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Neutrophil to lymphocyte ratio is a prognostic factor for disease free survival in patients with breast cancer underwent curative resection

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Abstract

The aim of this study was to explore the prognostic significance of neutrophil-to-lymphocyte ratio (NLR) in patients with breast cancer after curative resection. Furthermore, we aimed to confirm the prognostic significance of NLR in early stage and different molecular types of breast cancer, as well as patients treated with neoadjuvant chemotherapy (NACT).

A total of 2458 patients between January 2002 and December 2014 from 2 independent cohorts were analyzed retrospectively. The optimal cut-off value of NLR for recurrence was determined via receiver operating characteristic (ROC) curve analysis. Univariate and multivariate analyses were used to assess the relationship between NLR and disease-free survival (DFS).

Both univariate and multivariate analysis showed that patients with high NLR were more inclined to suffer postoperative recurrence in 2 independent cohorts. NLR was identified as independent prognostic factor for DFS of early stage breast cancer ($P < .05$), different types of breast cancer ($P < .05$) and patients treated with NACT ($P < .05$).

Our data suggest NLR is independent prognostic factor for breast cancer patients. In addition, the prognostic value of NLR was further confirmed in early stage and different molecular types of breast cancer as well as patients treated with NACT.

Abbreviations: DFS = disease-free survival, Her-2 = human epidermal growth factor receptor-2, HR = hormone recepto, NACT = neoadjuvant chemotherapy, NLR = neutrophil-to-lymphocyte ratio, ROC = receiver operating characteristic, SPSS = Statistical Product and Service Solutions, TEC = docetaxel + anthracyclines + cyclophosphamide, TNBC = triple-negative breast cancer, TX = docetaxel + platinum.

Keywords: breast cancer, disease free survival, neoadjuvant chemotherapy, neutrophil-to-lymphocyte ratio, prognosis

1. Introduction

In recent decades, breast cancer is still the leading cause of death for women globally.[1] In China, breast cancer has the highest incidence and is the leading cause of cancer-related mortality for females.[2] Despite the improvements in adjuvant chemotherapy and endocrine therapy for long-term breast cancer treatment, the prognosis remains poor in China.[2] Various factors affect the prognosis of the breast cancer, including age, tumor size, nodal metastasis, menopause status, and molecular types,[3] etc. Tumor-node-metastasis (TNM) system is a commonly used staging system in clinic rather than prognosis evaluation tool. Additionally, it is cumbersome when some variables were added into consideration such as the molecular type of breast cancer or adjuvant therapy after surgery. Consequently, clinically easily accessible and reliable markers to stratify the prognosis of breast cancer patients who underwent curative resection are urgently needed.

Inflammation and immunity are reported to play an important role in tumor progression,[4,5] which are also crucial hallmark of the neoplasms. Neutrophil-to-lymphocyte ratio (NLR), which has a comprehensive evaluation of the balance between systemic inflammation and immunity, plays a necessary role in prognostic prediction of various malignancies.[6,7] For example, previous researches confirmed NLR as the independent prognostic marker in patients with upper gastrointestinal tumor,[8] hepatocellular carcinoma,[9] cervical cancer[10] and renal carcinoma,[11] etc. It is therefore reasonable to dig further into the relationship between breast cancer and NLR.

Accumulating studies had shown that elevated NLR was associated with high mortality of breast cancer.[12,13] However, the prognostic value of NLR had not been tested in independent cohort. In addition, the feasibility of NLR in early breast cancer and different molecular types of breast cancer remain controversial, as well as in patients treated with neoadjuvant chemotherapy (NACT). NLR was reported to be independent predictor for poor survival in triple-negative breast cancer (TNBC),[14,15] while some researches only confirmed its prognostic value in hormone receptor positive (HR+) breast cancer.[16] So, the consensus on NLR accurately predicting outcome in breast cancer is far from achieved.

The goal of this study was to assess the prognostic value of NLR in patients with breast cancer underwent curative resection in 2 large independent cohorts. Further, we aimed to confirm the predictive ability of NLR in early stage and different molecular

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S-KG and S-MF contributed equally to this work.

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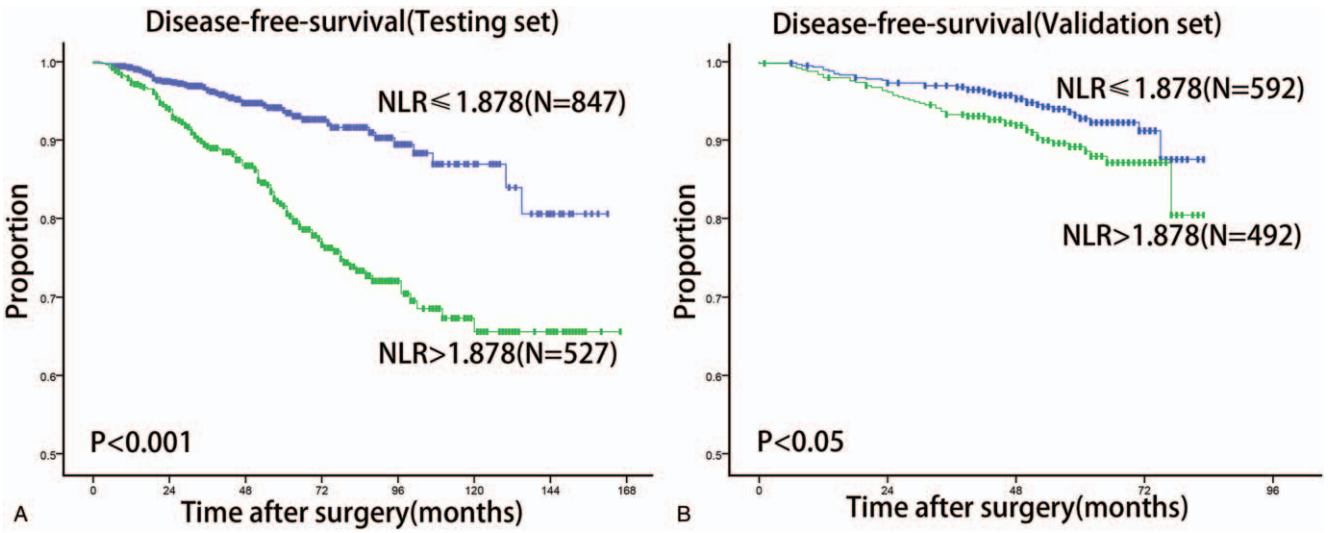

Figure 1. Kaplan–Meier analyses of NLR for DFS in both testing (A) and validation (B) sets. NLR = neutrophil-to-lymphocyte ratio, DFS = disease free survival.

types of breast cancer, as well as in breast cancer patients treated with NACT.

2. Materials and methods

2.1. Patients

A total of 2458 patients with breast cancer from 2 independent cohorts who underwent curative resection were enrolled in this study (patient number was calculated by the equation for case control study and we used 2 independent cohort to address potential bias). After obtaining Ethics Committee's approval, between January 2002 and December 2014, of whom 1374 were collected from the Zhongshan Hospital, Fudan University as the testing group and 1084 patients were from Ruijin Hospital, Shanghai Jiao Tong University as the validation group. Additionally, 96 patients who were treated with NACT were collected in this study from Zhongshan Hospital, Fudan University. The inclusion and exclusion criteria for the patients are as follows: all patients are diagnosed pathologically of breast cancer; all patients underwent resection defined as a complete resection; all the blood samples were obtained within 3 days before operations, all patients had complete records and follow-up data including baseline characteristics (including sex, age, menopause status, stage, molecular type, and preoperation routine blood test).

2.2. Follow-up

All patients had postoperative follow-up every 3 months during the first postoperative year and 6 months thereafter. Routine blood test, chest x-ray, and breast ultrasonography were performed in every follow-up. Bone-scan and tumor markers were performed every 6 months. The DFS time was defined as the interval between surgery and time of recurrence for relapsed patients or from the date of surgery to the date of last follow-up for nonrecurrent patients.

2.3. Statistical analysis

Statistical analysis was performed via SPSS version 22 (SPSS Inc, Chicago, IL). The association of clinicopathologic characteristics between testing cohorts and validation cohorts was analyzed using X^2 test or Fisher's exact test or *t*-test as appropriate. The survival curves were determined by the Kaplan–Meier analysis and compared by the log-rank test (Fig. 1). The cox proportional hazards regression model was used to perform univariate and multivariate analyses, and $P < .05$ (2 tailed) was considered statistically significant. The optimal cut-off value of preoperative NLR for recurrence was determined via receiver operating characteristic (ROC) curve analysis.

3. Results

3.1. Cut-off value of NLR

In the testing set, optimal cut-off value of the preoperative NLR associated with the strongest Youden index for the DFS was 1.878. The area under the ROC curve was 0.704 (95% confidence interval [CI], 0.663–0.744, $P < .001$) for preoperative NLR, showed in supplement Figure 1, http://links.lww.com/MD/C427.

3.2. Clinicopathological profiles of the patients

The clinicopathological characteristics of the patients from both cohorts are presented in Table 1. The median follow-up time was 51 months (range, 0–166 months) in testing cohort and 55 months (range, 0–83 months) in validation cohort, 24 months in the patients treated with NACT. Between testing set and validation set, there were significant differences in some aspects including the tumor size, lymph node metastasis, TNM stage, molecular type. At the end of follow-up, the DFS rates at 1, 3, 5 years of testing set and validation set were 98.5%, 93.5%, 88.3% and 98.5%, 95.2%, 91.1%, respectively. There were no statistically significant differences in the 1, 3, 5 years DFS rates between the 2 sets. There were 160 patients had recurrences in the testing set while 89 in the validation set. According to the TNM staging system, there were 86.7% (1186/1374) of the patients had stage I or II disease in the testing set while 92.3% (1000/1084) in the validation set. And about the chemical regime of patients treated with NACT, all patients were treated with docetaxel + anthracyclines + cyclophosphamide (TEC) plans except 10 patients with docetaxel + platinum (TX) regimes.

Table 1

Clinicopathological profiles of the patients in testing and validation sets.

Characters	Testing set N = 1374	Validation set N = 1084	P
Age	54.86 ± 12.18	55.53 ± 12.49	.177
< 40 years old	147 (10.7%)	120 (11.1%)	.769
>40 years old	1227 (89.3%)	964 (88.9%)	
No menopause	664 (48.3%)	423 (39.0%)	.001
Menopause	710 (51.7%)	661 (61.0%)	
T1	696 (50.7%)	677 (62.5%)	< .001
T2	628 (45.7%)	399 (36.8%)	
T3	49 (3.6%)	8 (0.7%)	
T4	1 (0.1%)	0	
N0	893 (65,0%)	751 (69.3%)	.005
N1	260 (18.9%)	213 (19.6%)	
N2	132 (9.6%)	70 (6.5%)	
N3	89 (6.5%)	50 (4.6%)	
Stage I	514 (37.4%)	504 (46.5%)	< .001
Stage II	672 (48.9%)	496 (45.8%)	
Stage III	188 (13.7%)	84 (7.7%)	
HR+	1038 (75.6%)	702 (64.7%)	< .001
HR-	336 (24.4%)	382 (35.3%)	
Her-2 positive	128 (9.3%)	170 (15.7%)	< .001
Her-2 negative	1246 (90.7%)	914 (84.3%)	
TNBC	208 (15.1%)	212 (19.6%)	.004
No TNBC	1166 (84.9%)	872 (80.4%)	
Recurrence	160 (11.6%)	89 (8.2%)	.005
No recurrence	1214 (88.4%)	995 (91.8%)	
Preoperation neutrophils	3.36 ± 1.50	3.46 ± 1.21	.063
Preoperation lymphocyte	1.87 ± 0.66	1.89 ± 0.60	< .001
Preoperation monocyte	0.36 ± 0.15	0.42 ± 0.39	< .001
Low NLR group	847 (61.6%)	592 (54.6%)	< .001
High NLR group	527 (38.4%)	492 (45.4%)	
One year DFS	98.50%	98.50%	.868
Three years DFS	93.50%	95.20%	
Five years DFS	88.30%	91.10%	

DFS = disease free survival, Her-2 = human epidermal growth factor receptor-2, HR = hormone receptor, NLR = neutrophil-to-lymphocyte ratio, TNBC = triple negative breast cancer.

3.3. Relationship between NLR and patient characteristics

The optimal cut-off value of NLR was 1.878 for DFS in the testing set, all patients were classified into 2 groups via the NLR, low NLR (NLR ≤1.878, N = 847 in testing set and N = 592 in validation set) and high NLR (NLR > 1.878, N = 527 in testing set and N = 492 in validation set). The clinicopathological characteristics for each group are listed in Table 2. High NLR was associated with high rates of recurrence in both sets ($P < .05$). About the menstrual state, significant differences can be seen in both sets between the 2 NLR groups. There were no significant differences between the NLR and tumor size, lymph node metastasis, and stage in both sets. The 1, 3, 5 years DFS rates for low and high NLR group of testing set was 99% (97.3%), 96.4% (89.2%), 93.7% (81.6%) with no significant differences ($P = .334$). Similarly, the results in the validation set which was 99% (98%), 96.8% (93.3%), 92.8% (88.6%), respectively ($P = .918$).

3.4. Prognostic value of NLR for DFS

In Table 3, the univariate analysis of the testing set for DFS, tumor TNM stage ($P < .001$, hazard ratio [HR] = 2.118; 95% [CI] 1.688–2.659), NLR ($P < .001$, [HR] = 2.886; [CI] 2.063–4.035) were identified as significant predictors. In multivariate analysis for DFS, tumor TNM stage ($P < .001$, [HR] = 2.099; [CI] 1.676–2.628), NLR group ($P < .001$, [HR] = 2.992; [CI] 2.137–4.189) were also identified as significant predictor. The results were confirmed in the validation set as shown in Table 3, NLR was identified as prognostic factor for DFS in both univariate analysis ($P < .05$, [HR] = 1.655; [CI] 1.088–2.520) and multivariate analysis ($P < .05$, [HR] = 1.637; [CI] 1.069–2.507). Furthermore, subgroup analyses were performed to ascertain the prognostic value of NLR as follows.

Firstly, when we focus on the stage I and II patients in both testing set and validation set, NLR was identified as prognostic factor for DFS ($P < .001$, [HR] = 3.122; [CI] 2.088–4.667 in univariate analysis and $P < .001$, [HR] = 3.280; [CI] 2.192–4.909 in multivariate analysis in testing set; $P < .05$, [HR] = 1.737; [CI] 1.069–2.824 in univariate analysis and $P < .05$, [HR] = 1.728; [CI] 1.055–2.832 in multivariate analysis in validation set, shown in Table 4).

Secondly, in the cohorts of the patients treated with NACT, the clinicopathological features were showed in supplement Table 1, http://links.lww.com/MD/C427. There were 13 out of 57 patients with recurrence in the high NLR group while 2 out of 39 in the low NLR group. There were statistically significant differences between the NLR groups and DFS rates ($P = .027$ in univariate analysis, $P = .025$ in multivariate analysis, shown in supplement Table 2, http://links.lww.com/MD/C427).

Additionally, when considering different molecular types of breast cancer, NLR had a significant prognostic effect on all three types of breast cancer (in univariate analysis, $P < .001$, [HR] = 2.516; [CI] 1.699–3.727; $P < .05$, [HR] = 2.958; [CI] 1.119–7.820; $P < .001$, [HR] = 5.242; [CI] 2.200–12.490, respectively, showed in supplement Table 3, http://links.lww.com/MD/C427).

4. Discussion

In this study, we confirmed NLR as a novel, easy-to-use, and effective predictive marker for DFS in patients with breast cancer underwent curative resection. Next, the significant association between NLR and early stage, or different molecular types of breast patients was identified as well. Furthermore, we showed the fact that NLR was confirmed to be an effective prognostic marker for patients with breast cancer underwent NACT.

The value of the NLR has been investigated in several solid malignancies, and it has been identified to be associated with significantly shorter overall survival by previous study.[17] Similarly, NLR had shown a significant prognostic value in patients with breast cancer (Fig. 2). Azab et al[12] found that patients with breast cancer who had higher NLR showed higher mortality rates compared with those with lower NLR ($P < .001$), of whom also possessed more severe tumor burden. In addition, Dirican A's retrospective study with 1527 breast cancer patients showed that disease-free survival and overall survival were both significantly associated with NLR.[18] In accordance with the previous studies, after stratifying patients into 2 groups according to the optimal cut-off value of NLR, we found patients with higher NLR (NLR > 1.878) were associated with high possibilities of recurrence. Next, higher NLR was identified as an independent predictor for DFS in both univariate and multivariate analysis ($P < .001$, [HR] = 2.886; [CI] 2.063–4.035 and $P < .001$, [HR] = 2.992; [CI] 2.137–4.189, respectively). Additionally, we confirmed the results in a large independent cohort ($P < .05$, [HR] = 1.655; [CI] 1.088–2.520 and $P < .05$, [HR] = 1.637; [CI] 1.069–2.507, respectively). To the best of our

Table 2

Relationship of different factors with NLR group in the testing and validation set.

	Testing set			Validation set		
Characters	Low NLR N = 847	High NLR N = 527	*P*	Low NLR N = 592	High NLR N = 492	*P*
Age	55.4 ± 12.3	54.0 ± 12.0	.033	55.7 ± 12.2	55.3 ± 12.8	.576
<40	87	60	.516	69	51	.501
>40	760	467		523	441	
No menopause	386	278	.01	198	225	<.001
Menopause	461	249		394	267	
T1	430	266	.887	370	307	.619
T2	386	242		219	180	
T3	30	19		3	5	
T4	1	0		0	0	
N0	554	339	.737	415	336	.882
N1	160	100		114	99	
N2	83	49		38	32	
N3	50	39		25	25	
Stage I	316	198	.231	278	226	.889
Stage II	425	247		270	226	
Stage III	106	82		44	40	
HR+	624	414	.04	382	320	.86
HR-	223	113		210	172	
Her-2 positive	80	48	.834	99	71	.302
Her-2 negative	767	479		493	421	
recurrence	50	110	<.001	38	51	.018
No recurrence	797	417		554	441	
One year DFS	99.00%	97.30%	.334	99.00%	98.00%	.918
Three years DFS	96.40%	89.20%		96.80%	93.30%	
Five years DFS	93.70%	81.60%		92.80%	88.60%	

DFS = disease free survival, Her-2 = human epidermal growth factor receptor-2, HR = hormone receptor, NLR = neutrophil-to-lymphocyte ratio, TNBC = triple negative breast cancer.

Table 3

Clinicopathological characteristics: univariate and multivariate survival analyses (testing set and validation set).

	DFS							
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Characters	Testing Set				Validation Set			
Age (<40 vs >40)	1.004 (0.991–1.018)	.674	1.379 (0.795–2.391)	.253	0.618 (0.355–1.077)	.086	0.565 (0.295–1.084)	.086
Menopause vs no menopause	1.017 (0.745–1.386)	.917	1.031 (0.747–1.422)	.853	1.164 (0.765–1.772)	.477	0.987 (0.601–1.621)	.959
Stage (III vs II vs I)	2.118 (1.688–2.659)	<.001	2.099 (1.676–2.628)	<.001	2.612 (1.905–3.580)	<.001	2.579 (1.877–3.545)	<.001
Molecular type (HR+ vs Her-2 vs TNBC)	1.078 (0.949–1.224)	.112	1.09 (0.958–1.239)	.19	1.228 (1.052–1.433)	.027	1.188 (1.016–1.389)	.03
High NLR vs Low NLR	2.886 (2.063–4.035)	<.001	2.992 (2.137–4.189)	<.001	1.655 (1.088–2.520)	.017	1.637 (1.069–2.507)	.023

DFS = disease free survival, Her-2 = human epidermal growth factor receptor-2, HR = hormone receptor, NLR = neutrophil-to-lymphocyte ratio, TNBC = triple negative breast cancer.

Table 4

Clinicopathological characteristics in early stage patients with BC: univariate and multivariate survival analyses (testing set and validation set).

	DFS							
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Characters	Testing set				Validation set			
Age (<40 vs >40)	1.293 (0.694–2.408)	.416	1.505 (0.788–2.872)	.215	0.654 (0.342–1.248)	.194	0.677 (0.322–1.423)	.304
Menopause vs no menopause	0.912 (0.633–1.315)	.621	0.93 (0.636–1.359)	.708	1.25 (0.772–2.023)	.363	1.056 (0.603–1.846)	.85
Stage (III vs II vs I)	2.164 (1.427–3.281)	<.001	2.279 (1.501–3.460)	<.001	1.981 (1.196–3.281)	.007	1.948 (1.173–3.235)	.01
Molecular type (HR+ vs HER-2 vs TNBC)	1.085 (0.934–1.260)	.41	1.01 (0.964–1.057)	.686	1.182 (0.988–1.415)	.181	1.148 (0.958–1.377)	.136
High NLR vs low NLR	3.122 (2.088–4.667)	<.001	3.28 (2.192–4.909)	<.001	1.737 (1.069–2.824)	.024	1.728 (1.055–2.832)	.03

DFS = disease free survival, Her-2 = Human epidermal growth factor receptor-2, HR = hormone receptor, NLR = neutrophil-to-lymphocyte ratio, TNBC = triple negative breast cancer.

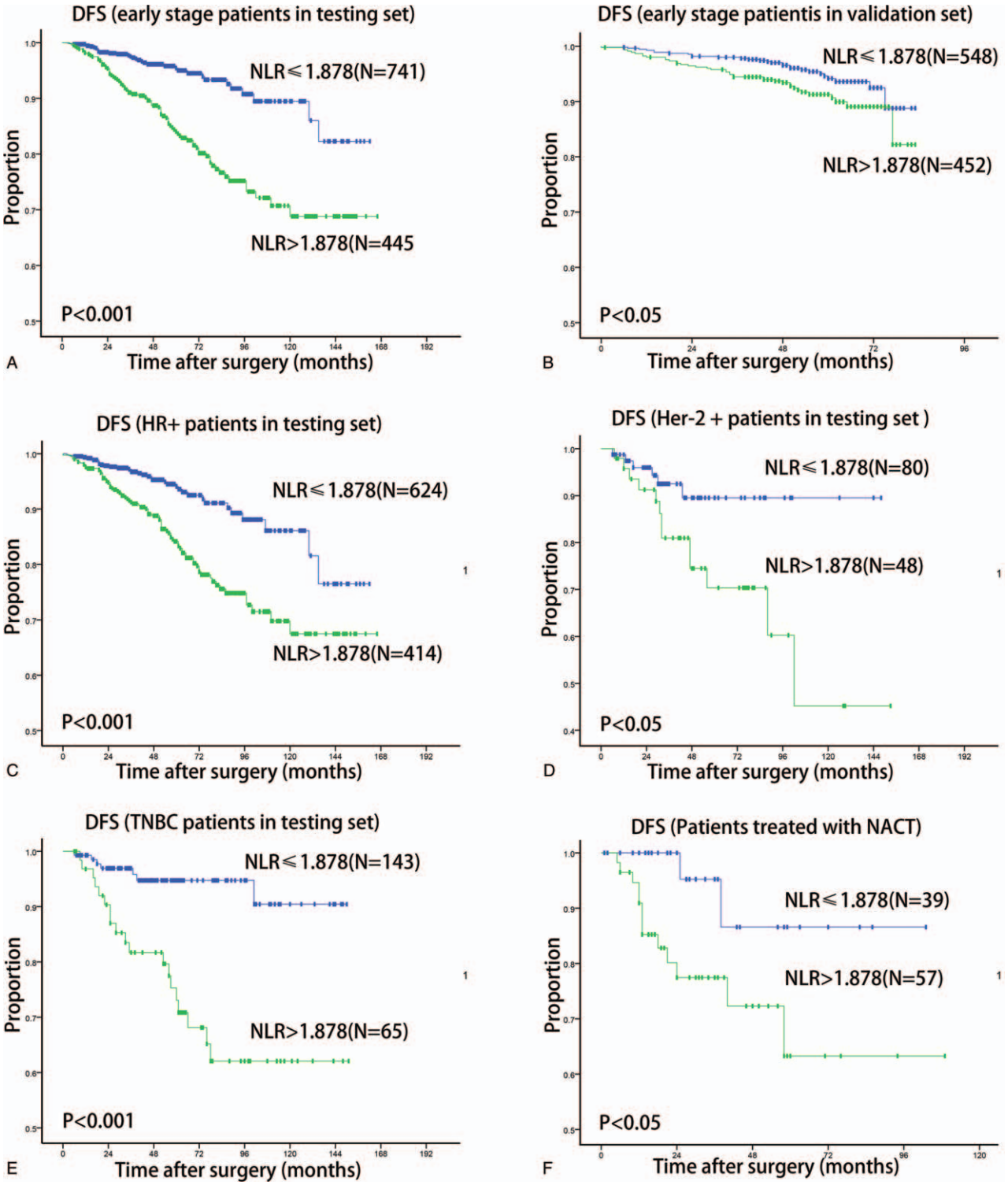

Figure 2. Prognostic value of NLR for DFS of early stage breast cancer patients (A), hormone receptor positive (HR+) breast cancer patients (C), Her-2 positive (Her-2 +) breast cancer (D) patients, triple negative breast cancer (TNBC, E) patients in testing set; Early stage breast cancer (B) in validation set, patients treated with neoadjuvant chemotherapy (F). Subgroup analysis indicated that significant differences in recurrence were found between high NLR and low NLR in patients with early stage/hormone receptor positive (HR+)/Her-2 positive (Her-2 +)/triple negative breast cancer, as well as patients treated with neoadjuvant chemotherapy. NLR = neutrophil-to-lymphocyte ratio, DFS = disease free survival.

knowledge, our research is the first large 2-center study to address this issue, which makes the results more convincible.

Furthermore, we conducted subgroup analyses as follows. When we focus on early stage patients with breast cancer, the NLR was confirmed to be a prognostic predictor for DFS in both testing and validation set ($P < .05$ in univariate and multivariate analysis), which ascertains that the NLR is a useful predictor of recurrence in patients with early-stage breast cancer.

When considering the relationship between NLR and different molecular types of breast cancer, Bozkurt et al's[15] study showed that TNBC patients with higher NLR had poorer DFS and OS than patients with lower NLR, but this study only comprised 85 patients. Jia et al's[14] study was retrospective research of 1570 breast cancer patients, showed that NLR significantly and independently indicated a poor prognosis for breast cancer and TNBC. While in 2013, in a study of 442 patients, Noh H found that higher NLR was significantly associated with poorer prognosis for the luminal A subtype,[19] not other molecular type of breast cancer. Koh et al's[16] analysis which comprised 157 breast cancer patients with ER/PR-positive and HER2-negative subtype who were treated with NACT found that NLR was significantly associated with the DFS and OS of the HR+ breast cancer patients received NACT. Although Ulas A's research in 2015 found HER-2+ breast cancer patients with high NLR had shorter DFS, the results were not confirmed in statistics ($P=.45$). (HR+, Her-2+, TNBC) of breast cancer ($P<.001$, $P=.022$, $P<.001$, respectively). In our study, we confirmed the NLR's prognostic value in all 3 molecular subtypes. There may be some reasons to explain our results: Firstly, our retrospective cohorts were larger than most of other researches. Secondly, Retsky M found that the early breast cancer relapses could have been effectively blocked by perioperative anti-inflammatory agents, unlike Jia et al's[14] study our patients did not receive any anti-inflammatory therapies, so there will be no confusing relationship between the recurrence rates and the inflammation maker, which makes our conclusion more reliable. Herein, NLR was identified as an independent prediction for DFS in all 3 different types of breast cancer patients.

When concerning about the patients treated with NACT, we revealed that the NLR was also significantly associated with DFS ($P=.027$), which was in accordance with the C. Marín research[20]. Conversely, the result was not consistent with the Suppan C' research.[21] The various of chemotherapy regiments may be the major reason to explain this. In our study, the chemotherapy regiments were all TEC (docetaxel, anthracyclines, cyclophosphamide) except 10 patients, whose chemotherapy treatment (CT) regiments were TX (docetaxel, platinum), while Suppan C's study used 5 different CT plans for the breast cancer patients. Thus, in our study, the heterogeneity caused by different CT plans was minimized, which makes the results more convincible.

Some limitations in the present study need to be considered. The first is that our study was a retrospective research. Secondly, the adjuvant therapy after the curative resection of breast cancer patients was not taken into consideration. So further studies should be carried out to overcome these problems.

In conclusion, our study suggested NLR, an easily accessible and valuable inflammation marker, to be a robust prognostic predictor for DFS in patients with breast cancer who underwent curative resection. Furthermore, the prognostic value of NLR was confirmed in the early stage and all 3 different molecular types of breast cancer, as well as patients treated with NACT.

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