ORIGINAL RESEARCH

Increased derived neutrophil-to-lymphocyte ratio and Breast Imaging-Reporting and Data System classification predict poor survival in patients with non-distant metastatic HER2+ breast cancer treated with neoadjuvant chemotherapy

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Introduction: The prognostic role of the derived neutrophil-to-lymphocyte ratio (dNLR) in human patients with HER2+ breast cancer is not well understood. Here, we aimed to investigate the prognostic significance of dNLR in patients with HER2+ breast cancer undergoing neoadjuvant chemotherapy.

Methods: A total of 310 patients with non-distant metastatic HER2+ breast cancer who had received neoadjuvant chemotherapy in our hospital from May 2006 to November 2013 were retrospectively included in this study. Kaplan–Meier curves were used to assess overall survival (OS) and disease-free survival (DFS). The Cox regression model was used to evaluate the prognostic value of dNLR and Breast Imaging-Reporting and Data System (BI-RADS) classification, as well as other clinicopathological parameters in patients with HER2+ breast cancer treated with neoadjuvant chemotherapy.

Results: We found that dNLR prior to treatment was positively correlated with tumor size, tumor stage, lymphovascular invasion, and histological grade ($P<0.05$). The median OS of patients with high dNLR and low dNLR were 44.2 and 69.9, respectively ($P<0.001$), and the median DFS of patients with high dNLR and low dNLR were 15.3 and 22.1 months, respectively ($P<0.001$). Multivariate analysis showed that dNLR was an independent risk factor for OS (HR =1.726; 95% CI: 1.072–2.662; $P=0.009$) and DFS (HR =1.658; 95% CI: 1.125–2.426; $P=0.026$). Moreover, increased BI-RADS classification independently predicted short OS (HR =1.609; 95% CI: 1.216–2.351; $P=0.015$) and DFS (HR =1.925; 95% CI: 1.526–2.635; $P=0.021$).

Conclusion : dNLR prior to treatment and BI-RADS classification are independent prognostic factors in patients with HER2+ breast cancer receiving neoadjuvant chemotherapy.

Keywords: breast cancer, inflammation, dNLR, Breast Imaging-Reporting and Data System, prognosis

Introduction

Breast cancer is the most common malignancy among women worldwide, including China.[1] Overexpression of HER2 is a poor prognostic factor in patients with breast cancer. Currently, drugs that target HER2, such as herceptin, lapatinib, ado-trastuzumab, emtansine, and pertuzumab, are primarily used to treat HER2+ breast cancer, thereby increasing the survival and quality of life of patients. However, the number of deaths per year due to HER2+ breast cancer remains high.[1] HER2+ breast cancer frequently

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recurs after first-line treatment, resulting in metastasis and ultimately death.[2] Therefore, it is particularly important to predict the prognosis of patients with HER2+ breast cancer. At present, prognostic factors in these patients mainly include age, tumor size, histological grade, and lymph node status. Although several novel prognostic factors, such as circulating-free DNA, lymphocyte infiltration, and circulating tumor cells, have been discovered in recent years,[3–6] the clinical application of these markers is limited due to the high cost associated with measuring them and lack of evidence regarding their prognostic value.

The increasing volume of evidence shows that systemic inflammation can be used to predict the prognosis of patients with a variety of cancer types, including breast cancer.[7–15] Systemic inflammation can be monitored using biochemical or hematological markers, such as elevated C-reactive protein, hypoalbuminemia, and leukocyte, neutrophil, and platelet cell numbers. Many studies have suggested that the levels of inflammation prior to first-line treatment represent prognostic factors in cancer. Among them, the elevation of peripheral blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio appear to be predictive of poor prognosis in lung cancer, breast cancer, pancreatic cancer, prostate cancer, hepatocellular carcinoma, colorectal cancer, gastric cancer, and endometrial cancer.[7–9,16–23] The leukocyte minus neutrophil count was considered to be equivalent to the lymphocyte count. The derived NLR (dNLR) was defined as neutrophil count/leukocyte count minus neutrophil count; therefore, the high dNLR may be due to the increased neutrophil count or decreased lymphocyte count. Several other studies have used the dNLR (neutrophil/leukocyte minus neutrophil) as a prognostic indicator; their results have shown that elevated dNLR is associated with poor prognosis of patients with lung cancer, renal cell carcinoma, gastric cancer, hepatocellular carcinoma, colorectal cancer, urothelial carcinoma, pancreatic cancer, and lymphoma.[24–30] In breast cancer, the prognostic role of dNLR is controversial, particularly in patients with HER2+ breast cancer who have received neoadjuvant chemotherapy. Thus, we aimed to investigate the prognostic role of dNLR in this patient population.

Materials and methods
Patients and data collection
This study was approved by the Ethics Committee of The Third People's Hospital of Bengbu. The Ethics Committee did not require written informed consent be obtained from all patients, as this was a retrospective study, and all data were anonymous. A total of 310 patients who were diagnosed with HER2+ breast cancer and received neoadjuvant chemotherapy in our hospital from May 2006 to November 2013 were retrospectively included in the study. Inclusion criteria were as follows: patients (1) had histologically confirmed HER2+ non-distant metastatic breast cancer and (2) received neoadjuvant chemotherapy followed by radical or breast-conserving surgery; and (3) data collection was performed prior to treatment for differential blood counts. Patients with the following conditions were excluded: (1) inflammatory or immune diseases that may affect peripheral blood cell counts, such as diabetes, hypertension, metabolic syndrome, coronary artery disease, kidney disease, and hematological diseases; (2) metastatic or inflammatory breast cancer; (3) use of anti-inflammatory or immunosuppressive drugs prior to enrollment; and (4) infectious disease within 1 month of the study start date.

Data for leukocyte count, neutrophil count, and lymphocyte count, as well as age, tumor size, lymph node metastasis, lymphovascular invasion, histological grade, Breast Imaging-Reporting and Data System (BI-RADS) classification, and antitumor treatment (eg, surgery, chemotherapy, radiotherapy, and targeted therapy), were collected. Patients received neoadjuvant chemotherapy with four cycles of anthracyclines and cyclophosphamide, and four cycles of paclitaxel with or without herceptin. There were 189 (61%) patients who received postoperative radiotherapy, while 121 (39%) patients did not receive radiotherapy. The radiation dose was 50–60 Gy/25–30 fractions.

BI-RADS classification
We collected BI-RADS data based on the fifth edition of the BI-RADS classification. The definitions for each classification (1–6) are as follows: BI-RADS 6, a confirmed malignant tumor; BI-RADS 5, a tumor highly suggestive of malignancy and requires biopsy; BI-RADS 4, a tumor with suspected malignancy and requires biopsy; BI-RADS 3, a possibly benign tumor with reexamination recommended after 6 months; BI-RADS 2, a benign tumor; BI-RADS 1, tumor-negative.

Treatment and follow-up
All patients received neoadjuvant chemotherapy followed by surgery. Patients were regularly followed until death or discontinuation from the study. We performed the follow-up every 3 months after surgery. To assess disease status, ultrasound imaging, MRI, positron emission computed tomography, and computed tomography were used. During the follow-up, we evaluated the extent of disease progression,

death, and discontinuation. The deadline for follow-up was January 30, 2018. Overall survival (OS) was defined as the time from pathological diagnosis to death, and disease-free survival (DFS) was defined as the time from surgery to the first instance of disease recurrence.

Statistical analysis

Data analysis was performed using SPSS version 21.0 software (IBM Corporation, Armonk, NY, USA). The dNLR was defined as neutrophil count/leukocyte count minus neutrophil count. Using the receiver operating characteristic (ROC) curve analysis, dNLR with the highest specificity and sensitivity was selected as the cutoff value to discriminate between long and short OS.[31,32] Patients were divided into two groups based on the dNLR cutoff point: the low-dNLR group (dNLR < cutoff point) and the high-dNLR group (dNLR ≥ cutoff point). The relationship between dNLR and clinicopathological features was evaluated by Chi-squared and Fisher exact tests. The Kaplan–Meier method was used to evaluate OS and DFS. The differences in survival between patients from the two groups were compared by log-rank test. The Cox regression model was used for multivariate analysis to verify independent prognostic factors in patients with HER2+ breast cancer. Differences with $P<0.05$ were considered statistically significant.

Results

Patients' characteristics

A total of 310 patients were included in the study. Among them, 156 patients underwent breast-conserving surgery and 154 patients underwent modified radical mastectomy. Further,159 cases were classified as BI-RADS 5, 148 cases were classified as BI-RADS 4, and three cases were classified as BI-RADS 3. All patients received preoperative neoadjuvant chemotherapy. According to the American Joint Committee on Cancer staging system, 42, 128, and 140 cases of patients had stage I, II, and III disease, respectively. There were 34, 152, and 106 patients with histopathological grade 1, 2, and 3 tumors, respectively, while the histological grade in 18 patients was unknown. The median follow-up time was 62.5 months (9.6–138.5 months). At the end of the follow-up, 270 patients had recurrent or metastatic disease, 246 patients had died, and 16 patients were lost to follow-up.

The average preoperative leukocyte count of the total patient population was 5.2±1.2 (10^9/L). The mean neutrophil count was 3.7±1.5 (10^9/L), and the average dNLR was 2.3±0.8. ROC curve analysis showed that the optimal cutoff value for dNLR was 2.7.

Relationship between dNLR and clinicopathological features

Table 1 shows the association between dNLR and clinicopathological parameters. Tumor size, disease stage, lymphovascular invasion, and histopathological grade were higher in the high-dNLR group (dNLR ≥2.7) than in the low-dNLR group (dNLR <2.7) ($P<0.05$). Moreover, patients with a higher extent of lymph node metastasis had an increased dNLR ($P=0.052$).

High dNLR and BI-RADS classification predict poor survival

The median OS was 44.2 and 69.9 months in patients with high dNLR and low dNLR, respectively ($P<0.001$; Figure 1), while the median DFS in patients with high dNLR and low dNLR was 15.3 and 22.1 months, respectively ($P<0.001$; Figure 2). Patients with BI-RADS classification of 5 had poor OS and DFS compared with those who had BI-RADS classification of 3 or 4 (42.3 vs 71.2 months, $P<0.001$ and

Table 1 Relationship between dNLR and clinicopathological features in 310 patients with HER2+ breast cancer

Parameters	dNLR <2.7	dNLR ≥2.7	P-value
Age	43.5±12.4	45.2±10.5	0.812
Tumor size			
T1	54	4	0.005
T2	120	48	
T3	50	22	
T4	8	4	
Lymph node metastasis			
N0	92	20	0.052
N1	46	24	
N2	38	10	
N3	56	24	
AJCC stage			
I	38	4	0.042
II	92	36	
III	102	38	
Lymphovascular invasion			
Yes	36	26	0.001
No	196	52	
Pathological type			
IDC	191	60	0.293
ILC	41	18	
Histological grade			
I	32	2	<0.001
II	110	42	
III	84	22	
Unknown	8	10	

Abbreviations: AJCC, American Joint Committee on Cancer; dNLR, derived neutrophil-to-lymphocyte ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma.
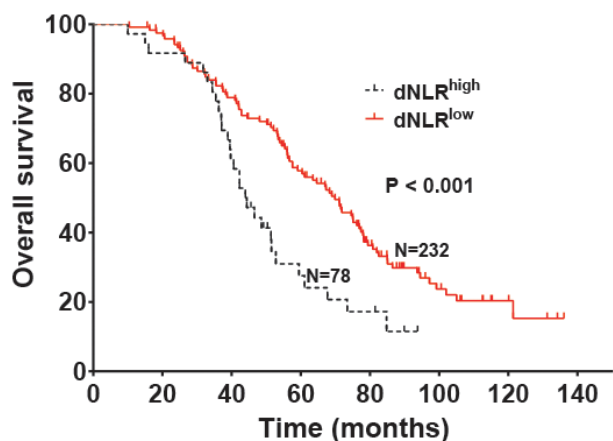
Figure 1 Overall survival of patients with HER2+ breast cancer stratified by dNLR.
Abbreviation: dNLR, derived neutrophil-to-lymphocyte ratio.
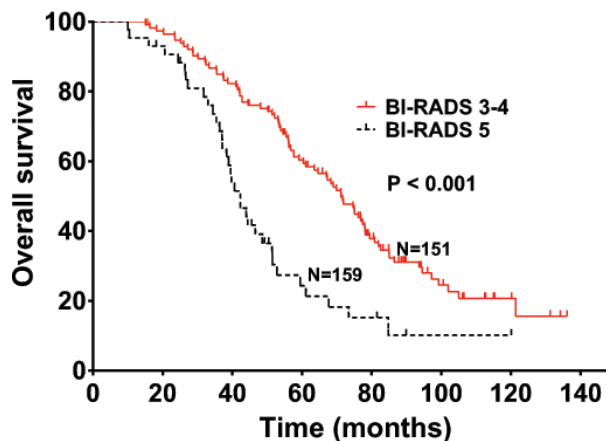

Figure 3 Overall survival of patients with HER2+ breast cancer stratified by BI-RADS classification.
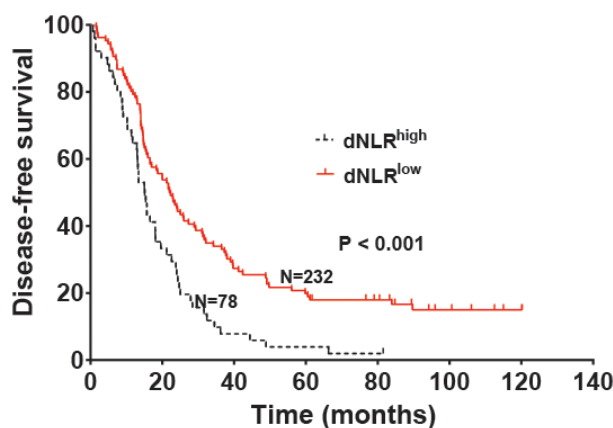**Abbreviation:** BI-RADS, Breast Imaging-Reporting and Data System.

Figure 2 Disease-free survival of patients with HER2+ breast cancer stratified by dNLR.
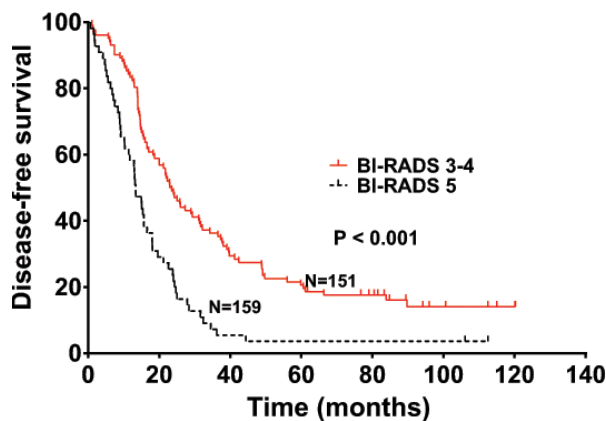**Abbreviation:** dNLR, derived neutrophil-to-lymphocyte ratio.

Figure 4 Disease-free survival of patients with HER2+ breast cancer stratified by BI-RADS classification.
Abbreviation: BI-RADS, Breast Imaging-Reporting and Data System.

13.4 vs 23.2 months, $P<0.001$, respectively; Figures 3 and 4). Univariate analysis showed that several patient characteristics, including large tumor size, lymph node metastasis, high-histopathological grade tumors, lymphovascular invasion, high BI-RADS classification, and high dNLR, were correlated with poor OS and DFS ($P<0.001$; Tables 2 and 3). Multivariate analysis showed that elevated dNLR independently predicted poor OS (HR =1.726, 95% CI: 1.072–2.662, $P=0.009$; Table 2) and DFS (HR =1.658, 95% CI: 1.125–2.426, $P=0.026$; Table 3). Furthermore, high BI-RADS classification independently predicted shorter OS (HR =1.609, 95% CI: 1.216–2.351, $P=0.015$; Table 2) and DFS (HR =1.925, 95% CI: 1.526–2.635, $P=0.021$; Table 3). We found that tumor size and histopathological grade were independent prognostic factors for patients with HER2+ breast cancer.

Discussion

Several recent studies have shown that systemic inflammation plays an important role in tumorigenesis and disease progression, suggesting the potential utility of inflammation as a prognostic marker.[8,9,16,33–35] Tumor-related inflammatory markers include biochemical and hematological indicators such as CA125, and leukocyte, neutrophil, and platelet cell count. Among them, neutrophils promote tumor development by remodeling the extracellular matrix and releasing ROS, nitric oxide, and arginase.[36–41] Previous reports have shown that neutrophils in circulating blood promote tumor growth and metastasis by producing tumor inflammatory mediators, while lymphocytes inhibit tumor progression through immune surveillance. Notably, tumor lymphocyte infiltration

Table 2 Univariate and multivariate analyses of OS in HER2+ breast cancer

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
≥50 vs<50	1.083 (0.731–1.652)	0.698	1.025 (0.632–1.686)	0.896
Tumor size				
≥2 vs<2	3.542 (2.038–5.695)	<0.001	2.623 (1.562–4.652)	<0.001
Lymph node metastasis				
Yes vs no	2.532 (1.815–3.726)	<0.001	1.426 (0.897–2.356)	0.132
Histological grade				
G3 vs G1/2	2.651 (1.786–3.689)	<0.001	2.013 (1.262–3.562)	0.001
Lymphovascular invasion				
Yes vs no	2.753 (1.952–3.856)	<0.001	1.653 (0.965–2.124)	0.086
BI-RADS				
5 vs 3–4	2.285 (1.512–3.263)	<0.001	1.609 (1.216–2.351)	0.015
dNLR				
≥2.5 vs<2.5	1.895 (1.152–2.862)	<0.001	1.726 (1.072–2.662)	0.009

Abbreviations: BI-RADS, Breast Imaging-Reporting and Data System; dNLR, derived neutrophil-to-lymphocyte ratio; OS, overall survival.

Table 3 Univariate and multivariate analyses of DFS in HER2+ breast cancer

Parameters	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)				
≥50 vs<50	0.963 (0.925–1.015)	0.562	0.826 (0.652–1.162)	0.216
Tumor size				
≥2 vs<2	2.862 (1.896–4.562)	<0.001	2.153 (1.352–3.653)	0.002
Lymph node metastasis				
Yes vs no	2.256 (1.547–3.256)	<0.001	1.315 (0.863–2.153)	0.268
Histological grade				
G3 vs G1/2	3.256 (2.356–5.125)	<0.001	2.562 (1.796–4.152)	<0.001
Lymphovascular invasion				
Yes vs no	2.956 (2.036–4.352)	<0.001	2.263 (1.265–2.965)	0.001
BI-RADS				
5 vs 3–4	2.562 (1.756–3.562)	<0.001	1.925 (1.526–2.635)	0.021
dNLR				
≥2.5 vs<2.5	1.856 (1.325–2.976)	<0.001	1.658 (1.125–2.426)	0.026

Abbreviations: BI-RADS, Breast Imaging-Reporting and Data System; DFS, disease-free survival; dNLR, derived neutrophil-to-lymphocyte ratio.

appears to be related to tumor prognosis.[5,6,42] T-cell activation status was positively associated with breast cancer patients' OS.[32,43] Besides, PD-L1+ tumor-infiltrating lymphocytes status showed an independent favorable prognostic value in patients with inflammatory breast cancer, suggesting that immune checkpoint immunotherapy should be explored and correlated with prognosis in these patients.[44]

Several studies have shown that high dNLR was associated with poor prognosis in multiple cancer types.[28,45–48] Among these, a few have investigated the role of dNLR in breast cancer; however, the results were inconsistent. Proctor et al[49] found that elevated dNLR was associated with poor prognosis in patients with breast cancer; however, this study did not take into account the clinical stage, tumor

histopathological grade, hormone receptor status, and previous treatments received by the patients, thus making it impossible to assess whether dNLR was associated with prognosis post adjustment of other factors. In another study, Dirican et al[47] analyzed 1,527 cases of breast cancer and found a significant association between elevated dNLR and DFS and OS; however, their multivariate analysis did not show that dNLR could be used as an independent prognostic indicator for breast cancer. Although the sample size of this study was relatively large, it had a short follow-up period, necessitating further verification.

Our study provides evidence that dNLR is significantly associated with OS and DFS in patients with HER2+ breast cancer. This correlation with OS and DFS remained

significant after adjusting for patients' age, tumor size, lymph node metastasis, and histopathological grading. Our results suggest that elevated dNLR is independently correlated with high mortality, suggesting its potential utility as an independent prognostic indicator for patients with HER2+ breast cancer. In our study, patients with breast cancer underwent routine blood tests prior to first-line treatment. Consequently, the assessment of dNLR was readily available without any additional costs. Therefore, preoperative dNLR may be used as an indicator to predict the survival of patients with HER2+ breast cancer. Moreover, we found that increased BI-RADS classification independently correlated with OS and DFS.

Few studies have reported on the relationship between dNLR and the prognosis of patients with HER2+ breast cancer, particularly in the Chinese population. To our knowledge, our study had the largest sample size compared with any other studies that investigated the prognostic value of dNLR in Chinese patients with HER2+ breast cancer. However, our study also had some limitations. First, selection bias in the retrospective single-center study was inevitable. Second, there was no external validation used in our study. Despite these caveats, our study still provides strong evidence for the prognostic role of dNLR and BI-RADS classification in patients with HER2+ breast cancer who have received neoadjuvant chemotherapy.

Conclusion

This study shows that dNLR and BI-RADS classification may represent independent prognostic factors in patients with HER2+ breast cancer who have received neoadjuvant chemotherapy. Prospective studies with a large sample are still needed to confirm the prognostic value of these factors.

Disclosure

The authors report no conflicts of interest in this work.

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