ORIGINAL RESEARCH

Predictive Value of Pretreatment Peripheral Neutrophil-to-Lymphocyte Ratio for Response to Neoadjuvant Chemotherapy and Breast Cancer Prognosis

Xiaomin Li [ID]*
Qiuwen Tan [ID]*
Hongjiang Li [ID]
Xiaoqin Yang [ID]

Department of Breast Surgery, West China Hospital, Sichuan University, Chengdu, People's Republic of China

*These authors contributed equally to this work

Background: Neutrophil-to-lymphocyte ratio (NLR) is connected with the response to neoadjuvant chemotherapy (NAC) and prognosis. In addition, residual lymph node burden after NAC is likely important for prognosis. However, most studies have focused on the predictive value of NLR for NAC pathological complete response (pCR) rate. The relationship between NLR and post-operative residual lymph node ratio (LNR), and their prognostic values remain to be determined.

Methods: We retrospectively studied 282 patients with breast cancer who underwent curative surgery after NAC from 2008 to 2018. We collected pretreatment NLR in peripheral blood, the response to NAC, and the amount of axillary lymph nodes (positive and total) from patients who received axillary lymph node dissection (ALND). We followed up all patients from 2 to 116 months, with an average of 63 months. We analyzed the predictive value of pretherapeutic NLR in peripheral blood on the response of NAC, including pCR rate and postoperative LNR. The prognostic value of NLR and LNR was also analyzed.

Results: A pCR was achieved in 20 (27.0%) of 74 patients with low NLR, and 34 (16.3%) of 208 with high NLR ($P = 0.045$). In luminal A and luminal B tumors, patients with high NLR tended to have elevated LNR (LNR>0.5; $P=0.041$). In Kaplan–Meier analysis, overall survival of patients with low NLR (NLR < 1.8; $P = 0.033$) was longer than that of patients with high NLR (NLR $\geq$ 1.8). Moreover, by multivariable analysis, LNR was negatively correlated with overall survival ($P < 0.05$) and disease-free survival (DFS) ($P < 0.05$).

Conclusion: pCR rate, post-operative remaining lymph node involvement and overall survival in all patients who received NAC may be predicted by NLR. Low NLR and LNR may suggest favorable outcomes.

Keywords: positive lymph node ratio, pathological complete response, lymph node ratio, positive lymph node ratio categories

Introduction

Great progresses have been made in neoadjuvant chemotherapy (NAC) for breast cancer.[1,2] The function of NAC has been evolving, from debulking tumor burden in local advanced breast cancer and increasing breast conservation rate in relatively large tumors, to prediction of better prognosis in patients who achieved pathological complete response (pCR), especially in triple negative and HER2-positive diseases.[3–7] Patients with residual tumors after NAC should receive treatments

Correspondence: Xiaoqin Yang
Department of Breast Surgery, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Wuhou District, Chengdu City, 610041, Sichuan Province, People's Republic of China
Tel +86-18980605792
Email XiaoqinYang2019@outlook.com

such as administration of capecitabine or TD-M1 to improve the prognosis.[8,9] Therefore, to schedule treatment individually, it is important to find predictive markers for NAC.

Cancer-related inflammation has a critical effect on cancer development and progression. In tumor patients, abnormalities occur in circulating white blood cells, with a main change in the proportions of neutrophils, lymphocytes, and monocytes.[10] Neutrophils release pro-inflammatory factors that promote cancer progression. In contrast to neutrophils, lymphocytes are a tumor-inhibiting factor.[11,12] Thus, the neutrophil-to-lymphocyte ratio may be associated with systemic inflammatory responses in tumor patients. In a variety of cancers, including breast cancer, a high NLR correlated with poor prognosis.[13–18] Furthermore, NLR had predictive value for chemosensitivity.[19,20]

Lymph node staging of breast cancer, on the basis of the 7th edition of the American Joint Committee on Cancer (AJCC) and International Union Against Cancer (UICC) TNM staging system,[21,22] is based on positive lymph node count but not the entire number of lymph nodes dissected or the negative lymph node count. Numerous studies have indicated that lymph node ratio (LNR) has prognostic value in breast cancer.[23–25] As total lymph nodes by axillary lymph node dissection (ALND) is comprised of positive and negative lymph nodes, it is essential to bring the negative lymph node count into consideration for predicting breast cancer prognosis. We have found that a combination of the negative lymph node count with LNR could be a substitute for positive lymph node count alone in predicting postoperative breast cancer survival.[26] Besides, concerning the optimal cutoff of LNR for predicting the prognosis of breast cancer patients, previous studies have still not reached a consensus.[27–29] Therefore, the prognostic value of LNR after NAC still needs to be determined.

In this study, we assessed the predictive value of NLR for NAC pCR rate and the prognostic value of both NLR and LNR after NAC. We also evaluated the correlation between NLR and LNR.

Methods
Patients
We retrospectively reviewed the medical records of 282 patients who were diagnosed with primary breast cancer and who received NAC in hospital from March 2008 to March 2018. The inclusion criteria were given below: (1) diagnosed as primary breast cancer by core needle biopsy before NAC; (2) female with clinical stage I–III; (3) obtained NAC and subsequent mastectomy or breast-conserving surgery. We excluded those patients with inflammatory breast cancer, stage IV disease, and pregnancy-associated breast cancer. This study was conducted in accordance with the Declaration of Helsinki. The Ethics Commission of West China Hospital of Sichuan University approved this research, and every participator signed informed consent.[30]

We collected information on age, pretreatment tumor size (T), tumor grade, lymph node status (N), status of metastasis (M), NAC regimen, surgical intervention, and outcomes (pathology results, response to NAC). Tumor stage was defined according to the TNM Classification of Malignant Tumors, UICC Seventh Edition.[22] Subgroup analysis was performed for three subtypes: luminal-HER2-negative breast cancer (hormone receptor (estrogen receptor (ER) and/or progesterone receptor (PR)) positive and HER2 negative), HER2-positive breast cancer (HER2 overexpressed and amplified with any ER/PR status), and triple-negative breast cancer (TNBC) (ER negative, PR negative, and HER2 not overexpressed nor amplified). Laboratory results included absolute neutrophil count and absolute lymphocyte count from peripheral blood obtained at the time of diagnosis, before NAC. Neutrophil-to-lymphocyte ratio (NLR) was defined as the ratio of neutrophil count to lymphocyte count from the peripheral blood sample.

Treatment
Every single patient got a standard protocol of NAC that comprised of 6 courses of TAC (75 mg/m2 docetaxel, 60 mg/m2 epirubicin, and 500 mg/m2 cyclophosphamide) every three weeks, or four courses of EC (90 mg/m2 epirubicin and 600 mg/m2 cyclophosphamide) every two weeks followed by 4 courses of 175 mg/m2 paclitaxel administered every two weeks or four courses of 100 mg/m2 docetaxel administered every three weeks. Patients with HER2-positive breast cancer got 6 mg/kg of trastuzumab every three weeks at the time of docetaxel treatment as well.[30]

The response to NAC was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1).[31] After NAC, all 282 patients underwent mastectomy or breast-conserving surgery. Among them, 258 patients went through ALND. Pathological complete response (pCR) was defined as

the complete disappearance of the invasive compartment of the lesion with or without intraductal components, including in the lymph nodes.[7] Positive lymph node ratio (LNR) was worked out by dividing the number of involved lymph nodes by the number of dissected lymph nodes. In accordance with former studies,[32–34] we grouped LNR values into LNR categories (LNRC: 0, 0.01–0.20, 0.21–0.65, >0.65), or by single LNR value 0.5 (high LNR: >0.5, low LNR: ≤0.5). The treatment (including NAC, surgery, radiotherapy, and endocrine therapy) of each patient was given in line with National Comprehensive Cancer Network (NCCN) guidelines.[35]

Follow-Up

After surgery, all the patients were assessed every three months for two years, and then every six months after two years. The median follow-up was 63 (range 2–116) months. Physical examination and ultrasound for breast and locoregional lymph nodes were performed at every visit to monitor tumor recurrence. Mammography and chest CT scans were performed every year.

Statistical Analysis

Statistical analysis was performed through the SPSS version 25.0 (IBM, Armonk, NY, USA). NLR cut-off points were analyzed using the Kaplan–Meier analysis. The Log rank test was used to compare the difference of variables between the two groups. We used a chi-square test to assess the association between NLR and clinical-pathological parameters as well as LNR. Overall survival and disease-free survival were evaluated using the Kaplan–Meier method (Log rank test) and Cox proportional hazard model as univariate and multivariate analysis. A value of $P < 0.05$ was considered to be statistically significant.
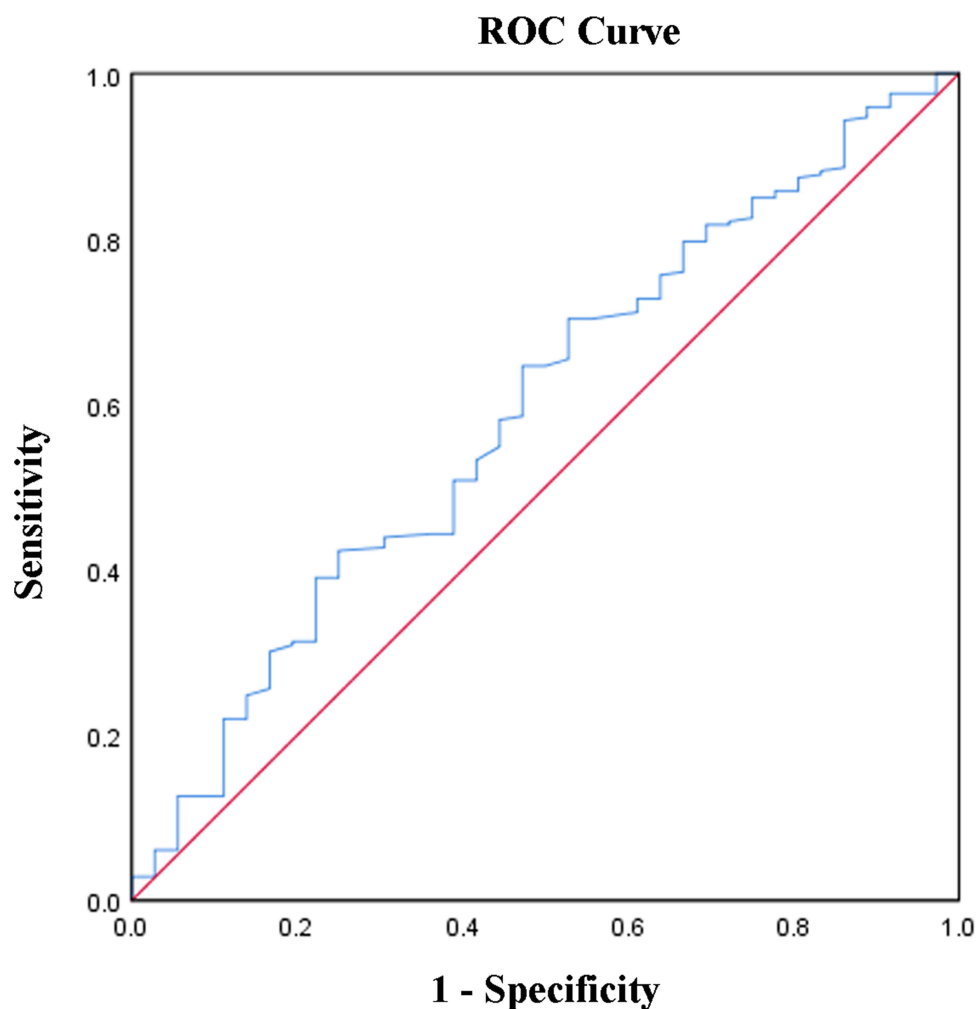

Figure 1 Receiver operating curve for response to neoadjuvant chemotherapy was plotted to determine the optimum cut-off for neutrophil-to-lymphocyte ratio (NLR).

Results

Optimal Cutoff Value of NLR

ROC analysis (Figure 1) revealed the optimal cutoff of NLR was 1.8, and the corresponding area under the ROC curve as 0.591 (P=0.043). We divided the patients into high NLR (> 1.8) and low NLR (≤ 1.8) groups.

Patient Features

We analyzed 282 patients, 208 with a high NLR and 74 with low NLR. Table 1 presents the baseline characteristics of the patients, showing the association of NLR with clinicopathological parameters. Low NLR was significantly correlated with pCR ($P = 0.045$, Pearson chi-square test) and decreased death events ($P = 0.033$, Pearson chi-square test). A pCR was achieved in 20 (27.0%) of 74 patients with low NLR and 34 (16.3%) of 208 patients with high NLR ($P = 0.045$; Figure 2).

Association Between NLR and LNR

After NAC, 258 patients experienced ALND. Our analysis showed an association between NLR and LNR for these patients according to the molecular subtyping (Table 2). A notable difference existed in luminal A and luminal B tumors ($P = 0.041$, Pearson test) and no statistical significance in HER2-enriched and TNBC as well as total patients (Fisher's Exact test, Fisher's Exact test and Pearson's test, respectively).

The Prognostic Value of NLR and LNR

Using Kaplan–Meier analysis (Log rank test), we found a lower NLR associated with longer overall survival ($P = 0.033$) but not with disease-free survival ($P = 0.413$; Figure 3). Moreover, patients with more residual lymph node involvement (high LNR) showed shorter overall survival ($P < 0.001$) and disease-free survival ($P < 0.001$; Figure 4). However, there was no significant difference in overall survival and disease-free survival between LNR=0 and NLR= 0.01–0.2 ($P > 0.05$; Supplementary Figure 1).

Univariate analysis for prognosis indicated that, either by LNRC or single LNR value 0.5, the rise in LNR was associated with less overall survival ($P < 0.001$) and disease-free survival ($P < 0.001$; Table 3); High NLR was related to unfavorable overall survival (P=0.042). Moreover, multivariate analysis showed that rising LNR was independently correlated to severe prognosis by LNRC (Table 4).

Table 1 Correlation Between Clinicopathological Parameters and NLR

Parameters	NLR		P value
	High (>1.8)	**Low (≤1.8)**	
Age (n=282)			0.753
≤40	51 (73.9%)	18 (26.1%)	
41–50	84 (76.4%)	26 (23.6%)	
>50	74 (71.8%)	29 (28.2%)	
Tumor stage (n=269)			0.486
cT1	34 (75.6%)	11 (24.4%)	
cT2	101 (71.6%)	40 (28.4%)	
cT3	35 (81.4%)	8 (18.6%)	
cT4	27 (67.5%)	13 (32.5%)	
Nodal status (n=267)			0.709
cN0	29 (78.4%)	8 (21.6%)	
cN1	74 (72.5%)	28 (27.5%)	
cN2	36 (70.6%)	15 (29.4%)	
cN3	60 (77.9%)	17 (22.1%)	
Clinical stage (n=274)			0.775
I–II	79 (73.1%)	29 (26.9%)	
III	124 (74.7%)	42 (25.3%)	
Molecular subtype (n=254)			0.154
Luminal A and B BC	127 (69.8%)	55 (30.2%)	
HER2+BC	25 (75.8%)	8 (24.2%)	
TNBC	33 (84.6%)	6 (15.4%)	
Response to NAC (n=282)			0.045
pCR	34 (63.0%)	20 (37.0%)	
Non-pCR	174 (76.3%)	54 (23.7%)	
Cancer recurrence (n=282)			0.257
Yes	56 (78.9%)	15 (21.1%)	
No	152 (72.0%)	59 (28.0%)	
Death (n=282)			0.033
Yes	35 (87.5%)	5 (12.5%)	
No	173 (71.5%)	69 (28.5%)	

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; cT and cN, clinical stages before neoadjuvant chemotherapy (NAC); luminal A, BC hormone-receptor positive (ER and/or PR positive), HER2 negative, and Ki-67 low; luminal B, BC hormone-receptor positive (ER and/or PR positive), and either HER2 positive or HER2 negative with high levels of Ki-67; HER2+BC, hormone-receptor negative (ER and PR negative) and HER2 positive; TNBC, triple-negative breast cancer; pCR, pathological complete response.

Discussion

In this study, we analyzed the association between NLR and prognosis (including the efficacy of NAC and survival outcomes) in breast cancer patients who received NAC. We found that low pretreatment NLR was a favorable prognostic predictor, which indicated that lower NLR (<1.8) was significantly associated with higher pCR rate and longer overall
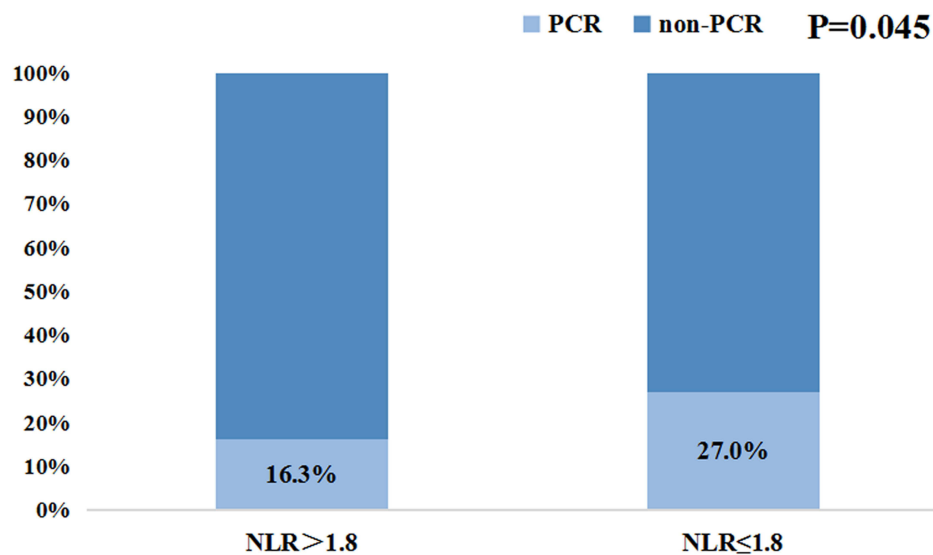
Figure 2 The response to neoadjuvant chemotherapy in neutrophil-to-lymphocyte ratio (NLR) high and low groups.

survival; these findings agreed with earlier reports.[7,18,36,37] However, our study did not show any significant correlation between pretreatment NLR and disease-free survival ($P = 0.413$). Therefore, additional prospective and multicenter research is needed to affirm the relationship between NLR and survival outcomes of breast cancer patients who receive NAC.

Among circulating immune cells, neutrophils secrete many factors that promote cancer development,[11,38,39] whereas lymphocytes exert a key function in the immune reaction against neoplasm. A high NLR in the

peripheral blood, reflecting systemic inflammatory response to tumors, was reported as a poor prognostic factor in breast cancer.[7,18,36,37] For patients who received NAC, we obtained a similar conclusion, ie, a high NLR was predictive for the inadequate reaction to NAC and poor survival. Our findings may have resulted from impaired host immune responses to malignancy.

Currently, axillary nodal status after NAC is based only on residual positive lymph node count and evaluated by TNM staging, according to the American Joint Committee on Cancer (AJCC). Axillary nodal status does not include the number of negative lymph node count. Rarely has the prognostic value of the negative lymph node count been reported. Wang et al.[40] found that patients with a high negative lymph node count (≥10) had better survival after NAC. In our study, we assessed the prognosis of patients who went through ALND after NAC by LNR. We found that the increase in LNR, which suggested more lymph node residue and less negative lymph nodes, was markedly correlated with poor prognosis. Besides, we found LNR by LNRC could be an independent prognostic factor. Thus, more negative lymph nodes after NAC may indicate stronger host lymphatic response to malignancy after treatment and better prognosis.

Few studies have emphasized on the association between pretreatment NLR and post-NAC axillary nodal residue in breast cancer patients. In our study,

Table 2 Correlation Between NLR and LNR in Various Subtypes

Molecular Subtype	NLR	LNR		P value
		≤0.5	>0.5	
Total	>1.8	155(82.4%)	33(17.6%)	0.531
	≤1.8	60(85.7%)	10(14.3%)	
LA+LB	>1.8	85(76.6%)	26(23.4%)	0.041
	≤1.8	46(90.2%)	5(9.8%)	
HER2-enriched	>1.8	22(88.0%)	3(12.0%)	0.137
	≤1.8	5(62.5%)	3(37.5%)	
TNBC	>1.8	27(90.0%)	3(10.0%)	0.535
	≤1.8	5(83.3%)	1(16.7%)	

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; LNR, positive lymph node ratio; luminal A, BC hormone-receptor positive (ER and/or PR positive), HER2 negative, and Ki-67 low; luminal B, BC hormone-receptor positive (ER and/or PR positive), and either HER2 positive or HER2 negative with high levels of Ki-67; HER2-enriched, hormone-receptor negative (ER and PR negative) and HER2 positive; TNBC, triple-negative breast cancer.
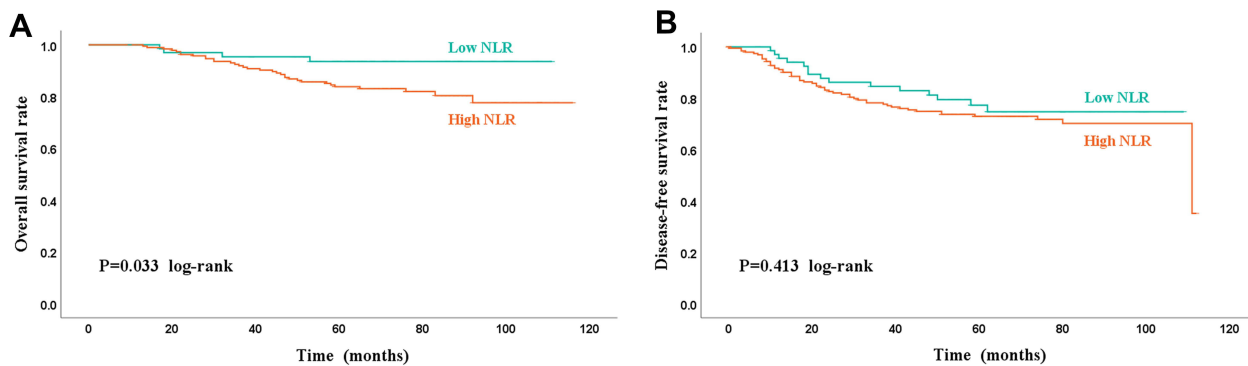
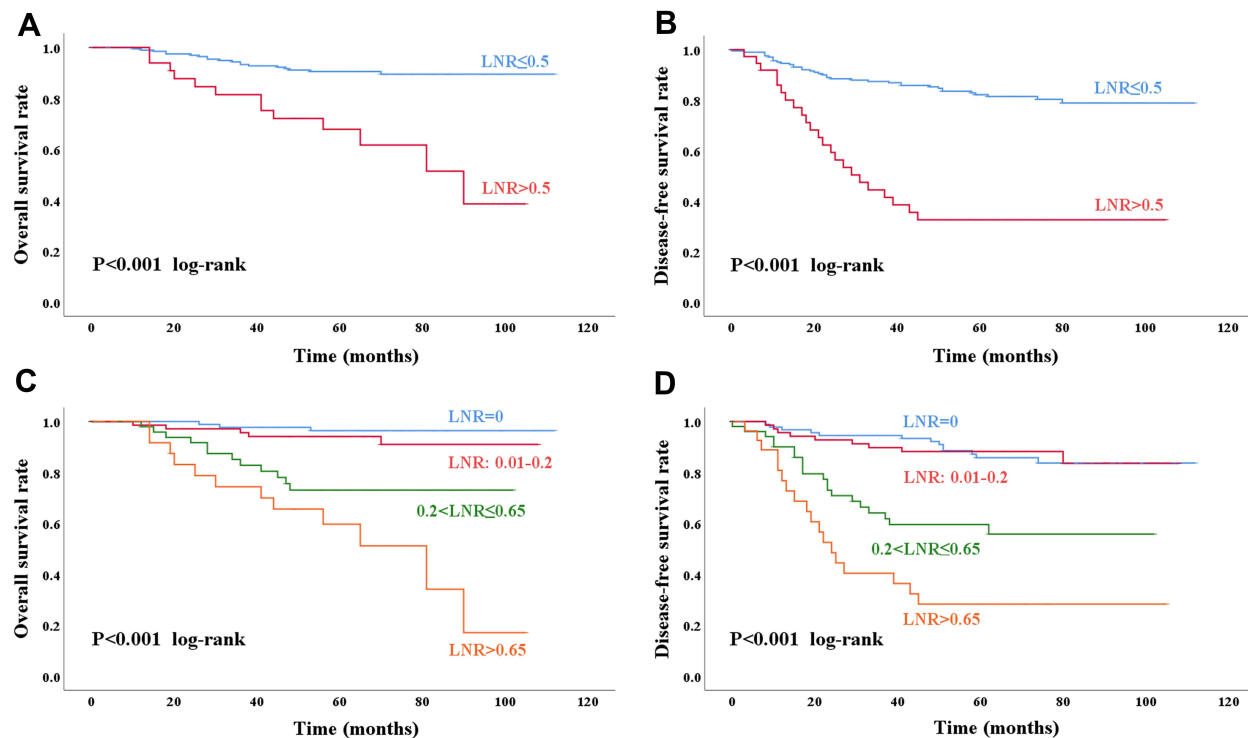**Figure 3** The prognostic value of NLR for overall survival (**A**) and disease-free survival (**B**).

Figure 4 Kaplan–Meier analysis of overall survival and disease-free survival of patients undergoing axillary lymph node dissection in (**A** and **B**) positive lymph node ratio categories (LNRC) and (**C** and **D**) single LNR value (0.5).

we found that NLR was a predictive factor for lymph node involvement in luminal A and luminal B patients after NAC. Patients with high NLR showed higher LNR. Thus, we combined immune response in peripheral blood and in axillary lymph nodes. We found that both measurements were parameters for superior clinical outcomes of patients who received NAC.

Our investigation was a single-center, retrospective study, and the strength of our conclusion was weakened.

Therefore, large-scale prospective clinical studies are needed to validate our results.

Conclusion

In summary, we have shown that decreased pretreatment NLR in peripheral blood of breast cancer patients predicted higher pCR rate after NAC and better overall survival. We reported for the first time that NLR was positively correlated with positive lymph node ratio in patients who went through ALND after NAC.

Table 3 Univariate Analysis of Factors Affecting Overall Survival and Disease-Free Survival

Parameters	Univariate Analysis			
	OS		DFS	
	HR(95% CI)	P	HR(95% CI)	P
Age				
≤40	I	0.293	I	0.729
41–50	2.027(0.743–5.535)	0.168	1.124(0.607–2.082)	0.710
>50	2.194(0.803–5.993)	0.125	1.272(0.693–2.335)	0.437
Tumor stage				
cT1	I	0.042	I	0.083
cT2	1.091(0.396–3.007)	0.866	1.479(0.712–3.074)	0.294
cT3	2.467(0.804–7.572)	0.115	2.473(1.068–5.724)	0.035
cT4	2.994(0.997–8.985)	0.051	2.396(1.021–5.620)	0.045
Nodal status				
cN0	I	0.324	I	0.046
cN1	2.487(0.556–11.125)	0.233	1.572(0.632–3.912)	0.331
cN2	3.637(0.771–17.157)	0.103	2.359(0.911–6.109)	0.077
cN3	3.545(0.799–15.720)	0.096	2.878(1.190–6.960)	0.019
Clinical stage				
I	I	0.024	I	0.021
II	11,661.315(0–3.984E+85)	0.922	2.037(0.474–8.755)	0.339
III	39,441.586(0–1.346E+86)	0.912	3.735(0.908–15.360)	0.068
ER				
Positive versus negative	1.218(0.619–2.396)	0.568	0.984(0.599–1.616)	0.949
PR				
Positive versus negative	1.529(0.785–2.975)	0.212	1.246(0.777–1.998)	0.361
HER2				
Positive versus negative	1.561(0.673–3.620)	0.299	0.837(0.486–1.440)	0.520
Molecular subtype				
Luminal A and B BC	I	0.815	I	0.902
HER2+BC	1.282(0.487–3.375)	0.615	1.179(0.578–2.407)	0.650
TNBC	1.249(0.507–3.075)	0.629	1.022(0.516–2.024)	0.950
Response to NAC (pCR)				
Yes versus no	2.805(0.861–9.135)	0.087	1.443(0.760–2.741)	0.262
Cancer recurrence				
Yes versus no	20.504(8.515–49.370)	< 0.001	–	–
LNR(I)				
≤0.5 versus >0.5	4.807(2.370–9.750)	< 0.001	4.730(2.826–7.917)	< 0.001
LNR(II)				
LNR:0–0.2	I	< 0.001	I	< 0.001
0.2<LNR≤0.65	6.117(2.491–15.019)	< 0.001	4.216(2.374–7.489)	< 0.001
LNR>0.65	13.598(5.529–33.445)	< 0.001	8.385(4.510–15.590)	< 0.001

(*Continued*)

Table 3 (Continued).

Parameters	Univariate Analysis			
	OS		DFS	
	HR(95% CI)	*P*	HR(95% CI)	*P*
NLR				
High versus low	2.940(1.041–8.298)	0.042	1.206(0.701–2.075)	0.500

Abbreviations: OS, overall survival; DFS, disease-free survival; cT and cN, clinical stages before neoadjuvant chemotherapy (NAC); luminal A, BC hormone-receptor positive (ER and/or PR positive), HER2 negative, and Ki-67 low; luminal B, BC hormone-receptor positive (ER and/or PR positive), and either HER2 positive or HER2 negative with high levels of Ki-67; HER2+, BC hormone-receptor negative (ER and PR negative) and HER2 positive; TNBC, triple-negative breast cancer; pCR, pathological complete response; LNR, positive lymph node ratio; NLR, neutrophil-to-lymphocyte ratio.

Table 4 Multivariate Analysis of Factors Affecting Overall Survival and Disease-Free Survival

Parameters	Multivariate Analysis			
	OS		DFS	
	HR(95% CI)	*P*	HR(95% CI)	*P*
Age				
≤40	1	0.198	1	0.259
41–50	1.648(0.33–8.242)	0.543	0.784(0.365–1.685)	0.533
>50	3.167(0.652–15.371)	0.153	1.393(0.654–2.968)	0.391
Tumor stage				
cT1	1	0.881	1	0.090
cT2	0.804(0.194–3.334)	0.764	1.901(0.671–5.389)	0.227
cT3	0.61(0.099–3.762)	0.595	4.433(1.267–15.507)	0.020
cT4	0.958(0.145–6.319)	0.964	2.199(0.594–8.144)	0.238
Nodal status				
cN0	1	0.082	1	0.939
cN1	0.688(0.103–4.585)	0.699	0.766(0.236–2.485)	0.658
cN2	0.231(0.025–2.103)	0.193	0.593(0.111–3.172)	0.541
cN3	0.124(0.012–1.23)	0.075	0.686(0.138–3.399)	0.644
Clinical stage				
I	1	0.203	1	0.839
II	4139.302(0–3.097E+77)	0.924	0.651(0.089–4.773)	0.673
III	19,822.98(0–1.50E+78)	0.909	0.497(0.047–5.305)	0.563
Response to NAC (pCR)				
No versus yes	1.227(0.245–6.137)	0.803	–	–
Cancer recurrence				
No versus yes	17.915(6.042–53.120)	< 0.001	–	–
LNR(I)				
≤0.5 versus >0.5	0.264(0.027–2.553)	0.250	2.524(0.807–7.895)	0.111
LNR(II)				
LNR:0–0.2	1	0.029	1	0.002
0.2<LNR≤0.65	4.345(1.236–15.271)	0.022	4.242(1.873–9.604)	0.001
LNR>0.65	17.074(1.417–205.782)	0.025	4.604(1.254–16.895)	0.021
NLR				
Low versus high	2.056(0.517–8.172)	0.306	–	–

Abbreviations: OS, overall survival; DFS, disease-free survival; cT and cN, clinical stages before neoadjuvant chemotherapy (NAC); pCR, pathological complete response; LNR, positive lymph node ratio; NLR, neutrophil-to-lymphocyte ratio.

Abbreviations

NLR, neutrophil-to-lymphocyte ratio; NAC, neoadjuvant chemotherapy; pCR, pathological complete response; LNR, lymph node ratio; AJCC, the American Joint Committee on Cancer; UICC, International Union Against Cancer; LNRC, positive lymph node ratio categories; ALND, axillary lymph node dissection.

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Disclosure

The authors report no conflicts of interest in this work.

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