Superiority of Pathologic Lymph Node Ratio over Positive Lymph Node Count in Operated Early-Stage Breast Cancer

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AIM: In early-stage breast cancer, the axillary lymph nodes play a crucial role in determining the prognosis of the disease. The rate of lymph node involvement might be a more valuable prognostic factor than the number of positive lymph nodes. Therefore, we aimed to evaluate whether the lymph node ratio (LNR) is a superior prognostic indicator compared to the pathologic lymph node count in early-stage disease.

METHODS: We included 3053 non-metastatic, lymph node-positive breast cancer patients who were treated and followed at 6 medical oncology centers in Türkiye between 2004–2018. Based on LNR, patients were classified into three risk groups: high (>0.65), intermediate (0.21–0.65), and low (≤0.20).

RESULTS: Classification of patients according to the TNM8 system based on the number of positive lymph nodes revealed that pathologic lymph node count (pN)1 accounted for 49.0% (n = 1495), pN2 for 30.0% (n = 917), and pN3 for 21.0% (n = 641). Based on the LNR risk group, the low-risk group accounted for 45.4% (n = 1385), intermediate for 36.2% (n = 1105), and high for 18.4% (n = 563) of the total patients. For the entire patient cohort, the 5- and 10-year disease-free survival (DFS) were 93% and 67%, respectively, while overall survival (OS) rates were 95% and 75%, respectively. The median DFS for patients with N1, N2, and N3 disease was 149 months (94.2–203.7), 120.1 months (108.2–132.0), and 81.8 months (68.4–131.1), respectively ($p < 0.001$). The median DFS for the three LNR risk groups (low, intermediate, and high risk) was 148.9 months (95.3–202.6), 118.7 months (99.9–137.7), and 81.8 months (68.2–95.3) respectively. Increasing LNR rate was an independent prognostic factor for DFS, according to multivariate analysis ($p < 0.001$). Furthermore, the median DFS was 133 months for pathologic N1 patients in the LNR intermediate-high risk group, while the median DFS was not reached in patients with LNR and the pN2 low risk group ($p = 0.034$).

CONCLUSIONS: This study confirms the significance of LNR as a prognostic factor for DFS. The results show that in certain specific subgroups, LNR provides more information than pathologic lymph node counts.

Keywords: breast cancer; early-stage breast cancer; lymph node ratio; pathologic lymph node staging; prognosis; lymph node count

Introduction

The number of lymph nodes involved in early-stage breast cancer (BC) plays a crucial role in determining the prognosis of the disease [1, 2, 3]. The American Joint Committee on Cancer (AJCC) staging system for breast cancer categorizes axillary lymph node status based on the number of metastatic lymph nodes [4]. The axillary approach has gained substantial attention in BC surgery. In recent years, a significant shift has occurred in managing axillary lymph nodes. Additionally, the surgical approach for the axillary region may vary according to the oncology center and the experience of the surgeon and pathologist. These factors can affect the number of axillary lymph nodes removed and subsequently impact staging [5]. Inaccurate staging due to an incorrect determination of the number of involved axillary lymph nodes may lead to incomplete treatment and incorrect assessment of the prognosis [6].

In the current TNM classification, staging is based on the number of metastatic lymph nodes without considering the total number of lymph nodes removed [7]. Recent studies have indicated that positive lymph node ratio (LNR) might

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be a better prognostic factor than positive lymph node number [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18]. According to these studies, LNR can be used as an alternative indicator to the pathologic lymph node staging system for predicting prognosis [5, 8, 9, 11, 18, 19]. Based on LNR, there are three risk groups: high (>0.65), intermediate (0.21–0.65), and low (≤0.20) [5]. This classification has been used in several subsequent investigations on LNR. While there is a concordance between LNR and pathologic lymph node count, some studies have reported significant discordance in specific subgroups, especially between pathologic lymph node count (pN)1 and intermediate-high-risk group, and pN2 and low-risk group [11, 12, 13, 14, 15, 16, 17, 18, 19].

Therefore, this study aimed to determine whether the LNR is superior to the pathological lymph node number in patients with non-metastatic BC.

Materials and Methods

Characteristics of Study Subjects

This study included 3053 non-metastatic, lymph node-positive BC patients, who were treated and followed at 6 medical oncology centers in Türkiye (Dicle University, Medeniyet University, Ankara City Hospital, Erciyes University, Okmeydanı Training and Research Hospital, and İnönü University) between 2004–2018. Demographic information, medical history, menopausal status, and disease-related clinicopathological parameters (including histological subtype, tumor size, grade, Ki-67 index, presence of lymph node involvement, hormone, and Human epidermal growth factor receptor 2 (HER2) receptor status), and treatment-related information, such as type of surgery (breast-conserving surgery vs. total mastectomy), adjuvant treatment (chemotherapy, hormonal treatment, and adjuvant radiotherapy) were retrospectively analyzed through the hospital file records. Histopathological diagnosis such as axillary lymph node involvement and primary tumor, was confirmed in all patients. Pathologic staging of BC was performed according to AJCC version 8 [4].

Inclusion and Exclusion Criteria

Women who underwent axillary lymph node dissection, with the total number of nodes examined in the pathology report, were included in this study. However, the patients with a small number of lymph nodes removed in axillary dissection (less than 10 lymph nodes), who received neoadjuvant treatment, or who had distant organ metastases detected at diagnosis were excluded.

Test Methods and Procedures

Immunohistochemistry (IHC) was used to determine estrogen receptor (ER) and progesterone receptor (PR) status. HER2 status was evaluated utilizing IHC (Dako) and fluorescence *in situ* hybridization (Roche). A three-point intensity scale (0 to 3+) was used for IHC scoring. Tumors with a HER2 score of 0 or 1+ were categorized as negative, while those with a score of 3+ were called positive. However, for those with a borderline HER2 score of 2+, HER2 amplification was reevaluated and confirmed by Fluorescence *in situ* hybridization (FISH).

Missing data constituted a small portion of the database. The deficiencies in data collection were associated with the retrospective and the multicenter nature of the study. Due to differences in pathology reports of different centers, there was missing data regarding some postoperative pathology findings (histological type, tumor grade, lymphovascular invasion vs.).

The LNR was calculated by dividing the number of involved axillary lymph nodes by the total number of axillary lymph nodes removed. Based on LNR, patients were classified into three risk groups as previously defined: high (>0.65), intermediate (0.21–0.65), and low (≤0.20). This study was approved by the Ethics Committee of Dicle University (399-1.9.2021). The study was conducted following the principles of the Declaration of Helsinki. Furthermore, informed consent of the patients was waved by Dicle University, as the study utilized publicly available data.

Statistical Analysis

Disease free survival (DFS) was defined as the period from the beginning of treatment until documented disease progression or death. Overall survival (OS) was defined as the period from the first day of treatment until the last follow-up or death. The prognostic factors for breast cancer identified in previous studies were included in the analysis model. Statistical analyses were conducted employing SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to evaluate patient characteristics and parameter frequencies. Numerical variables with a normal distribution were analyzed using Student's *t* test, while non-normally distributed or non-parametric variables were analyzed employing the Mann-Whitney U test. Furthermore, categorical variables were evaluated utilizing the Chi-square test. Descriptive statistics methods, multiple imputation methods and expectation maximization (EM) little's MCAR test was used for missing data analysis. For missing data imputation, series mean and missing data replacement method, Expectation Maximization algorithm (EMA) and Regression Base Imputation (RBI) methods were used, models were created with original data and data sets where cases with missing data were excluded, and analyses were repeated. Mann Whitney U and student *t* tests were used to understand the connection between parameters with missing data. Cox regression analysis was performed for univariate and multivariate survival analyses. The confidence interval was accepted as 95%, and the two-sided p-value < 0.05 was considered statistically significant.

Table 1. Histopathological and baseline characteristics of the study subjects.

All patients (n = 3053)	pN1 (n = 1495)	pN2 (n = 917)	pN3 (n = 641)	*p*-value
	median/n (%)	median/n (%)	median/n (%)	
Age	50 (21–83)	49 (23–85)	50 (18–87)	0.672
Menopausal status				
Premenopausal	641 (47.1%)	402 (46.5%)	269 (44.3%)	0.515
Postmenopausal	720 (52.9%)	462 (53.5%)	338 (55.7%)	
Histology				
Ductal	1203 (84.8%)	743 (83.9%)	486 (80.2%)	0.116
Lobular	78 (5.5%)	45 (5.1%)	40 (6.6%)	
Others	138 (9.7%)	98 (11.1%)	80 (13.2%)	
Grade				
1	90 (6.6%)	51 (6.0%)	31 (5.3%)	<0.001
2	804 (59.2%)	456 (53.7%)	277 (47.5%)	
3	465 (34.2%)	342 (40.3%)	275 (47.2%)	
ER				
Positive	1023 (72.5%)	616 (69.8%)	411 (67.3%)	0.054
Negative	389 (27.5%)	266 (30.2%)	200 (32.7%)	
PR				
Positive	1008 (71.3%)	591 (67.1%)	387 (63.4%)	0.001
Negative	406 (28.7%)	290 (32.9%)	223 (36.6%)	
HER2				
Positive	187 (13.0%)	132 (15.3%)	152 (25.2%)	<0.001
Negative	1246 (87.0%)	732 (84.7%)	452 (74.8%)	
Tumor size				
T1–2	1200 (88.6%)	719 (83.3%)	433 (72.4%)	<0.001
T3–4	154 (11.4%)	144 (16.7%)	165 (27.6%)	
Ki-67				
≥14	990 (70.0%)	574 (65.2%)	390 (63.9%)	0.008
<14	424 (30.0%)	307 (34.8%)	220 (36.1%)	
LVI				
Positive	398 (32.6%)	400 (46.8%)	244 (42.5%)	<0.001
Negative	822 (67.4%)	454 (53.2%)	330 (57.5%)	

ER, estrogen receptor; PR, progesterone receptor; HER2, Human epidermal growth factor receptor 2; pN, pathologic lymph node count; pT, pathological Tumor; LVI, lymphovascular invasion.

Results

This study included 3053 female BC patients from 6 medical oncology centers. The median age at diagnosis was 50 years (18–87 years), and 53.7% (n = 1520) of the patients were postmenopausal. The median number of axillary lymph nodes removed was 17 (10–99), while the median number of metastatic axillary lymph nodes was 4 (1–95). According to TNM8 classification based on the number of positive lymph nodes, the patients were categorized as follows: pN1 (n = 1495; 49.0%), pN2 (n = 917; 30.0%), and pN3 (n = 641; 21.0%). Furthermore, based on the LNR, patients were divided into low (n = 1385; 45.4%), intermediate (n = 1105; 36.2%), and high (n = 563; 18.4%) LNR groups. Moreover, the rates of ER-positive, PR-positive, and HER2-positive disease were 70.6% (n = 2050), 68.4% (n = 1986), and 16.2% (n = 471), respectively. Additionally, among them, 83.5% (n = 2432) had ductal histology, 38.8% (n = 1082) had grade 3 disease, and 39.4% (n = 1042) had lymphovascular invasion. Patient characteristics and tumor histopathological features are shown in Table 1.

Among the patients, 3013 (98.7%) received at least one form of systemic therapy. 2976 (97.5%) patients underwent chemotherapy, 2312 (75.7%) received hormonal therapy, and 322 (10.5%) received anti-HER2 treatment. Breast-conserving surgery was performed on 715 (23.4%) patients and mastectomy was performed on 2112 (69.2%) patients. Furthermore, 2756 (90.3%) patients were treated with adjuvant radiotherapy.

Moreover, the median follow-up time was 68 months (16–156). During this time, we observed 558 (18.3%) recurrences and 294 (9.6%) deaths. For the entire patient cohort, the 5- and 10-year disease-free survival (DFS) were 93% and 67%, respectively, while OS rates were 95% and 75%, respectively. Among patients with N1, N2, and N3 disease,

Table 2. Univariate and multivariate analyses of disease-free survival (DFS).

	Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (≤50/>50 years)	1.01 (0.99–1.01)	0.970	1.01 (0.99–1.01)	0.072
Histological type				
Ductal	1			
Other	1.02 (0.89–1.17)	0.737		
Grade				
1–2	1			
3	1.05 (0.90–1.17)	0.486		
LVI				
Negative	1		1	
Positive	2.04 (1.54–2.71)	<0.001	2.06 (1.56–2.72)	<0.001
ER status				
Negative	1		1	
Positive	0.78 (0.62–0.99)	0.042	0.71 (0.59–0.86)	0.001
PR status				
Negative	1			
Positive	0.87 (0.69–1.10)	0.256		
HER2 status				
Negative	1		1	
Positive	1.25 (0.99–1.58)	0.053	1.28 (1.01–1.61)	0.036
pT stage				
T1–2	1		1	
T3–4	1.52 (1.22–1.89)	<0.001	1.52 (1.22–1.89)	<0.001
pN				
N1	1	0.008	1	0.008
N2	0.69 (0.51–0.94)	0.021	0.70 (0.52–0.951)	0.026
N3	0.98 (0.69–1.42)	0.997	1.01 (0.71–1.45)	0.931
Ki-67 index				
≤30%	1		1	
>30%	0.78 (0.66–0.98)	<0.001	1.06(0.74–1.28)	0.742
LNR				
Low	1	0.001	1	0.020
Intermediate	1.59 (1.17–2.14)	0.002	1.57 (1.16–2.13)	0.030
High	2.01 (1.37–2.94)	<0.001	1.98 (1.35–2.90)	<0.001

LNR, lymph node ratio.

the median DFS was 149 months (94.2–203.7 months), 120.1 months (108.2–132.0), and 81.8 months (68.4–131.1 months), respectively ($p < 0.001$, Fig. 1). Furthermore, for the three LNR risk groups (low, intermediate, and high), the median DFS was 148.9 months (95.3–202.6 months), 118.7 months (99.9–137.7 months), and 81.8 months (68.2–95.3 months), respectively ($p < 0.001$, Fig. 2).

In the univariate analysis, LNR, pN stage, pathological Tumor (pT) stage, ER positivity, lymphovascular invasion and Ki-67 index were observed as significant prognostic factors for DFS. However, in the multivariate analysis, LNR, lymphovascular invasion, ER positivity, pN, pT stage, and HER2 positivity were identified as independent prognostic factors for DFS (Table 2).

In the study, there was missing data regarding some postoperative pathology findings (histological type, tumor grade, lymphovascular invasion vs.). The frequency and distribution of missing data are shown in Table 3. In missing data analysis, missing data were distributed randomly ($p > 0.05$) and no significant relationship was observed between missing data ($p > 0.05$). Sensitivity analysis showed that missing data did not significantly affect the results.

Furthermore, we assessed the relationship between LNR and pN groups (Table 4). According to the LNR risk group, 85.5% of pathologic N1 patients were in the low LNR risk group, 77.0% of pN2 patients were in the intermediate LNR risk group, and 68.8% of pN3 patients were in the high LNR risk group. There were no pathologic N3 patients in the low LNR risk group. However, the proportion of pathologic N1 patients in the high LNR risk group was very low (1.2%).

After this distribution, we evaluated the DFS of pN2/LNR low-risk (n = 107, 11.7%) and pN1/LNR intermediate-high-

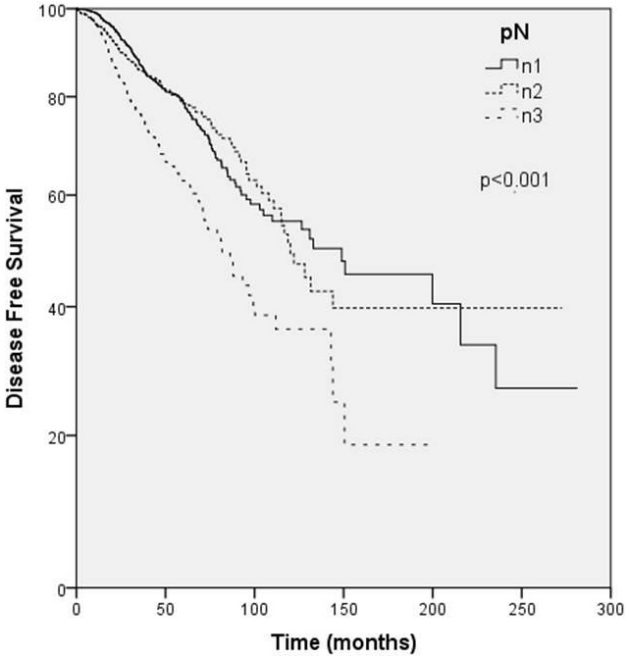

Fig. 1. Disease free survival based on the pN staging.

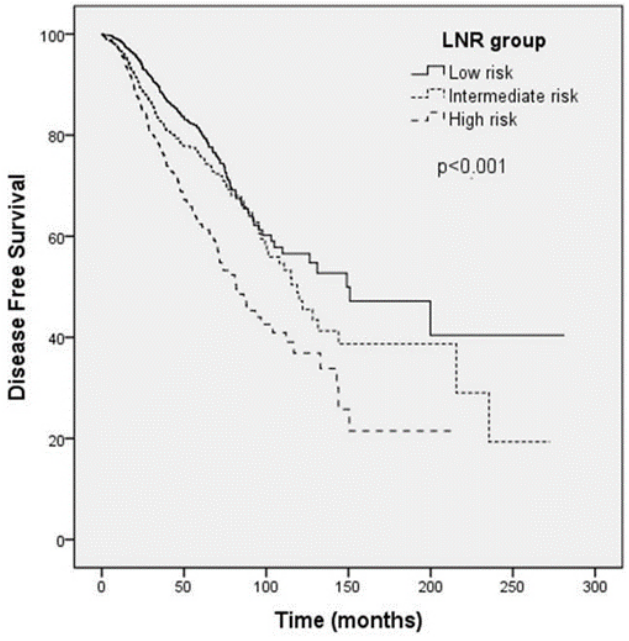

Fig. 2. Disease free survival based on the LNR staging.

risk (n = 217, 14.5%) patients. We observed that the median DFS was 133 months for pathologic N1 patients in the intermediate-high LNR risk group, while the median DFS did not reach pN2 in the low-risk group (p = 0.034, Fig. 3).

Discussion

In this study, we investigated the prognostic significance of LNR. We evaluated whether the ratio of involved lymph nodes provides better prognostic value than the number of positive lymph nodes. TNM is a globally accepted system

Table 3. Frequency and distribution of missing data.

	N	Missing	
		Count	Percent
Histological type	2911	142	4.7
Grade	2791	262	8.6
LVI	2648	405	13.3
ER status	2905	148	4.8
PR status	2905	148	4.8
HER2 status	2901	152	5.0
Tumor size	2815	238	7.8
Ki-67	2905	148	4.8
Menopausal status	2832	221	7.2

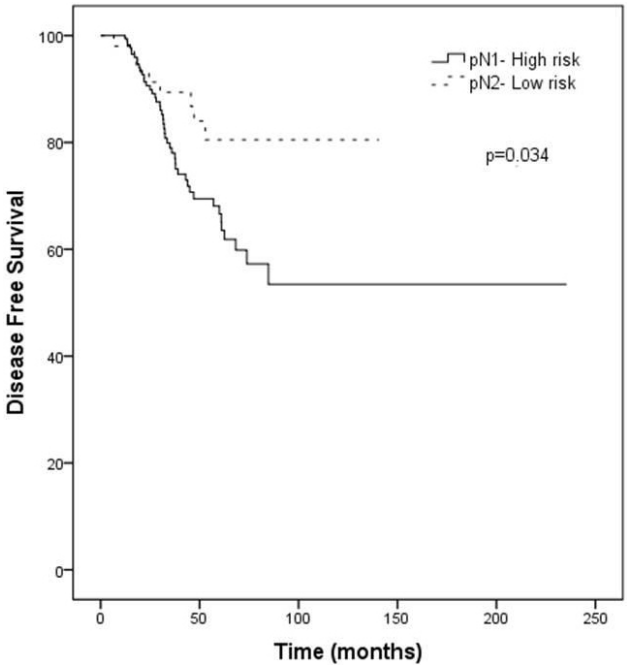

Fig. 3. Disease-free survival for pN1 patients in the intermediate-high risk group and pN2 patients in the low-risk group.

for staging. In this system, the nodal stage increases as the number of affected regional lymph nodes rises [20]. The recent advances in sentinel lymph node techniques have made sentinel lymph node sampling a common technique. However, axillary lymph node dissections remain a crucial method for accurate staging of BC. Our study did not report the number of patients who underwent axillary lymph node dissection after sentinel lymph node sampling. The axillary lymph node status is crucial in planning adjuvant therapies and predicting prognosis [2, 21, 22]. According to the TNM system, the pathologic lymph node status is determined by the numerical value of the positive lymph node removed. Various factors can affect this value, such as the size of the lymph node dissection and the number of lymph nodes in the postoperative pathology specimen.

Table 4. The proportion of the patients is based on LNR and pN-stage.

	pN1 n = 1495 (49.0%)	pN2 n = 917 (30.0%)	pN3 n = 641 (21.0%)
LNR low n = 1385 (45.4%)	1278 (85.5%)	107 (11.7%)	0 (0%)
LNR intermediate n = 1105 (36.2%)	199 (13.3%)	706 (77.0%)	200 (31.2%)
LNR high n = 563 (18.4%)	18 (1.2%)	104 (11.3%)	441 (68.8%)

Numerous studies have shown that the LNR is a better parameter for predicting prognosis than positive lymph node count [6, 9, 10, 11, 14, 17, 18, 23, 24]. Our study analyzed a larger patient cohort than many previous studies. Consistent with several studies, our analysis revealed that LNR and pN are independent prognostic factors for DFS. Furthermore, we observed that LNR did not perform significantly superior to pN in predicting prognosis across all study subjects. Strikingly, our study showed that low-risk LNR and pN2 patients had a substantially longer DFS than those with intermediate or high-risk and pN1 patients. These findings suggest that LNR may better predict survival in specific patient groups. Moreover, in the multivariate analysis, LNR was observed as an independent prognostic factor, unlike pN, which supports the idea that LNR might offer prognostic significance over pN staging.

The optimal cut-off value for the lymph node ratio remains undetermined. Previous studies have reported various cut-off values for Neutrophil lymphocyte ratio (NLR), making it challenging to implement a standard LNR [6, 14, 17, 18, 24]. In this study, we categorized NLR groups based on the cut-off values determined by Vinh-Hung *et al*. [5], regarded as a reference study due to its large patient population, extended follow-up period, and accurate analysis method. Several studies have investigated the prognostic significance of LNR using Vinh-Hung's stratification [11, 12, 14, 15, 25]. Consequently, previous studies have argued for the integration of LNR into the pathologic lymph node staging system in the future [11, 14]. Similarly, LNR has been reported as a crucial prognostic factor for DFS and OS [23]. Additionally, a recent study by Zhu *et al*. [26] investigated the prognostic significance of LNR in 732 T1–2 breast cancers, indicating the association of a higher LNR with a worse overall survival outcome in these patients.

According to the survival results of many studies, the LNR is a more informative parameter than pN in non-metastatic BC patients and has been shown to be superior to pN [6, 14, 17, 18, 24, 26]. However, it is crucial to consider that previous studies differ in various factors, including patient selection and number, follow-up duration, surgery type, and adjuvant therapies. Some studies have not indicated any additional benefit of LNR over the standard TNM classification [13, 25]. In these studies, survival time was similar between the three pN and LNR groups. Similarly, our study observed comparable survival outcomes in the entire patient population based on LNR and pN subgroups. The median DFS for the low, intermediate, and high LNR groups was 148.9, 118.7, and 81.8 months, respectively, which was similar to the median DFS for pN1, pN2, and pN3 of 149, 120.1, and 81.8 months, respectively. However, subtype and multivariate analyses found LNR to be superior to pN staging. Liao *et al*. [27] reported that LNR had a higher ratio and worse survival outcomes in molecular subtypes, while pN-stage indicated no association with BC subtypes. In the present study, LNR was found to predict prognosis regardless of receptor status.

In our study, we defined 3 risk groups based on the lymph node ratio (LNR) for each patient (low-risk group $\leq$0.20; intermediate-risk group, 0.21–0.65; and high-risk group, $>$0.65). According to the LNR risk classification, 14.5% of pN1 patients and 11.3% of pN2 patients moved to the LNR risk group with a worse prognosis. In contrast, 11.7% of pN2 patients and 31.2% of pN3 patients were categorized into a lower-risk group based on the LNR classification (Table 4). Similarly, previous studies have reported the highest discordance rates, especially among pN3 patients [18, 23]. Because of these discordance results, we aimed to compare two different patient groups (pN2/LNR-low and pN1/LNR-intermediate or high) based on the DFS, unlike previous studies. In our study, there were no pathologic N3 patients in the low LNR risk group, and the proportion of patients with pathologic N1 in the high LNR risk group was very low (1.2%). Therefore, we evaluated the pN2/LNR low-risk and pN1/LNR intermediate-high-risk groups. The median DFS was 133 months for pathologic N1 patients in the intermediate-high LNR risk group, while it was not reached for patients with pN2 in the low-risk group (p = 0.034, Fig. 3). This study revealed that patients with different pN stages might fall into different prognostic risk groups according to LNR risk stratification. LNR was found to be a better prognostic indicator than pathological lymph node status. The study of Jin *et al*. [28] compared the predictive value of the TNM nodal staging system with ratio-based nodal staging systems, demonstrating that LNR can be a powerful component of lymph node staging, particularly in patients with a limited number of LN dissections. Based on the findings of this study and other previous studies, LNR

should be considered alongside TNM nodal staging for routine clinical decision-making in non-metastatic breast carcinoma.

Besides some promising observations, our study has several limitations that must be addressed. The deficiencies in data collection associated with the retrospective and the multicenter nature of the study led to difficulties in accessing certain details. Missing data (some postoperative pathology findings) constituted a small portion of the database. Sensitivity analysis was conducted to assess the impact of missed data on the results of the study. Lost missing data were found not to have significantly affected the results. The therapy options were not standardized, and pathologic parameters were not centrally verified due to the retrospective design. However, the strengths of this study include a long median follow-up period, a high number of patients, and its multicentric design. In recent years, a dramatic change has occurred in the management of axillary lymph nodes. The number of patients who underwent sentinel lymph node sampling followed by axillary dissection is unknown. Additionally, this study does not include patients with triple-negative (TNBC) or HER2+ cancer who received neoadjuvant therapy, which is the standard for these two subgroups. Furthermore, we cannot exclude the possibility that LNR may reflect the extent of axillary surgery. The more extensive the resection of axillary lymph nodes, including benign ones, the lower the LNR. Despite the limitations, the present study has provided significant information.

Conclusions

This study confirmed that LNR is a crucial prognostic factor for DFS. Moreover, we demonstrated that in a specific subgroup, LNR was a superior predictor for survival compared to the pN stage. This finding suggests that LNR may be a superior predictor of survival than the pN stage. In the treatment management of non-metastatic BC patients, even if adjuvant treatment is planned for most lymph node-positive patients, LNR can still provide clinicians with better prognostic information for predicting survival. Although this study has provided promising insights, the results should be validated through prospective, randomized clinical trials.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

ZU designed the research study and wrote the article. ZO, MG, DU, MÖ, ETE and SG ensured the acquisition of clinical data. MAK, SE, ÇG and SG analyzed the data and interpreted it. ZU, ZO, SE, MAK wrote the article. All authors revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Dicle University (399-1.9.2021). The study was conducted following the principles of the Declaration of Helsinki. Furthermore, informed consent of the patients was obtained.

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Conflict of Interest

The authors declare no conflict of interest.

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