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# Prognostic Value of Lymph Node Ratio in Breast Cancer Patients with Adequate Pathologic Evidence After Neoadjuvant Chemotherapy

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**Background:** The prognostic role of axillary lymph node ratio (LNR) after neoadjuvant chemotherapy (NAC) in breast cancer has not been illuminated. This study was designed to investigate the prognostic role of LNR in breast cancer compared with traditional ypN stage.

**Material/Methods:** A total of 306 breast cancer patients diagnosed with positive axillary lymph nodes from January 2007 to December 2014 were eligible for this retrospective analysis. All enrolled patients were treated with a median of 4 cycles of NAC followed by mastectomy and level I, II, and III axillary lymph node dissection (ALND).

**Results:** The median duration of follow-up was 78 months (range, 7–147 months). Univariate analysis indicated that both the LNR category ( $P < 0.001$ ) and ypN stage ( $P < 0.001$ ) were significant associated with event-free survival (EFS) and overall survival (OS). However, multivariate analysis indicated that the LNR category was independently associated with EFS ( $P < 0.001$ ) and OS ( $P < 0.001$ ), while the ypN stage showed no statistical effect on EFS ( $P = 0.391$ ) or OS ( $P = 0.081$ ). On additional analyses stratified by molecular subtypes, we found that the prognosis of triple negative breast cancer could be better discriminated when the cutoff value of LNR was set at 0.15.

**Conclusions:** LNR showed a superior predictive value in evaluating prognosis of breast cancer patients after NAC. In addition, the LNR cutoff point 0.15 can accurately discriminate survival outcomes for different triple negative breast cancer subtypes.

**MeSH Keywords:** **Breast Neoplasms • Lymph Node Excision • Neoadjuvant Therapy • Survival Analysis**

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## Background

The clinical outcomes for breast cancer are associated with many clinicopathologic factors, and the regional lymph node (LN) status is a significant prognostic indicator of survival in BC patients. Currently, the LN staging of BC is mainly based on the American Joint Committee on Cancer (AJCC) TNM staging system. Nowadays, neoadjuvant chemotherapy (NAC) is widely used in the comprehensive treatment of BC, aiming at downstaging of primary cancer as well as LNs to provide a better opportunity for surgery [1]. The pathologic status of LNs in patients with a good response to NAC may have already changed before surgery [2]. According to the 7<sup>th</sup> version of the AJCC [3], TNM stage was directly adopted in the ypN stage, although its prognostic significance was not the same. Therefore, the ypN stage of BC patients may need to be improved and complemented.

The lymph node ratio (LNR) is defined as the proportion of positive LNs over the number of examined LNs, and it has been demonstrated to have a significant prognostic role in many cancers including BC [4,5]. Recent studies have indicated that the LNR is prognostically superior to pN stage [6–8]. Vinh-Hung et al. [9] identified the applicable LNR cutoff values of 0.20 and 0.65, which they found could predict prognosis more appropriately than the pN stage for patients with BC. Nevertheless, the prognostic role of LNR has not been fully elucidated in different molecular subtypes. In addition, limited studies have reported the prognostic role of LNR after NAC in BC patients.

In theory, the greater the number of axillary LNs removed in ALND, the greater the chance that LN metastasis will be discovered, resulting in improved exactitude of the postoperative pN stage [10]. According to the National Comprehensive Cancer Network (NCCN) guidelines, LN level III dissection of the thoracic inlet should be performed in cases with level II and/or III gross disease [11]. The number of removed LNs in the prognosis of BC is controversial, although the 8<sup>th</sup> reversion of AJCC proposes that at least 6 LNs should be removed and examined [12].

In the present study, we investigated the prognostic role of the LNR comparing with ypN stage in BC patients treated with NAC followed by mastectomy and level I, II, and III ALND. Furthermore, we also investigated the prognostic role of the LNR for different BC subtypes.

## Material and Methods

### Identification of patients

Clinicopathological data on BC patients presenting to the Breast Disease Center, Southwest Hospital, The Army Medical

University between January 2007 and December 2014 were retrospectively screened. Among 5389 patients, 306 invasive BC patients who underwent NAC followed by mastectomy and ALND were eligible for inclusion in this study. All patients were diagnosed as invasive BC pathologically before NAC, accompanying with positive axillary LNs diagnosed by either ultrasonography or pathology.

Other inclusion criteria of the study were as follows: 1) no chemotherapy or radiotherapy before NAC, 2) received mastectomy with level I, II, and III ALND, and 3)  $\geq 10$  axillary LNs were removed and examined. The exclusion criteria were as follows: 1) distant metastases at diagnosis, 2) supraclavicular lymph node metastases, 3) bilateral BC, 4) other malignant tumors, and 5) no standardized treatment.

All included patients were assessed by clinical history, findings on physical examination, ultrasonography, mammography, chest computed tomography (CT), and bone scintigraphy. Breast magnetic resonance imaging (MRI) was recommended when the results of ultrasonography or mammography could not define the boundary of the lesion.

### Study variables

We evaluated the clinicopathological variables for each case, including age, tumor quadrant (inner, outer, or central), primary tumor size (defined as the longest continuous diameter of the tumor according to the ultrasonography results before NAC), clinical N stage, clinical TNM stage, histological type, estrogen receptor (ER, positivity defined as  $>1\%$ ), progesterone receptor (PR, positivity defined as  $>1\%$ ), human epidermal growth factor receptor 2 (HER2) status, molecular subtype, number of removed axillary LNs, number of involved axillary LNs, infraclavicular lymph node status, LNR category and ypN stage. ER, PR, and HER2 status were evaluated immunohistochemically; fluorescence *in situ* hybridization (FISH) was performed as required for HER2 status. Patients were classified into 3 molecular subtypes, namely, hormone receptor-positive (HR+, ER, and/or PR positive, HER2 negative), HER2-positive (HER2+), and triple negative breast cancer (TNBC), ER and PR negative and HER2 negative)

### Treatment

#### NAC

The NAC regimens included regimen #1: anthracycline combined with taxane (TE: docetaxel, 75 mg/m<sup>2</sup>+epirubicin, 75 mg/m<sup>2</sup>, on day 1 every 3 weeks, TEC: docetaxel, 75 mg/m<sup>2</sup>+epirubicin, 75 mg/m<sup>2</sup>+cyclophosphamide 500 mg/m<sup>2</sup>, on day 1 every 3 weeks) and regimen #2: anthracycline-based (CEF: cyclophosphamide 500 mg/m<sup>2</sup>+epirubicin

**Table 1.** Patient clinicopathological characteristics and univariate survival analyses of prognostic factors.

Characteristic	n=306		EFS		OS	
	No.	(%)	5-yr (%)	P value	5-yr (%)	P value
Age (years)						
<40	61	(19.9)	62.3	0.284	68.3	0.417
≥40	245	(80.1)	66.0		77.9	
Tumor quadrant						
Inner	49	(16.0)	65.3	0.512	77.6	0.371
Outer	172	(56.2)	66.7		77.1	
Central	85	(27.8)	62.3		72.8	
Primary tumor size*						
T1	47	(15.4)	76.6	<0.001	80.7	<0.001
T2	186	(60.8)	71.9		80.1	
T3	43	(14.1)	51.2		76.0	
T4	30	(9.8)	26.7		42.9	
Clinical N stage						
N1	183	(59.8)	77.6	<0.001	84.1	<0.001
N2	58	(19.0)	51.5		68.3	
N3	65	(21.2)	42.9		59.4	
Clinical TNM stage						
IIA	35	(11.4)	91.4	<0.001	94.3	<0.001
IIB	109	(35.6)	81.6		86.2	
IIIA	76	(24.8)	59.2		73.5	
IIIB	21	(6.9)	28.6		51.9	
IIIC	65	(21.2)	41.1		57.6	
Histological type						
Invasive ductal carcinoma	281	(91.8)	66.1	0.237	76.7	0.053
Invasive lobular carcinoma	14	(4.6)	57.1		71.4	
Other types	11	(3.6)	54.5		63.6	
ER						
Negative	115	(37.6)	57.4	0.010	66.6	0.005
Positive	191	(62.4)	70.0		81.5	
PR						
Negative	124	(40.5)	55.6	0.001	65.0	<0.001
Positive	182	(59.5)	71.9		83.4	
HER-2						
Negative	232	(75.8)	65.4	0.761	77.0	0.666
Positive	74	(24.2)	64.9		72.6	
Molecular subtype						
HR+	210	(68.6)	70.4	0.003	81.8	0.001
HER2+	41	(13.4)	56.1		67.5	
TNBC	55	(18.0)	52.7		59.9	
ypN						
ypN0	63	(20.6)	85.7	<0.001	96.8	<0.001
ypN1	100	(32.7)	82.0		84.9	
ypN2	31	(10.1)	67.7		77.1	
ypN3	112	(36.6)	38.1		55.7	
LNR category						
0	63	(20.6)	85.7	<0.001	96.8	<0.001
0.01–0.20	107	(35.0)	80.3		84.9	
0.21–0.65	88	(28.8)	53.4		68.8	
>0.65	48	(15.7)	26.4		41.2	

**Table 1.** Patient clinicopathological characteristics and univariate survival analyses of prognostic factors.

Characteristic	n=306		EFS		OS	
	No.	(%)	5-yr (%)	P value	5-yr (%)	P value
Involvement of infraclavicular lymph node						
No	201	(65.7)	81.0	<0.001	88.0	<0.001
Yes	105	(34.3)	35.1		52.8	
NAC Response						
PD+SD	87	(28.4)	51.5	<0.001	66.6	<0.001
PR+CR	219	(71.6)	70.8		79.7	

ER – estrogen receptor; PR – progesterone receptor; HER-2 – human epidermal growth factor receptor-2; TNBC – triple negative breast cancer; LNR – lymph node ratio; NAC – neoadjuvant chemotherapy; PD – progressive disease; SD – stable disease; PR – partial disease; CR – complete disease. \* Defined as the longest continuous diameter of the tumor according to ultrasonography results before NAC.

**Table 2.** Pathologic information of axillary lymph nodes.

Pathologic findings	Median	Mean	Lower-upper
No. of lymph nodes removed	19.0	20.0	10–47
No. of involved axillary lymph nodes	3.0	5.7	0–46
Lymph node ratio (LNR)	0.15	0.28	0–1

60 mg/m<sup>2</sup>+5-fluorouracil 500 mg/m<sup>2</sup>, on day 1 every 3 weeks, EC: epirubicin 75 mg/m<sup>2</sup>+cyclophosphamide 600 mg/m<sup>2</sup>, on day 1 every 3 weeks). A total of 273 patients underwent NAC regimen #1, and another 33 patients received regimen #2. All patients received at least 2 cycles of NAC, and the median number of cycles of NAC was 4 (range, 2–8).

### Surgery

All patients underwent modified radical mastectomy after NAC and level I, II, and III ALND were performed within 4 weeks after NAC. According to the 8<sup>th</sup> edition of AJCC guidelines, the scope of ALND contained level I (low-axilla): lymph nodes lateral to the lateral border of pectoralis minor muscle, level II (mid-axilla): lymph nodes between the medial and lateral borders of pectoralis minor muscle and the interpectoral (Rotter's) lymph nodes, and level III (apical axilla): lymph nodes medial to the medial margin of pectoralis minor muscle and inferior to the clavicle. These are also known as apical or infraclavicular nodes.

### Additional adjuvant treatment

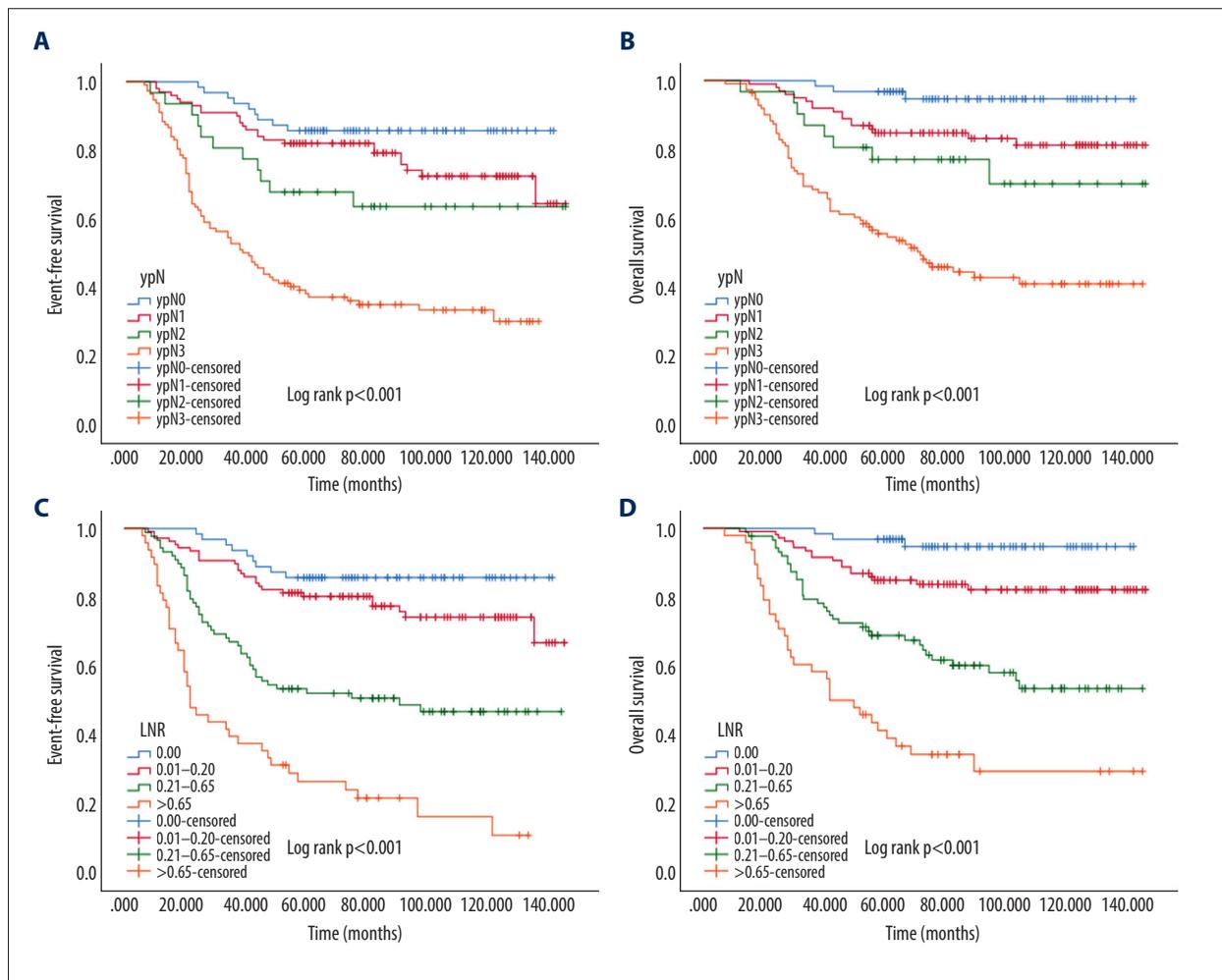
Further postoperative adjuvant treatment was administered in accordance with the recommendations of the NCCN guidelines. Adjuvant regional radiotherapy was recommended for appropriate patients, and the scope and dose of radiotherapy were determined by radiation oncologist. Additional chemotherapy was administered after the surgery to complete a total of 6–8 cycles. All hormone receptor-positive patients received endocrine therapy.

### Assessment of efficacy

Event-free survival (EFS) was defined as the time starting from the date of NAC to relapse or death. Overall survival (OS) was defined as the time from the date of NAC until death from any cause. The efficacy of NAC was evaluated every 2 cycles, using ultrasound or MRI according to the response evaluation criteria in solid tumors (RECIST) version 1.1, which defines response as follows: progressive disease (PD): a ≥20% increase in the total length of the baseline lesion or a new lesion; stable disease (SD): a decrease in the total length of the baseline lesions not sufficient for partial response (PR) or an increase without reaching PD; partial response (PR): a decrease ≥30% in the total length of the baseline lesions; and complete response (CR): disappearance of all target lesions. PR+CR and PD+SD were defined as valid and invalid responses, respectively. LNR was classified into 3 groups according to previous studies: 0, 0–0.20, 0.2–0.65, 0.66–1.00.

### Follow-up

Every patient was evaluated 1, 3, 6, and 12 months after surgery. Patients were examined every 3–6 months for 2 years after the surgery, every 6–12 months between 3–5 years, and once a year after 5 years. The contents of the follow-up included evaluations of general health status, physical examination, ultrasonography of the breast and accessory lymph nodes, chest radiographs, and other imaging examinations.



**Figure 1.** Kaplan-Meier cumulative survival curves for different ypN stages and lymph node ratio (LNR). (A) Kaplan-Meier estimates of event-free survival for all patients by ypN stages. (B) Kaplan-Meier estimates of overall survival for all patients by ypN stages. (C) Kaplan-Meier estimates of event-free survival (EFS) for all patients by LNR. (D) Kaplan-Meier estimates of overall survival for all patients by LNR

## Statistical analysis

Continuous variables were compared using independent 2-sample t tests. Pearson's chi-square test was used to compare the clinicopathologic categorical variables. The Kaplan-Meier method was used to estimate of survival outcomes, which were compared using log-rank tests. Univariate and multivariate Cox proportional hazards regression models were employed to analyze the factors associated with survival. Variables with statistical significance ( $P < 0.05$ ) in univariate analysis were included as in multivariate analysis. In terms of the cutoff value for the LNR for determining of the prognosis of TNBC, receiver operating characteristic (ROC) curve analyses were applied.  $P < 0.05$  was considered statistically significant, and all  $P$ -values were 2-sided. All the statistical analyses were performed using SPSS statistical software, version 25.0 (IBM Corp, Armonk, NY, USA).

## Results

### Patient characteristics

A total of 306 patients were finally enrolled in this study and patient clinicopathological characteristics are summarized in Table 1. The median age was 46.8 years (range, 25–70 years). Most of the patients (56.2%) had primary tumors in the outer quadrant. The primary tumor sizes in 47 patients (15.4%), 186 patients (60.8%), 43 patients (14.1%), and 30 patients (9.8%) were T1, T2, T3, and T4, respectively. The majority of patients had advanced tumors ( $\geq$ IB). Invasive ductal carcinoma was the predominant histological type (91.8%). ER and PR were positive in 62.4% and 59.5% of cases, respectively. In all, 24.2% of patients presented with HER2 overexpression. HR+ (68.6%) was the majority molecular subtype. Postoperative pathology showed that 63 patients (20.6%) were classified

**Table 3.** Multivariable analyses of factors associated with survival outcomes.

Characteristics	EFS		OS	
	HR (95% CI)	P value	HR (95% CI)	P value
<b>Model 1</b>				
NAC			*	
PD+SD vs. PR+CR	1.645 (1.091–2.481)	0.018		0.141
Primary tumor size**		0.002		
T2 vs. T1	0.942 (0.510–1.741)	0.849	*	0.145
T3 vs. T1	1.897 (0.919–3.914)	0.083		
T4 vs. T1	2.350 (1.125–4.911)	0.023		
PR (+) vs. PR (–)	0.378 (0.259–0.552)	<0.001	0.369 (0.242–0.562)	<0.001
ypN		<0.001		<0.001
ypN1 vs. ypN0	2.187 (1.008–4.745)	0.048	4.302 (1.259–14.705)	0.020
ypN2 vs. ypN0	3.297 (1.358–8.004)	0.008	7.223 (1.913–27.277)	0.004
ypN3 vs. ypN0	7.160 (3.469–14.778)	<0.001	20.131 (6.289–64.445)	<0.001
<b>Model 2</b>				
NAC			*	
PD+SD vs. PR+CR	1.592 (1.062–2.388)	0.024		0.182
Primary tumor size**		0.002		
T2 vs. T1	1.004 (0.546–1.847)	0.990	*	0.080
T3 vs. T1	1.936 (0.950–3.948)	0.069		
T4 vs. T1	2.539 (1.236–5.217)	0.011		
PR (+) vs. PR (–)	0.367 (0.252–0.535)	<0.001	0.368 (0.242–0.560)	<0.001
LNR		<0.001		<0.001
0.01–0.20 vs. 0	2.117 (0.980–4.572)	0.056	4.282 (1.259–14.559)	0.020
0.21–0.65 vs. 0	5.089 (2.446–10.587)	<0.001	12.829 (3.937–41.803)	<0.001
>0.65 vs. 0	10.893 (5.062–23.443)	<0.001	29.985 (9.132–98.452)	<0.001

ER – estrogen receptor; PR – progesterone receptor; NAC – neoadjuvant chemotherapy; PD – progressive disease; SD – stable disease; PR – partial disease; CR – complete disease; LNR – lymph node ratio. \* Hazard ratio (HR) (95% confidence interval [CI]) was not given when  $P > 0.05$  in Cox proportional hazards regression analysis. \*\* Defined as the longest continuous diameter of the tumor according to ultrasonography results before NAC.

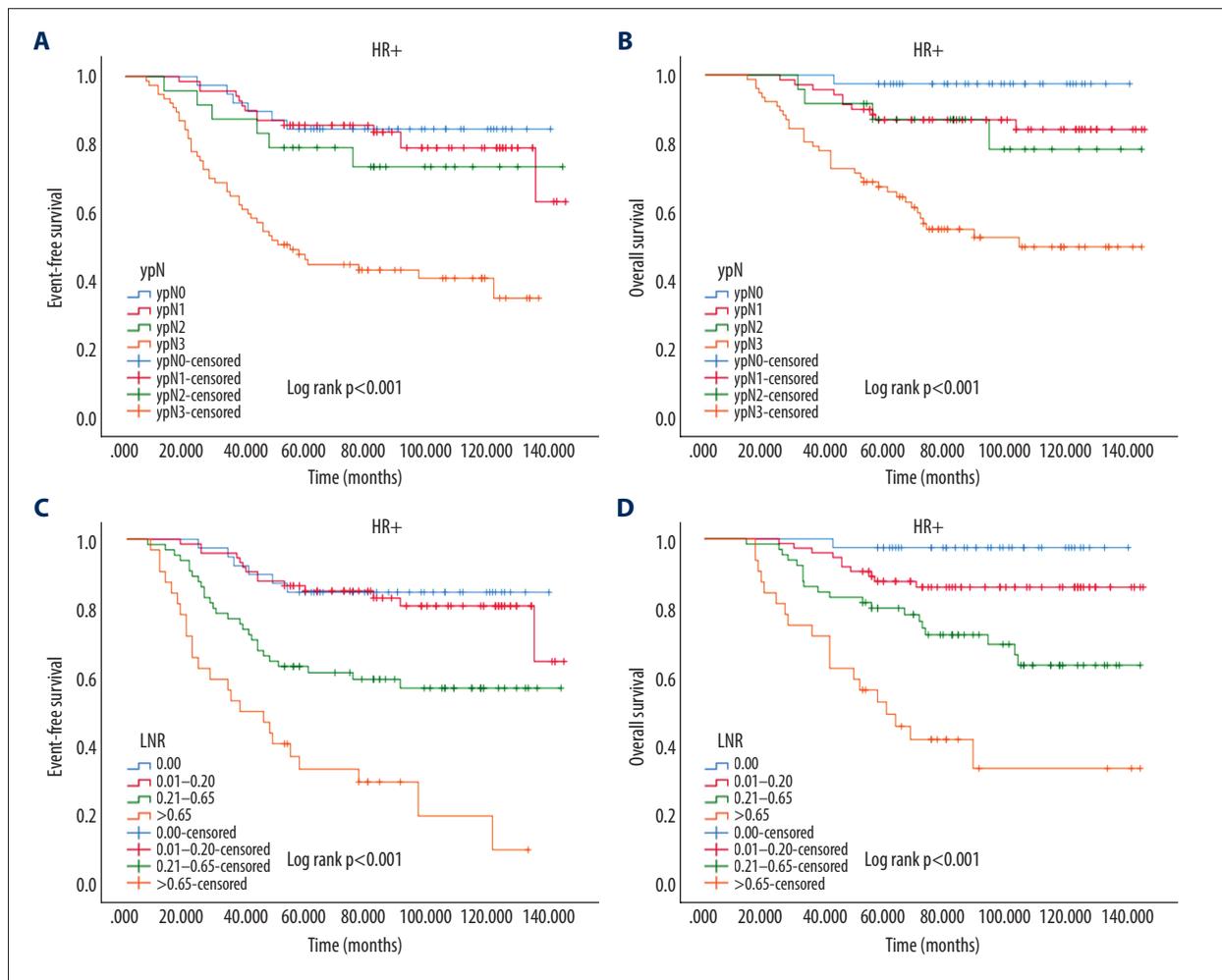
with ypN0, 100 patients (32.7%) as ypN1, 31 patients (10.1%) as ypN2, and 112 patients (36.6%) as ypN3. The LNR categories in 63 patients (20.6%), 107 patients (35.0%), 88 patients (28.8%), and 48 patients (15.7%) were 0, 0.01–0.20, 0.21–0.65, and >0.65, respectively. Out of the 306 patients who underwent level I, II, and III ALND, 105 patients (34.3%) had positive infraclavicular lymph nodes. A total of 219 patients (71.6%) achieved CR or PR after NAC. The median and mean numbers of removed LNs and involved LNs were 19.0 and 20.0 (range, 10–47) and 3.0 and 5.7 (range, 0–46), respectively. The median and mean values of the LNR were 0.15 and 0.28 (range, 0–1), respectively (Table 2).

### Survival outcomes

The median duration of follow-up was 78 months (range, 7–147 months).

### Univariate analysis for survival

We compared all clinicopathological characteristics with univariable analysis, and no significant association was noted between age, tumor quadrant, histological type, HER2 status, and EFS and OS. However, a large primary tumor size (EFS:  $P < 0.001$ , OS:  $P < 0.001$ ), advanced N stage (EFS:  $P < 0.001$ , OS:  $P < 0.001$ ), advanced clinical TNM stage (EFS:  $P < 0.001$ , OS:  $P < 0.001$ ), negative ER status (EFS:  $P = 0.010$ , OS:  $P = 0.005$ ), negative PR status (EFS:  $P = 0.001$ , OS:  $P < 0.001$ ) and positive infraclavicular lymph nodes (EFS:  $P = 0.001$ , OS:  $P < 0.001$ ) were associated with poor prognosis. The molecular subtype (EFS:  $P = 0.003$ , OS:  $P = 0.001$ ) and the efficacy of NAC (EFS:  $P < 0.001$ , OS:  $P < 0.001$ ) were significantly associated with both EFS and OS. Specifically, the ypN stage (EFS:  $P < 0.001$ , OS:  $P < 0.001$ ) and the LNR category (EFS:  $P < 0.001$ , OS:  $P < 0.001$ ) were significantly associated with both EFS and OS according to univariable analysis (Table 1).



**Figure 2.** Kaplan-Meier cumulative survival curves for hormone receptor positive ((HR+) breast cancer according to ypN stages and lymph node ratio (LNR). (A) Kaplan-Meier estimates of event-free survival (EFS) for HR+ breast cancer by ypN stages. (B) Kaplan-Meier estimates of overall survival (OS) for HR+ breast cancer by ypN stages (C) Kaplan-Meier estimates of EFS HR+ breast cancer by LNR. (D) Kaplan-Meier estimates of OS for HR+ breast cancer by LNR.

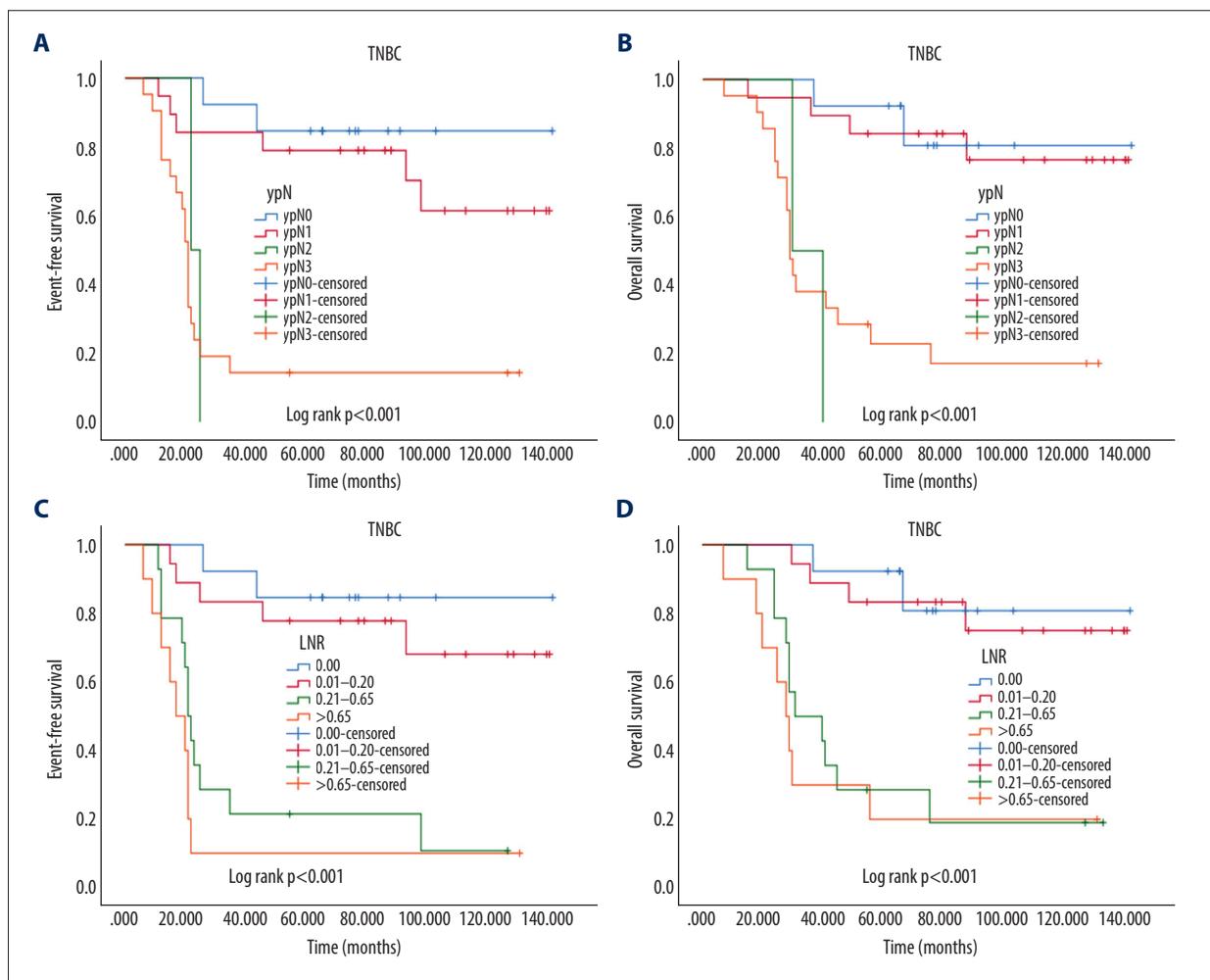
### Cox proportional hazards models for mortality

Multivariate analysis with adjustment of interference variables in relation to EFS and OS was conducted to identify the independent variables associated with EFS and OS. In model 1, after controlling for significant covariables from univariable analysis including primary tumor size, clinical N stage, ER, PR, molecular subtype, ypN, and NAC in the Cox multivariable model, NAC ( $P=0.018$ ), primary tumor size ( $P=0.002$ ), PR status ( $P<0.001$ ), and ypN stage ( $P<0.001$ ) showed independent prognostic value for EFS. However, only PR status ( $P<0.001$ ) and ypN stage ( $P<0.001$ ) were independent prognostic variables associated with OS. Separate Kaplan-Meier curves comparing the survival times stratified by ypN stage are shown in Figure 1A and 1B. In model 2, the LNR was added into the Cox regression analysis. Interestingly, ypN stage was no longer an independent prognostic factor for EFS or OS. Conversely, the LNR

was significantly associated with both EFS ( $P<0.001$ ) and OS ( $P<0.001$ ) (Table 3). Survival curves comparing the survival times stratified by the LNR category are shown in Figure 1C and 1D.

### Stratified analysis with molecular subtype

According to the results of the survival analysis, ER and PR were prognostic factors for survival, which suggested that the survival of different molecular subtypes may vary significantly among different ypN stages and LNR categories. Therefore, patients were stratified by molecular subtype to determine the effects of ypN stage and LNR category on the survival of different molecular subtypes. There were 210, 41, and 55 cases diagnosed with HR+, HER2+, and TNBC, respectively. For HR+ BC, both the ypN stage and LNR category could distinguish the prognosis of different subgroups, but the LNR category had a stronger resolution (Figure 2A–2D). Due to the limited number



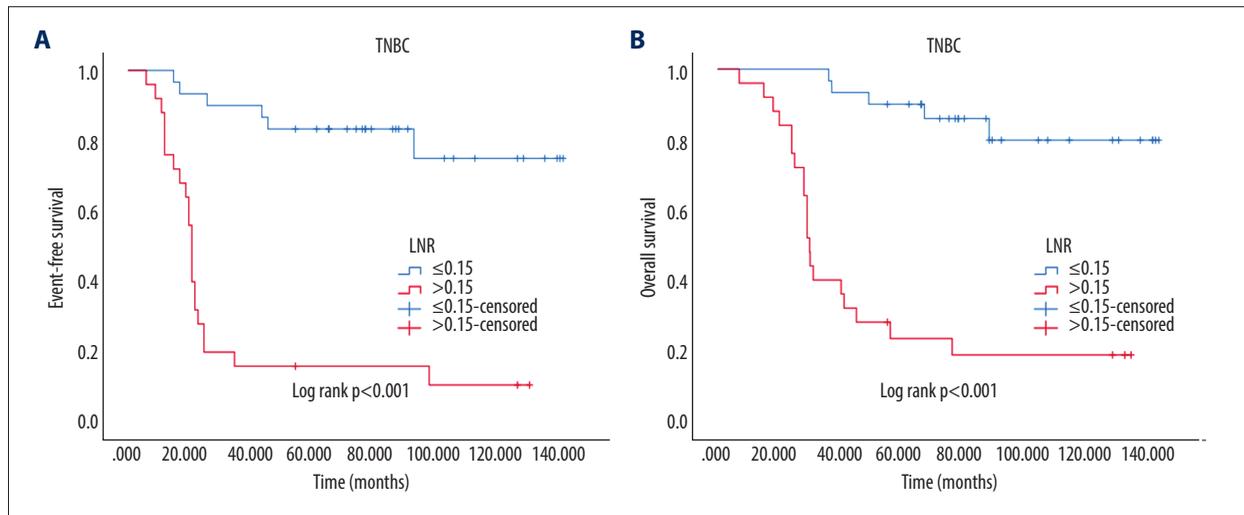
**Figure 3.** Kaplan-Meier cumulative survival curves for triple negative breast cancer (TNBC) according to ypN stages and lymph node ratio (LNR). (A) Kaplan-Meier estimates of event-free survival for TNBC by ypN stages. (B) Kaplan-Meier estimates of overall survival for TNBC by ypN stages. (C) Kaplan-Meier estimates of event-free survival TNBC by LNR. (D) Kaplan-Meier estimates of overall survival for TNBC by LNR.

of cases of HER2+ BC in this study, no further stratified analysis was carried out. However, neither the ypN stage nor the LNR category could distinctly indicate the prognosis of the TNBC subgroup (Figure 3A–3D). Accordingly, discrimination of the cutoff value of the LNR which might distinguish the prognosis in different subgroups of TNBC, was displayed with receiver operating characteristic (ROC) curves. According to the ROC curve, the area under the ROC curve was 0.849 (95% CI 0.873–0.945,  $P < 0.001$ ). The maximum value of the Jordan index reached 0.675 when the cutoff value was 0.15. The sensitivity and specificity of the prediction were 78.6% and 88.9%, respectively. An LNR  $> 0.15$  was significantly associated with worse EFS ( $P < 0.001$ ) and worse OS ( $P < 0.001$ ) in TNBC cases (Figure 4A, 4B).

### Discussion

The LNR has been reported to be a significant prognostic factor in the survival of BC patients in many recent studies [13–16], and some studies have also reported that the LNR is superior to traditional pN stage in predicting BC prognosis. Currently, NAC is broadly used in the systematic treatment of BC. However, few studies of the LNR have focused on patients who receive NAC due to the potential effect of NAC on axillary LN status. Obviously, the number of examined and involved LNs is affected by NAC, leaving the prognostic role of the LNR in NAC setting controversial.

In the present study, we also confirmed the independent prognostic role of the LNR compared with ypN stage in BC patients treated with a median of 4 cycles of NAC. Similarly, Keam et al. [17] reported that the LNR was superior to ypN



**Figure 4.** Kaplan-Meier analysis in patients with triple negative breast cancer (TNBC) tumors adopting lymph node ratio (LNR) value 0.15. **(A)** Kaplan-Meier estimates of event-free survival (EFS) for TNBC. **(B)** Kaplan-Meier estimates of overall survival (OS) for TNBC.

stage in stage II/III BC patients treated with 3 cycles of NAC. The same result was confirmed by Wu et al. [18]. However, Saxena et al. [19] found that the LNR was not superior to traditional ypN stage in a multicenter study of 314 patients. Additionally, Kim et al. [20] even denied the prognostic role of the LNR in the NAC setting. The different results of these studies may be caused by population heterogeneity, eligible patient criteria, different NAC cycles and regimens, different numbers of removed axillary LNs and different adjuvant treatments.

Different studies have adopted LNR cutoff points varying from 0.1 to 0.7 [21–24]. The cutoff points of 0.20 and 0.65, defined by Vinh-Hung et al. [9], have generally been accepted as the optimal thresholds of the LNR that could accurately predict the survival of BC patients. However, in our study, the cutoff points of 0.20 and 0.65 failed to distinguish the difference in prognosis in TNBC patients. Based on the results of the ROC curve, we found that 0.15 was the best cutoff value for predicting the prognosis of TNBC. An LNR greater than 0.15 was associated with poor clinical outcomes in both EFS and OS for TNBC patients. Interestingly, Tsai et al. [25] came to the same conclusion that 0.15 was an optimized cutoff value for discriminating the prognosis of TNBC patients treated with NAC. Additionally, Liao et al. [26] also failed to predict the prognosis of TNBC patients without NAC, adopting cutoff points of 0.20 and 0.65. Furthermore, our data revealed the predictive value of both the LNR and ypN stage for EFS and OS in HR+ patients. However, the prognosis of HER2+ BC was not well discriminated by either the LNR or ypN stage. Our results were consistent with those reported by Liao et al. [26]. Therefore, the cutoff point selection for the LNR in NAC settings may need to be optimized according to different molecular subtypes.

An adequate number of removed LNs is important in the accurate assessment of pN stage [10]. It is widely accepted that a minimum of 6 to 10 axillary LNs is required for accurate staging in patients without NAC [27]. However, in the NAC setting, the adequate number of removed LNs has not been determined. Although the type of surgical technique is a significant influencing factor of the number of axillary LNs removed in ALND [28], several studies have reported that patients undergoing NAC are more likely to have fewer than 10 LNs retrieved compared to patients undergoing surgery directly [29,30]. In the present study, all patients underwent level I, II, and III ALND on account of suspected metastasis, which provided sufficient evidence for a comprehensive assessment of LN status. Additionally, the minimum number of removed LNs in our study was 10, which allowed us to assess the ypN stage and LNR more accurately without underestimation. In previous studies on the prognostic role of the LNR after NAC, these strict criteria in the present study for LN screening were not applied.

This study provides relatively reliable evidence for the role of the LNR compared with ypN stage in predicting the prognosis of BC patients after NAC. All patients received a median of 4 cycles of NAC followed by level I, II, and III ALND. Furthermore, at least 10 axillary LNs were retrieved from all patients. This allowed us to fully evaluate the survival effect of the LNR after NAC after a median follow-up of 78 months.

Our study nevertheless had some limitations. First, the present study was a retrospective design from a single institution, which may have resulted in potential selection bias. The consecutive included patients and standard surgery made it possible to minimize this bias. Second, the prognostic role of the LNR in different BC subtypes after NAC could not be determined

due to the limited number of cases. Further prospective studies with larger sample sizes should be performed to further confirm the value of the LNR and the different cutoff points in patient with different subtypes of BC treated with NAC.

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## Conclusions

The present study demonstrated the prognostic role of the LNR in predicting EFS and OS in BC patients in the NAC setting. The LNR cutoff point of 0.15 is of prognostic value and can optimally discriminate between favorable and unfavorable EFS and OS in TNBC patients treated with NAC.

## Conflict of interest

None.