysis was done using Cox proportional hazards test. Due to multicollinearity between pathological nodal staging and LNR, separate multivariate models were created for both with same set of covariates and a comparison was done using likelihood ratios. RFS and OS analysis was done using Kaplan Meier curves and log rank test.

Table 1 Patient Characteristics

Characteristics	Numbers
Age (Mean)	49.3 y
Sex	
Males	65
Females	3995
cT stage	
T1	242
T2	1394
T3	753
T4	1671
cN	
N0	1318
N1	1809
N2	776
N3	157
NACT received	1291
pN	
N0	1554
N1	1034
N2	1051
N3	421
ENE	586
Molecular subtype	
Luminal	1832
Her 2 enriched	705
TNBC	1090
Her 2 unknown, ER/PR negative	423
Adjuvant chemotherapy	2273
Adjuvant radiation	2456
Recurrence	1012
Axillary recurrence	120
Local recurrence	205
Mortality	1286

Results

Mean age of patients was 49.3 years. Of these, 65 were males. (Table 1) T3 and T4 stage was seen at presentation in 59.7% (2424) patients. Clinically, 67.5% patients were clinically node positive. But pathologically, after surgery, 61.7% (2506) were node positive. A total of 1012 patients had recurrences (24.9%) of which 120 had axillary recurrences (2.9% of total, 11.8 % of recurrences). The mean number of lymph nodes excised was 13.69.

Figure 1 Correlation of LNR with survival.

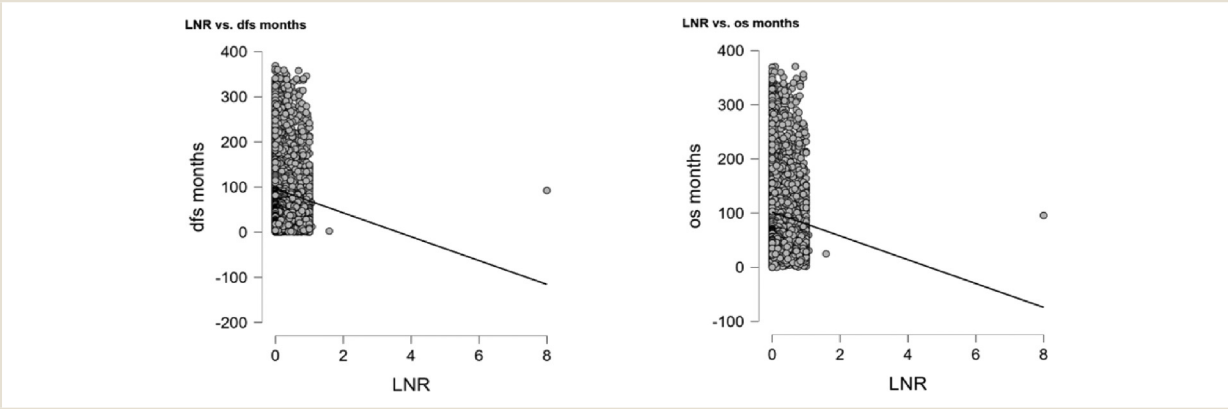


Table 2 Correlation With Survival

Variable	DFS Correlation (r)	DFS *P*-Value	OS Correlation (r)	OS *P*-Value
Tumor size	−0.06	< .001	−0.055	< .001
Number of positive nodes	−0.127	< .001	−0.111	< .001
pN	−0.11	< .001	−0.104	< .001
LNR	−0.069	< .001	−0.07	< .001
Extranodal extension	−0.07	< .001	−0.069	< .001

Lymph Node Ratio

Higher lymph node ratio correlated significantly with poorer DFS (Pearson's $r = -0.118$, $P < .001$) and OS (Pearson's $r = -0.101$, $P \leq .001$)(Figure 1). Pathological nodal status (pN) was also significantly associated with poorer RFS (Pearson's $r = -0.110$, $P < .001$) and OS (Pearson's $r = -0.104$, $P < .001$) (Table 2).

Using Youden's index, the LNR cutoff value for DFS was found to be 0.24 and for OS, it was 0.21.

Univariate and Multivariate Analysis

On univariate analysis, multiple factors were significantly associated with both DFS and OS (Table 3), suggesting a strong individual impact on survival outcomes. For DFS, LNR exhibited the most pronounced prognostic effect, showing a strong dose-response relationship. Patients with LNR 0.2 to 0.5 experienced more than double the hazard of recurrence or death (HR = 2.11, $P < .001$), while those with LNR > 0.5 had over 3.5-fold increased risk (HR = 3.53, $P < .001$), both compared to LNR < 0.2. For OS, LNR showed similar relationship. Patients with LNR 0.2 to 0.5 experienced a 1.75-fold increased mortality risk (HR = 1.75, $P < .001$), while those with LNR > 0.5 had a 2.63-fold increased risk (HR = 2.63, $P < .001$) (Table 3).

On multivariate analysis for DFS, the dose-response relationship persisted, with LNR 0.2 to 0.5 patients exhibiting double the recurrence risk (HR = 2.00, $P < .001$) and LNR > 0.5 patients showing over triple the risk (HR = 3.29, $P < .001$). The minimal attenuation of LNR effect sizes from univariate to multivariate analysis (LNR > 0.5: 3.53 → 3.29) underscores its robust independent prognostic value. For OS, the dose-response relationship strengthened, with LNR 0.2 to 0.5 patients exhibiting a 1.77-fold increased mortality risk (HR = 1.77, $P < .001$) and LNR > 0.5 patients showing a 2.77-fold increased risk (HR = 2.77, $P < .001$). Notably, the hazard ratio for LNR > 0.5 increased from 2.63 in univariate analysis to 2.77 in multivariate analysis, indicating an even stronger independent effect after accounting for confounding variables.

Statistical Comparison of Nodal Staging Systems

Due to multicollinearity between pathological nodal stage and LNR, we assessed whether LNR stratification offered a prognostic advantage over the conventional pathological nodal (pN) classification. For both overall survival (OS) and disease-free survival (DFS), 2 nested multivariable Cox models were constructed, 1 with pN status and the other with LNR stratification. The models were compared using likelihood ratio tests. LNR stratification, demonstrated a significantly better fit than pN stage for both OS. The improvement in model fit is evidenced by the substantial increase in log-likelihood for both endpoints (Table 4).

Survival analysis

The median follow-up time was 93.8 months. Kaplan–Meier survival analysis demonstrated a significant difference in both overall survival (OS) and disease-free survival (DFS) when patients were stratified by lymph node ratio (LNR) categories - < 0.2, 0.2 to 0.5 and > 0.5. Patients with a low LNR (≤ 0.20) exhibited the most favorable outcomes, while those with a high LNR (> 0.5) had markedly reduced OS and DFS. The differences among the 3 groups

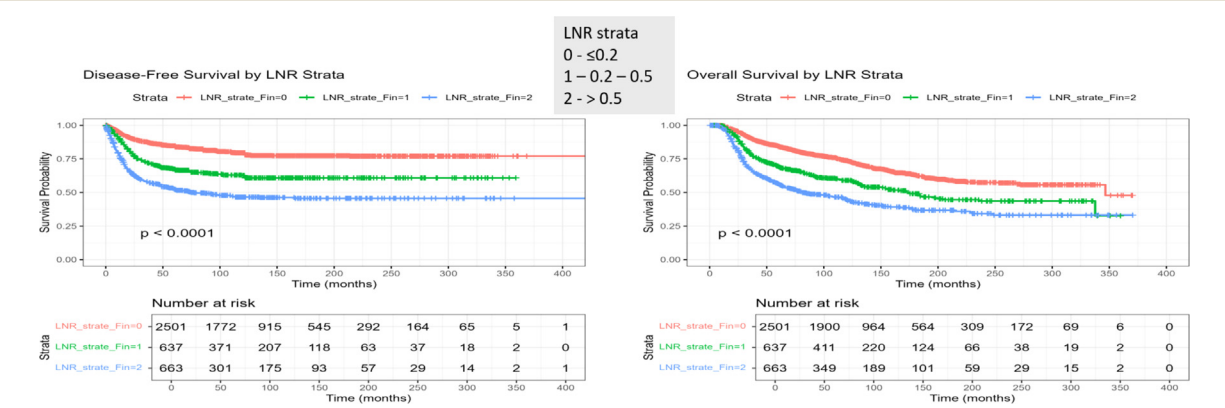
Table 3 Univariate and Multivariate Analysis

Variable	Univariate DFS		Multivariate DFS		Univariate OS		Multivariate OS	
	HR (95% CI)	*P*-Value	HR (95% CI)	*P*-Value	OS HR (95% CI)	*P*-Value	OS HR (95% CI)	*P*-Value
Tumor size (per mm)	1.12 (1.10-1.14)	< .001	1.07 (1.04-1.09)	< .001	1.11 (1.09-1.13)	< .001	1.08 (1.06-1.10)	< .001
pN1	1.33 (1.12-1.58)	.001	—	—	1.16 (1.01-1.35)	.041	—	—
pN2	2.67 (2.26-3.15)	< .001	—	—	2.04 (1.75-2.36)	< .001	—	—
pN3	3.42 (2.86-4.08)	< .001	—	—	2.42 (2.05-2.84)	< .001	—	—
Extranodal extension (ENE)	2.40 (2.09-2.76)	< .001	—	—	2.00 (1.76-2.28)	< .001	—	—
LNR (0.2-0.5)	2.11 (1.79-2.47)	< .001	2.00 (1.63-2.46)	< .001	1.75 (1.51-2.02)	< .001	1.77 (1.45-2.16)	< .001
LNR (> 0.5)	3.53 (3.06-4.08)	< .001	3.29 (2.72-3.98)	< .001	2.63 (2.31-3.00)	< .001	2.77 (2.30-3.32)	< .001
Age (per year)	0.99 (0.98-0.99)	< .001	0.99 (0.98-1.00)	.005	1.02 (1.01-1.02)	< .001	1.01 (1.00-1.02)	.013
Neoadjuvant chemo	2.23 (1.96-2.53)	< .001	1.66 (1.30-2.10)	< .001	1.89 (1.68-2.13)	< .001	1.36 (1.08-1.71)	.009
Adjuvant chemo	0.63 (0.55-0.71)	< .001	0.67 (0.53-0.85)	< .001	0.53 (0.47-0.59)	< .001	0.57 (0.46-0.71)	< .001
Adjuvant RT	1.55 (1.35-1.79)	< .001	1.07 (0.87-1.31)	.5	1.15 (1.03-1.30)	.017	1.02 (0.84-1.23)	.8
Her 2 enriched	2.75 (2.22-3.41)	< .001	2.85 (2.27-3.56)	< .001	2.37 (1.92-2.92)	< .001	2.67 (2.15-3.31)	< .001
Triple negative (TNBC)	2.03 (1.68-2.47)	< .001	2.25 (1.85-2.75)	< .001	1.85 (1.54-2.22)	< .001	2.17 (1.79-2.62)	< .001

Table 4 Statistical Comparison of Nodal Staging Systems

Endpoint	Model	Nodal Variable	Log-Likelihood	Likelihood Ratio χ^2	df	*P*-Value
Overall survival	1	pN stage	−5009.1	(Reference)		
	2	LNR Stratification	−5001.1	15.94	1	< .001
Disease-free survival	1	pN stage	−4616.3	(Reference)		
	2	LNR Stratification	−4610.0	12.62	1	.00038

Figure 2 Kaplan–Meier curves showing DFS and OS stratified according to LNR.



were statistically significant (log-rank $P < .001$ for both OS and DFS) (Figure 2).

Discussion

The AJCC nodal staging for breast cancer is mainly based on the number of positive nodes, and for those where an ALND is required, NCCN recommends a minimum of 10 nodes to be excised for adequate staging since the early 2000s. This was based on studies conducted in the early 1990s. With the advent of neoadjuvant therapies, it was realized over the past few years that post NACT patients had a lower lymph node yield with less than 10 nodes being reported in up to 35% patients.[7] There also exists variability in surgical expertise and pathological handling, leading to underestimation of lymph nodal burden, under staging and inadequate treatment.

Lymph node ratio has been described as a prognostic marker for breast cancer, some studies claiming it to be better than the current N staging.[6,8] In our study also, on univariate analysis for both DFS and OS, the magnitude of association observed for LNR strata exceeded that of conventional pN staging, particularly for intermediate and high-risk categories, suggesting LNR may provide superior risk stratification for disease recurrence. The enhanced prognostic performance of LNR in multivariate analysis, with effect sizes that increased for OS and showed minimal attenuation for DFS, provides compelling evidence for its robust independent value in predicting survival in a large real-world cohort of breast cancer patients undergoing axillary lymph node dissection at a high-volume tertiary oncology center. On comparing with pathological nodal staging using separate models, the improvement in model fit for LNR stratification over pN stage is evidenced by the substantial increase in log-likelihood for both endpoints. We therefore conclude that lymph node ratio stratification may be statistically superior predictor of patient survival compared to the pN classification in this cohort.

The cutoff values for LNR have been variably described in various studies. Multiple studies have shown a cutoff value of 0.2 to 0.25 to consistently predict a poorer survival.[6,9-12] We found that a cutoff of 0.24 and 0.21, predicted poorer DFS and OS respectively. Atahan et al.[13] stratified patients using ≤ 0.25, 0.26 to 0.50, and > 0.50, and confirmed the prognostic significance of this model for both disease-free and overall survival. Kim et al.[14] showed using cutoffs of 0.25 and 0.55, that LNR was a better prognosticator than pathological N stage for DFs and disease specific survival. Liu et al.[8] published a meta-analysis and described how multiple cutoffs ranging from 0.2 to 0.6 have all been shown to predict a poorer survival outcome.[14] Vinh Hung et al.[6] validated cutoffs of 0.2, 0.2-0.65 and > 0.65 for prediction of poorer survival. We found a cutoff of 0.24 for DFS and 0.21 for OS. On stratifying patients into 3 categories based on LNR, we found a significant difference in survival of patients with LNR ≤ 0.2, 0.-0.5 and > 0.5.

Even though most initial studies evaluated the prognostic value of LNR in patients undergoing upfront surgery only, LNR has shown to retain its prognostic value across various clinical settings. Keam et al.[9] demonstrated that LNR > 0.25 predicted worse outcomes in patients receiving NACT, where nodal yields may be suppressed due to chemotherapy-induced fibrosis. A recent meta-analysis published by Liu et al. suggested higher LNR associated with shorter DFS and OS in patients receiving neoadjuvant chemotherapy.[15] A possible role in radiation planning was also suggested when Fortin et al., Atahan et al. and Tai et al. reported that nodal irradiation conferred survival benefit primarily in patients with LNR > 0.40 or > 0.50.[13,16,17] Since our data includes all subset of patients, as treatment has evolved over the last 3 decades, and yet the LNR cutoffs are similar to above studies, it suggests a uniformity in the prognostic value of LNR across all subsets.

The value of number of positive lymph nodes on prognosis is well known. More recently, various studies are emphasizing on the prognostic value of negative lymph node count.[18,19] We believe, LNR provides a balance as it represents all 3 facets, ie, the number of positive nodes, number of total nodes harvested and thus, also the number of negative nodes. For a given number of metastatic lymph nodes, removing more total nodes will result in a lower lymph node ratio (LNR). Therefore, LNR captures not only the extent of nodal tumor burden but also reflects the adequacy of the lymphadenectomy performed. In this way, it serves as a surrogate marker for both oncologic thoroughness and the safety margin within the regional lymphatic basin, thus accounting for the heterogeneity in lymph node dissection. However, overly aggressive nodal dissection may artificially reduce the LNR without offering additional survival benefit, while increasing the risk of morbidity. This underscores the need for standardized surgical techniques to ensure both accurate staging and clinically meaningful LNR interpretation.

This study has various limitations including the retrospective nature of data. The dataset represents 3 decades of patients and we concede that the management of breast cancer and axilla has fundamentally changed with many Western trials showing a move away from axillary LND to sentinel lymph node biopsy and more recently, omission of axillary staging altogether. These trials, though valid for a Western population, are away from the reality of many low and middle income countries including India where a significant number of patients present with locally advanced or metastatic cancers with lack of SLNB facilities in many government and private hospitals, leading to axillary dissection still being performed. It is in these patients that LNR can be used as a prognostic factor.

Conclusion

This study reinforces the prognostic value of lymph node ratio (LNR) as an independent predictor of survival and more accurate than pathological nodal staging alone in breast cancer patients undergoing axillary lymph node dissection. Stratification into LNR categories of ≤ 0.20, 0.21 to 0.50, and > 0.50 provided clear differentiation in both overall and disease-free survival, with higher LNRs correlating with significantly poorer outcomes. Our findings are consistent with a growing body of international evidence and support the integration of LNR into routine risk assessment models.

Clinical Practice Points

- Pathological nodal (pN) staging may underestimate prognostic risk due to variability in nodal yield after ALND.
- Lymph node ratio (LNR) provides a robust, surgery-independent measure of nodal tumor burden.
- LNR independently predicts disease-free and overall survival, outperforming conventional pN staging.
- LNR-based stratification needs prospective validation and assessment for use to guide treatment decisions.

Consent to Participate

Each patient has given consent to be included in academic research at the time of admission.

Disclosure

The authors have stated that they have no conflicts of interest.

CRediT authorship contribution statement

Ashutosh Mishra: Writing – review & editing, Validation, Resources, Project administration, Methodology, Data curation,

Conceptualization. **SVS Deo:** Resources, Project administration, Methodology, Investigation, Conceptualization. **Chinmay Bagla:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Sandeep Bhoriwal:** Methodology, Data curation. **Jyoti Sharma:** Investigation, Data curation. **Naveen Kumar:** Writing – review & editing, Data curation. **Jyoutishman Saikia:** Writing – review & editing, Resources, Data curation. **Babul Bansal:** Resources, Data curation. **Sunil Kumar:** Supervision, Project administration. **Ajay Gogia:** Investigation, Data curation. **Atul Batra:** Validation, Investigation. **DN Sharma:** Validation, Investigation. **Sandeep Mathur:** Investigation, Data curation.

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