

Usefulness of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in hormone-receptor-negative breast cancer

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Purpose: We aimed to investigate the relationship between pretreatment neutrophil-to-lymphocyte ratio (NLR)/platelet-to-lymphocyte ratio (PLR) and the estimation of hormone-receptor-negative (HR-) breast cancer patients' survival in a Chinese cohort.

Patients and methods: Of 434 consecutive HR- nonmetastatic breast cancer patients treated between 2004 and 2010 in the Affiliated Hospital of Academy of Military Medical Sciences, 318 eligible cases with complete data were included in the present study. Kaplan-Meier analysis was performed to determine the overall survival (OS) and disease-free survival (DFS). Univariate and multivariate Cox proportional hazards models were used to test the usefulness of NLR and PLR.

Results: Univariate analysis indicated that both elevated NLR and PLR (both $P < 0.001$) were associated with poor OS. The utility of NLR remained in the multivariate analysis ($P < 0.001$), but not PLR ($P = 0.104$). The analysis results for DFS were almost the same as OS. Subgroup analysis revealed a significant association between increased NLR and PLR ($P < 0.001$ and $P = 0.011$) and poor survival in triple-negative breast cancer. However, for human epidermal growth factor receptor 2-positive breast cancer, only NLR was significantly associated with OS in the multivariate analysis ($P = 0.001$).

Conclusion: The present study indicates that both increased NLR and PLR are associated with poor survival in HR- breast cancer patients. Meanwhile, NLR is independently correlated with OS and DFS, but PLR is not.

Keywords: inflammatory markers, breast cancer, survival

Introduction

Breast cancer is the most frequently diagnosed cancer in females worldwide, including within the People's Republic of China.¹ Newly diagnosed Chinese patients account for 12.2% of those all over the world. In spite of the falling mortality, the number of deaths is still sufficiently numerous each year.² Hormone-receptor-negative (HR-) breast cancer, including human epidermal growth factor receptor 2-positive (HER2+, nonluminal B) breast cancer, and triple-negative breast cancer (TNBC), has high recurrence and distant metastasis rates and the worst prognosis among subtypes.³ Consequently, it is highly significant to predict the prognosis of these patients, which influences clinicians' treatment decision. Currently, the main prognostic factors for HR- breast cancer are age, tumor size, grade, nodal status, and HER2 status.⁴ Although the usefulness of some new predictors (such as gene profiling, circulating tumor cells, and tumor T-cell infiltration) has been investigated, their clinical use is limited because of the uncertain role and high costs.⁵⁻⁷

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Recently, there is growing evidence that systemic inflammation is associated with the prognosis of various cancers, including breast cancer.^{8,9} Systemic inflammatory response could be expressed by some biochemical or hematological markers, such as raised C-reactive protein levels, hypoalbuminemia, and the elevation of white cell, neutrophil, and platelet counts. A combination of these factors was used to derive prognostic scores for inflammation, such as the Glasgow prognostic score, the neutrophil-to-lymphocyte ratio (NLR), and the platelet-to-lymphocyte ratio (PLR).¹⁰

To date, the unfavorable role of elevated NLR and PLR was deeply investigated in gastrointestinal tumors and non-small-cell lung cancers.^{11–16} However, the usefulness of NLR and PLR in breast cancer patients is not well studied, especially in HR–breast cancer patients on account of its low incidence.^{8,17–22} Three studies suggested that increased NLR is associated with poor prognosis in TNBC,^{8,17,19} but another two did not.^{21,22} The correlation between increased PLR and the prognosis of TNBC is conflicting.^{8,19,20} For HER2+ breast cancer, the utility of NLR and PLR is vague.^{8,19,21} In addition to these conflicting results, the scales of published studies for HR–breast cancer are small. Therefore, we aimed to further investigate the usefulness of pretreatment NLR and PLR in a comparatively large cohort of Chinese HR–breast cancer patients.

Patients and methods

We retrospectively evaluated HR–breast cancer patients treated between June 2004 and June 2010 in Affiliated Hospital of Academy of Military Medical Sciences. Among 434 HR–breast cancer patients, a total of 318 eligible patients were included. The inclusion criteria were as follows: histologically confirmed HR–nonmetastatic breast cancer, with pretreatment data of differential blood counts, and no history of inflammatory and immune disease, diabetes, hypertension, metabolic syndrome, coronary artery disease, renal disease, and hematological disease. Patients with metastatic and inflammatory breast tumors and infectious diseases were excluded.

Estrogen receptor (ER) negative and progesterone receptor (PR) negative were defined as <10% of positive invasive tumor nuclei by immunohistochemistry test. HER2 status was negative when the immunohistochemistry result was 0 and positive when the result was 3+ or when fluorescence in situ hybridization confirmed positivity for 1+ and 2+ patients. Blood count results from pretreatment (surgery and neoadjuvant chemotherapy) tests were obtained and confirmed by online records. Clinical and pathological characteristics included age, tumor size, lymph node involvement,

tumor stage (American Joint Committee on Cancer [AJCC]-6 criteria), grade, and ER, PR, and HER2 status. The treatments for HR–breast cancer included surgery (breast-conserving surgery and mastectomy), chemotherapy (adjuvant and neoadjuvant chemotherapy), targeted therapy (trastuzumab and lapatinib), and adjuvant radiotherapy.

The NLR/PLR was calculated by dividing the neutrophil/platelet count by the lymphocyte count. The primary end points were overall survival (OS) and disease-free survival (DFS). OS was defined as the interval between the date of histological diagnosis and the time of death of any cause. DFS was calculated from the time of surgery to the time of first relapse or death. The follow-up time was calculated from the time of diagnosis to the time of death or end up. Follow-up was censored when the patient was dead or at the end time of October 20, 2015. Nineteen patients were lost to follow-up at the end time. This study was approved by the ethical committee of the Affiliated Hospital of Academy of Military Medical Sciences. The ethical committee of the Affiliated Hospital of Academy of Military Medical Sciences did not require written informed consent be obtained from all patients, as this was a retrospective study, and all data was anonymous.

Statistical analysis

The optimal cutoff values for NLR and PLR were determined by employing receiver operating curve (ROC) analysis to discriminate high and low OS. The association between the NLR/PLR and pathological characteristics was evaluated by nonparametric tests. Kaplan–Meier method and log-rank test were used to study the primary end points. Univariate and multivariate Cox proportional hazards models were performed to obtain prognostic factors and corresponding hazard ratios (HRs) for different factors with 95% confidence intervals (CIs). To investigate the prognostic effect of NLR and PLR in different subtypes, HR–breast cancer was also divided into HER2+ breast cancer and TNBC. The multivariate analysis included age, tumor size, lymph node status, tumor grade, HER2 status, NLR, and PLR. All tests were two sided, and *P*-value <0.05 was considered statistically significant. Statistical Package for Social Sciences Version 20.0 (IBM Corporation, Armonk, NY, USA) was used to analyze the statistics.

Results

Among 318 eligible patients, 157 (49.4%) and 161 (50.6%) patients were classified into HER2+ breast cancer patients and TNBC patients, respectively. The baseline characteristics of

Table 1 Baseline characteristics

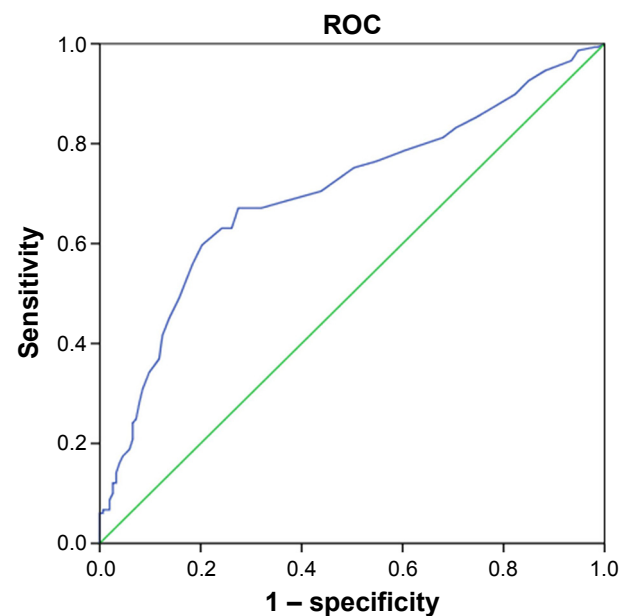
Characteristics	Number of patients (%)
Age (years)	
≤35	55 (17.3)
>35	263 (82.7)
Tumor stage	
T1	67 (21.1)
T2	178 (56)
T3	61 (19.2)
T4	10 (3.1)
Unknown	2 (0.6)
Lymph node status	
N0	127 (39.9)
N1	87 (27.4)
N2	47 (14.8)
N3	55 (17.3)
Unknown	2 (0.6)
AJCC stage	
I	47 (14.8)
II	151 (47.5)
III	118 (37.1)
Unknown	2 (0.6)
Tumor grade	
G1	29 (9.1)
G2	170 (53.5)
G3	107 (33.6)
Unknown	12 (3.8)
Surgery	
BCS	46 (14.5)
Mastectomy	271 (85.2)
Unknown	1 (0.3)
Chemotherapy	
NAC	56 (17.6)
AC	259 (81.5)
None	3 (0.9)
Adjuvant radiotherapy	
Yes	193 (60.7)
None	122 (38.4)
Unknown	3 (0.9)
Targeted therapy	
Yes	76 (23.9)
None	235 (73.9)
Unknown	7 (2.2)
HER2 status	
Positive	157 (49.4)
Negative	161 (50.6)
NLR	
<3	195 (61.3)
≥3	123 (38.7)
PLR	
<147	146 (45.9)
≥147	172 (54.1)

Abbreviations: AJCC, American Joint Committee on Cancer; BCS, breast-conserving surgery; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; HER2, human epidermal growth factor receptor 2; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

all patients are shown in Table 1. The median age at the time of diagnosis was 45 years (range 19–71 years). The median follow-up time was 58.1 months (range 5.9–136.1 months). The median OS and DFS were 63.5 months and 21.2 months, respectively.

The mean neutrophil, lymphocyte, and platelet counts were 3.8 ± 1.2 , 1.5 ± 0.5 , and 226.4 ± 60.5 , respectively. The mean NLR and PLR were 2.8 ± 1.3 and 164.0 ± 68.9 , respectively. ROC analysis revealed the optimal cutoff values of NLR and PLR as 3.0 and 147, respectively. The values of area under the curve were 0.70 and 0.67 for NLR (Figure 1) and PLR (Figure 2), respectively. The number of patients divided by high NLR/PLR and low NLR/PLR ratio is shown in Table 1. Nonparametric tests indicated that high NLR was associated with tumor size, lymph node status, AJCC stage, and surgery type. An increasing PLR significantly correlated with tumor size, lymph node status, AJCC stage, and HER2 status.

Among 318 patients, 283 (89.0%) and 278 (87.4%) developed recurrence disease and distant metastases at the end time, respectively. In all, 234 (73.6%) patients died for any cause. OS and DFS of different groups divided by cutoff values of NLR and PLR are shown in Figures 3–6, respectively. In high NLR (≥ 3) and PLR (≥ 147) groups, the estimated median OSs were 42.3 months and 51.5 months, respectively. In the contrary, in low NLR and PLR groups, the estimated median OSs were 78.2 months and 79.3 months, respectively.

**Figure 1** ROC analysis to discriminate high and low OS by NLR.

Note: The value of area under the curve is 0.70.

Abbreviations: ROC, receiver operating curve; OS, overall survival; NLR, neutrophil-to-lymphocyte ratio.

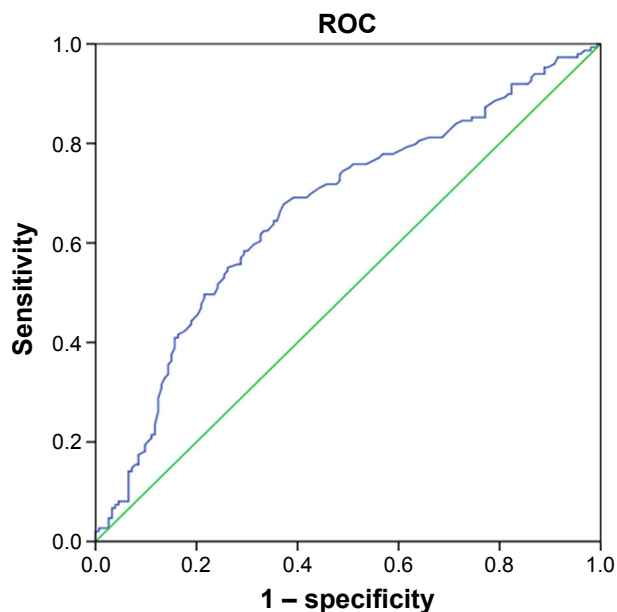


Figure 2 ROC analysis to discriminate high and low OS by PLR.
Note: The value of area under the curve is 0.67.
Abbreviations: ROC, receiver operating curve; OS, overall survival; PLR, platelet-to-lymphocyte ratio.

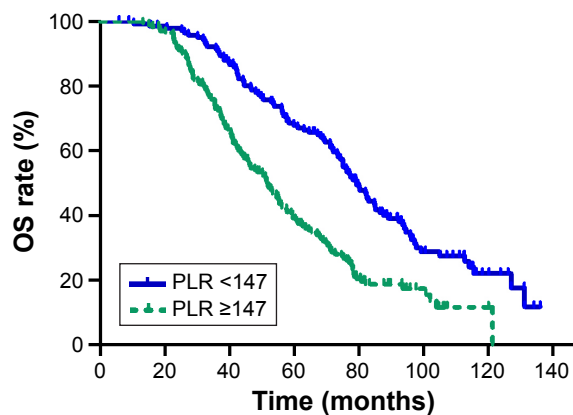


Figure 5 OS rate by low and high PLR ($P < 0.001$).
Abbreviations: OS, overall survival; PLR, platelet-to-lymphocyte ratio.

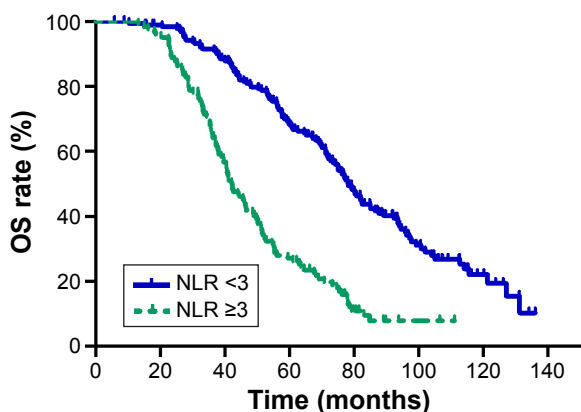


Figure 3 OS rate by low and high NLR ($P < 0.001$).
Abbreviations: OS, overall survival; NLR, neutrophil-to-lymphocyte ratio.

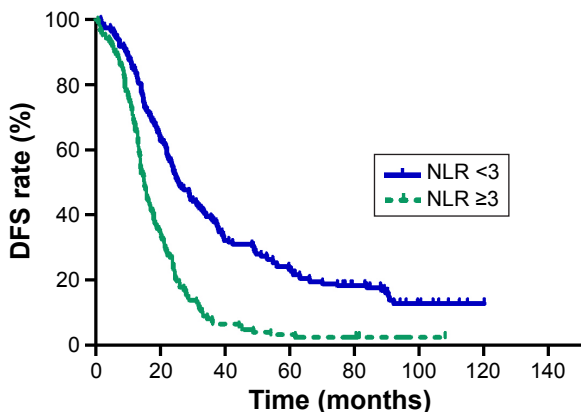


Figure 4 DFS rate by low and high NLR ($P < 0.001$).
Abbreviations: DFS, disease-free survival; NLR, neutrophil-to-lymphocyte ratio.

For OS, univariable analysis showed a significant association of high NLR and PLR with poor survival (Table 2). The predictive value of elevated NLR and PLR remained in the multivariable analysis (HR: 2.334, 95% CI: 1.712–3.182, $P < 0.001$; Table 2), but not PLR (HR: 1.302, 95% CI: 0.947–1.789, $P = 0.104$; Table 2). In addition, high tumor stage, grade, and lymph node involvement were recognized as indicators of poor survival in the multivariable analysis. High NLR and PLR also suggested poor outcome of patients' DFS in the univariable analysis. Meanwhile, the predictive value of high PLR was not found in the multivariable analysis, but NLR was found (Table 2). Furthermore, increased tumor size and high tumor grade were independent indicators for patients' DFS.

Subgroup analysis for different breast cancer subtypes revealed that elevated NLR (HR: 2.546, 95% CI: 1.627–3.984, $P < 0.001$; Table 3) and PLR (HR: 1.709, 95% CI: 1.130–2.585, $P = 0.011$; Table 3) were both independent prognostic factors for OS of TNBC patients. However, PLR did not retain

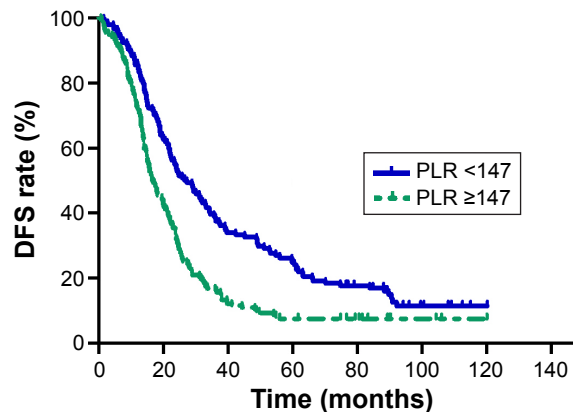


Figure 6 DFS rate by low and high PLR ($P < 0.001$).
Abbreviations: DFS, disease-free survival; PLR, platelet-to-lymphocyte ratio.

Table 2 Association between clinicopathologic parameters and OS/DFS in 318 HR- breast cancer patients

Variables	OS				DFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)								
≤35 vs >35	0.834 (0.062–1.157)	0.277	0.808 (0.575–1.136)	0.220	0.805 (0.596–1.086)	0.155	0.756 (0.553–1.033)	0.079
Tumor size								
<2 vs ≥2	2.628 (1.828–3.776)	<0.001	1.863 (1.264–2.747)	0.002	2.186 (1.615–2.959)	<0.001	1.607 (1.162–2.222)	0.004
Lymph node involvement								
No vs yes	2.048 (1.555–2.697)	<0.001	1.364 (1.009–1.843)	0.044	1.771 (1.389–2.559)	<0.001	1.263 (0.968–1.147)	0.085
Tumor grade								
G1/2 vs G3	3.009 (2.273–3.983)	<0.001	2.042 (1.52–2.744)	<0.001	2.903 (2.236–3.770)	<0.001	2.083 (1.577–2.753)	<0.001
HER2 status								
+ vs -	1.012 (0.782–1.309)	0.930	0.853 (0.647–1.126)	0.262	1.093 (0.866–1.381)	0.453	1.103 (0.862–1.412)	0.436
NLR								
<3 vs ≥3	3.091 (2.354–4.059)	<0.001	2.334 (1.712–3.182)	<0.001	2.369 (1.852–3.030)	<0.001	1.888 (1.421–2.508)	<0.001
PLR								
<147 vs ≥147	2.066 (1.580–2.702)	<0.001	1.302 (0.947–1.789)	0.104	1.728 (1.361–2.194)	<0.001	1.182 (0.900–1.154)	0.229

Abbreviations: OS, overall survival; DFS, disease-free survival; HR-, hormone-receptor negative; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2; +, positive; -, negative; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.

its significance for DFS. In the univariable analysis, both increased NLR and PLR indicated poor OS and DFS. For HER2+ patients, increased NLR was represented as an independent prognostic factor for both OS and DFS, but PLR was not (Table 3). The result of the univariable analysis suggested that elevated NLR and PLR were associated with poor OS and DFS.

Discussion

Inflammation plays a positive role in tumor initiation, occurrence, development, and progression.^{23–25} Neutrophils, as inflammatory and immune parameter, were recognized to be associated with tumor proliferation and metastasis by the release of inflammatory mediators, such as interleukin-8,

neutrophil elastase, and matrix metalloproteinase-9.^{26–29} Besides, platelets could not only promote tumor angiogenesis and metastases but also prevent tumor cells from the anti-tumor immune response by shielding them.^{30,31} Conversely, tumor-infiltrating lymphocytes could prevent the growth and spread of tumors by their antitumor immune response and are associated with better survival in patients with cancer.^{32,33} However, in some studies, the presence of several kinds of infiltrating lymphocytes, such as regulatory T cells and programmed death-1 positive lymphocytes, is associated with worse survival.^{34,35}

Previously, as a combination of neutrophil/platelet and lymphocyte, NLR and PLR were proposed to be predictive markers in various solid tumors, including nasopharyngeal,

Table 3 Association between NLR/PLR and OS/DFS in different breast cancer subtypes

Variables	OS				DFS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
HER2+ breast cancer								
NLR								
<3 vs ≥3	2.390 (1.633–3.647)	<0.001	2.210 (1.373–3.557)	0.001	2.159 (1.522–3.065)	<0.001	2.113 (1.362–3.278)	0.001
PLR								
<147 vs ≥147	1.733 (1.173–2.560)	0.006	0.953 (0.577–1.574)	0.852	1.720 (1.212–2.442)	0.002	0.911 (0.582–1.424)	0.682
TNBC								
NLR								
<3 vs ≥3	4.055 (2.733–6.015)	<0.001	2.546 (1.627–3.984)	<0.001	2.585 (1.829–3.654)	<0.001	1.916 (1.294–2.838)	0.001
PLR								
<147 vs ≥147	2.517 (1.725–3.672)	<0.001	1.709 (1.130–2.585)	0.011	1.727 (1.238–2.411)	0.001	1.396 (0.972–2.006)	0.071

Abbreviations: NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; HER2+, human epidermal growth factor receptor 2 positive; TNBC, triple-negative breast cancer.

pleural, lung, breast, gastric, hepatocellular, pancreatic, colorectal, prostate, endometrial, and ovarian cancers.^{8,11–13,36–46} However, the underlying mechanisms related to NLR/PLR and cancer are unclear. The main hypothesis is that elevated NLR and PLR resulted from increased neutrophils and platelets and/or decreased lymphocytes, which may suggest tumor progression and poor survival. Four recent meta-analysis studies confirmed the association between elevated NLR and poor prognosis in gastric, colorectal, and non-small-cell lung cancers.^{9,12,15,39} For breast cancer, studies about the predictive value of NLR and PLR were rare, especially for HR–breast cancer.^{8,17,19–22}

In the present study, we validated the utility of high NLR for HR–breast cancer. Elevated PLR was significantly associated with poor OS and DFS, but this association did not remain in the multivariable analysis adjusted for age, tumor stage, lymph node involvement, tumor grade, HER2 status, and NLR. The subanalysis showed the same result in HER2+ breast cancer. However, increased NLR and PLR were both independently associated with high mortality of TNBC.

To date, there are sparse data directly investigating the usefulness of elevated NLR/PLR in HER2+ breast cancer and TNBC. Different cutoff values of NLR (3.0, 4.0, and 5.0) and PLR (185 and 292) were used in different studies. Considering the differences between human races, we used ROC analysis to find out the optimal cutoff values for this study population. As a result, the cutoff value of NLR (3.0) was consistent with that of most of previous studies. Meanwhile, the PLR value of 147 was lower than that of most of published studies, but higher than that of a research from the People's Republic of China.¹⁹ These results may contribute to differences in race and study population.

In this study, we provided additional powerful evidence for the utility of NLR in HR–breast cancer, which is consistent with most of the published studies in spite of the cutoff value.^{8,17,19} However, two studies did not detect a significant association between elevated NLR and both DFS and OS in HR–breast cancer patients, which may account for small sample size.^{21,22} For the predictive value of PLR, only two studies performed Cox proportional hazards model in HR–breast cancer. In TNBC, the most recent study revealed that it is statistically significant between groups of high PLR (>185) and low PLR (\leq 185) in the multivariable analysis, but the HR was 1.27 (0.76–2.14).⁸ Another study validated the association of increased PLR (\geq 292) and clinical outcomes, but it did not remain in the multivariable analysis.²⁰ In the present study, we found that it is independently associated with patients' survival of TNBC. In HER2+ breast cancer, our result is in agreement with the most recent study with

similar HR that high PLR was not independently correlated with decreased survival.⁸

To the best of our knowledge, this is the largest research aimed to study the utility of NLR/PLR in Chinese HR–breast cancer patients. In addition, accurate measurement of ER, PR, and HER2 status and detailed clinicopathologic parameters and treatment information are also major strengths of our study.

Nevertheless, there are some limitations in our study. First, a selection bias of retrospective, single-center study was unavoidable, and we lacked external validation. Second, substandard and delayed treatment for patients might influence patients' survival. Third, although we excluded patients with diseases that influenced NLR and PLR, there might still be patients with these diseases but not recorded in the electronic medical records. Besides, some factors that may impact the value of NLR and PLR were not recognized because of limited studies. In spite of these limitations, our study provides a robust evidence for the evaluation of the NLR/PLR effect on HR–breast cancer patients.

Conclusion

Pretreatment NLR and PLR are useful biomarkers for HR–breast cancer patients. As convenient, inexpensive, and effective biomarkers, NLR and PLR may be added to existing prognostic factors to determine treatment options in the future. Prospective investigations are needed to confirm our findings and investigate the optimal cutoff value for different races.

Disclosure

The authors report no conflicts of interest in this work.

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