

Prognostic value of preoperative inflammatory markers in Chinese patients with breast cancer

Minya Yao¹
Yu Liu¹
Hailong Jin²
Xiaojiao Liu¹
Kezhen Lv¹
Haiyan Wei¹
Chengyong Du¹
Shuqian Wang¹
Bajin Wei¹
Peifen Fu¹

¹Department of Breast Center,
²Gastrointestinal Surgery, First
Affiliated Hospital, College of
Medicine, Zhejiang University,
Hangzhou, Zhejiang Province,
People's Republic of China

Abstract: Cancer-associated inflammation is a key determinant of disease progression and survival in most cancers. The aim of our study was to assess the predictive value of preoperative inflammatory markers, such as the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio, red cell distribution width (RDW), and mean platelet volume, for survival in breast cancer patients. In total, 608 breast cancer patients operated on between January 2009 and December 2011 were included in this observational study. The association between preoperative inflammatory markers and survival outcomes was analyzed. Patients with high NLR (>2.57) or high RDW ($>13.45\%$) showed a significantly lower overall survival rate than those with lower NLR (≤ 2.57) or lower RDW ($\leq 13.45\%$). NLR and RDW, along with node stage and molecular subtypes, were independent prognostic factors. There was a significant survival difference according to NLR in the luminal A and triple-negative subtypes (93.3% versus 99.3%, $P=0.001$; 68.8% versus 95.1%, $P=0.000$, respectively). The triple-negative subtype was the only subtype in which higher RDW patients showed significantly poor prognosis (81.3% versus 95.5%, $P=0.025$). Pre-operation NLR and RDW is a convenient, easily measured prognostic indicator for patients with breast cancer, especially in patients with the triple-negative subtype.

Keywords: neutrophil-to-lymphocyte ratio, NLR, red cell distribution width, RDW, overall survival

Introduction

Breast cancer is the most common cancer among females, and the incidence has increased greatly in recent years. Despite advances in treatment and the fact that mortality has dropped since 1990, breast cancer remains the leading cause of cancer death in females worldwide.^{1,2} Patient age, lymph node stage, tumor size, histological traits, hormonal receptors, human epidermal growth factor receptor 2 (HER2) status, and molecular typing are used for the stratification of breast cancer patients for prognostic purposes and for determining the appropriate treatment strategy.^{3,4} Nevertheless, some patients present with combinations of features/markers and thus have very different clinical outcomes.

It is now widely recognized that outcomes in patients with cancer are not determined by tumor characteristics alone, but patient-related factors are also key factors.⁵ Cancer-associated inflammation is a key determinant of disease progression and survival in most cancers.^{6,7} The inflammatory response involves systemic alterations triggered by circulating cytokines and chemokines, such as an increase in neutrophil count or a slight increase in platelet count.⁸ In addition, there are other parameters like red cell distribution width (RDW) and mean platelet volume (MPV) that are routine

Correspondence: Peifen Fu
Breast Center of the First Affiliated
Hospital, College of Medicine,
Zhejiang University, 79 Qingchun Road,
Hangzhou, 310003, Zhejiang Province,
People's Republic of China
Tel +86 571 87235125
Fax +86 571 87235125
Email fupeifen@hotmail.com

and easy-to-measure inflammatory markers.^{9–11} Studies have shown that the neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) may be predictive of mortality in various cancer populations, including breast, lung, colon, stomach, liver, pancreatic, and esophageal cancer,^{12–20} but there is no study regarding these markers in breast cancer patients from the People’s Republic of China. On the other hand, a few studies regarding RDW and MPV have suggested that they might be associated with cancer prognosis. Thus, the aim of this study was to determine the prognostic value of NLR, PLR, RDW, and MPV in Chinese breast cancer patients.

Materials and methods

Patients and methods

A retrospective analysis was conducted of 608 female patients who were diagnosed with primary breast cancer and who were operated on at the First Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, People’s Republic of China) from January 2009 to December 2011.

Medical records were reviewed, and each patient’s medical history, age, and pathologic results (such as tumor size, lymph node status, hormonal status, HER2, and laboratory data) were obtained.

Estrogen receptor (ER) and progesterone receptor (PR) status were obtained from immunohistochemistry, and a value $\geq 10\%$ was considered positive. HER2 status was obtained from immunohistochemistry or fluorescent in situ hybridization (FISH). The C-erbB-2 scores of three in immunohistochemistry or with a ≥ 2.2 -fold increase in HER2 gene amplification, as determined by FISH, were considered to be positive for HER2. The C-erbB-2 scores of two in immunohistochemistry without FISH were considered to be uncertain for HER2.

Molecular subtype was determined using the following criteria: luminal A, ER-positive and/or PR-positive and HER2-negative; luminal B, ER-positive and/or PR-positive and HER2-positive; HER2 enriched, ER- and PR-negative with positive HER2; and triple-negative, ER-negative, PR-negative, and HER2-negative.¹²

Complete blood count (CBC) test results were obtained within 1 week prior to surgery. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count, and PLR was defined as the absolute platelet count divided by the absolute lymphocyte count. RDW and MPV values were obtained directly from the CBC test (normal range: 11.5%–14.5% and 7.4–12.5 fl).

Patients with any inflammatory signs or conditions, hematological disease, coronary artery disease, end-stage renal

disease, heart failure, cerebrovascular disease, peripheral arterial disease, or a lack of information pertaining to pathologic or laboratory results were excluded. We also excluded patients undergoing neoadjuvant chemotherapy, those who were lost to follow-up, or those who died from causes other than breast cancer.

Patients were followed up every 3–6 months for the first 2 years after the operation, then annually. The last follow up was in March 2014.

The study was approved by the Ethical Committees of the First Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, People’s Republic of China.

Statistical analysis

Disease-free survival (DFS) and overall survival (OS) were calculated from the date of operation to the date of disease recurrence and death, respectively. The cutoff values of NLR, PLR, RDW, and MPV were determined using receiver operating characteristic (ROC) curve analysis, and the dependent variable was the DFS for 2 years. The optimal cutoff levels for NLR, PLR, RDW, and MPV were established at 2.57, 107.64, 13.45, and 9.05, respectively, and these cutoff values were used to categorize high and low NLR, PLR, RDW, or MPV groups. ROC curves were also plotted to verify the accuracy of NLR and RDW for OS prediction. The association between each marker and DFS and OS was analyzed using the Kaplan–Meier method with the log-rank test. Frequency distributions between categorical variables among the groups were compared using the chi-square test. If the expected frequency was < 5 , Fisher’s exact test was used. Univariate analysis was used to assess significant differences in clinical characteristics, and variables with $P < 0.10$ were entered into multivariate analyses. A P -value of < 0.05 was considered statistically significant. Analyses were performed using SPSS (IBM Corporation, Armonk, NY, USA) software, version 19.0.

Results

Baseline characteristics and factors affecting prognosis

Among the 608 patients in this study, the age range was 26–86 years, and the mean age was 52.4 ± 10.8 years. The follow-up time ranged from 8 to 62 months, and the median follow-up time was 42 months. The baseline characteristics of the study subjects are shown in Table 1.

The median levels of NLR, PLR, RDW, and MPV were 1.75 (0.55–7.22), 117.28 (13.33–428.29), 13% (11.6%–20.2%), and 11 fl (6.6–14.9 fl), respectively.

Table 1 Baseline patient characteristics (n=608) and univariate analysis of prognostic factors of DFS and OS by the Kaplan–Meier method

Characteristic	No (%)	Recurrence (%) (n=57)	DFS (%) (P-value)	Death (%) (n=24)	OS (P-value)
Age (years), mean ± SD	52.4±10.8				
Age (years)			0.795		0.308
≤35	26 (4.3)	2 (7.7)		0 (0)	
>35	582 (95.7)	55 (10.4)		24 (4.5)	
Menopausal status			0.923		0.321
Premenopausal	292 (48)	28 (9.6)		14 (4.8)	
Postmenopausal	316 (52)	29 (9.2)		10 (3.2)	
Hypertension			0.394		0.775
Yes	115 (18.9)	13 (11.3)		5 (4.3)	
No	493 (81.1)	44 (8.9)		19 (3.8)	
Diabetes			0.421		0.876
Yes	29 (4.8)	4 (13.8)		1 (3.5)	
No	579 (95.2)	53 (9.2)		23 (4.0)	
Histology			0.908		0.179
CIS	72 (11.8)	6 (8.3)		0 (0)	
IDC	497 (81.8)	48 (9.7)		21 (4.2)	
ILC	17 (2.8)	1 (5.9)		1 (5.9)	
Others	22 (3.6)	2 (9.1)		2 (9.1)	
T stage			0.005		0.007
Tis	72 (11.8)	6 (8.3)		0 (0)	
T1	322 (53.0)	19 (5.9)		8 (2.5)	
T2	211 (34.7)	32 (15.2)		16 (7.6)	
T3	3 (0.5)	0 (0)		0 (0)	
Node stage			0.000		0.000
N0	370 (60.9)	25 (6.7)		9 (2.4)	
N1	146 (24)	15 (10.3)		4 (2.7)	
N2	58 (9.5)	5 (8.6)		4 (6.9)	
N3	34 (5.6)	12 (35.3)		7 (20.6)	
ER status			0.016		0.014
Negative	208 (34.2)	28 (13.5)		14 (6.7)	
Positive	400 (65.8)	29 (7.2)		10 (2.5)	
PR status			0.014		0.009
Negative	267 (43.9)	34 (12.7)		17 (6.4)	
Positive	341 (56.1)	23 (6.7)		7 (2.1)	
HER2 status			0.021		0.198
Negative	428 (70.4)	33 (7.7)		15 (3.5)	
Positive	142 (23.4)	22 (15.5)		9 (6.3)	
Uncertain	38 (6.3)	2 (5.3)		0 (0)	
Molecular subtype (n=570)			0.006		0.008
Luminal A	330 (57.9)	20 (6.1)		6 (1.8)	
Luminal B	59 (10.3)	7 (11.9)		4 (6.8)	
HER2 enriched	83 (14.6)	15 (18.1)		5 (6.0)	
Triple-negative	98 (17.2)	13 (13.3)		9 (9.2)	
NLR			0.084		0.000
≤2.56	496 (81.6)	42 (8.5)		13 (2.6)	
>2.56	112 (18.4)	15 (13.4)		11 (9.8)	
PLR			0.273		0.051
≤107.64	243 (40.0)	19 (7.8)		5 (2.1)	
>107.64	365 (60.0)	38 (10.4)		19 (5.2)	
RDW			0.095		0.018
≤13.45%	398 (65.5)	31 (7.8)		10 (2.5)	
>13.45%	210 (34.5)	26 (12.4)		14 (6.7)	
MPV			0.056		0.279
≤9.05 fl	90 (14.8)	4 (4.4)		2 (2.2)	
>9.05 fl	518 (85.2)	53 (10.2)		22 (4.2)	

Abbreviations: CIS, carcinoma in situ; DFS, disease-free survival; ER, estrogen receptor; IDC, infiltrative ductal carcinoma; ILC, infiltrative lobular carcinoma; MPV, mean platelet volume; NLR, neutrophil–lymphocyte ratio; OS, overall survival; PLR, platelet–lymphocyte ratio; PR, progesterone receptor; RDW, red cell distribution width; SD, standard deviation; T stage, tumor stage; Tis, tumor in situ; HER-2, human epidermal growth factor receptor 2.

Table 2 Prognostic factors for overall survival

Factors	Univariate analysis ^a (P-value)	Multivariate analysis ^b		
		P-value	Relative risk	95% CI
T stage	0.007	0.072		
PLR	0.051	0.250		
Node stage	0.000	0.000	2.094	1.472–2.978
Molecular subtype	0.008	0.000	1.918	1.364–2.696
NLR	0.000	0.002	3.628	1.594–8.261
RDW	0.018	0.043	2.341	1.027–5.339

Notes: ^aPerformed using the Kaplan–Meier analysis model and the log-rank test; values of $P < 0.10$ in the univariate analysis were entered into a multivariate analysis; ^bperformed using Cox proportional hazards models with the forward likelihood method.

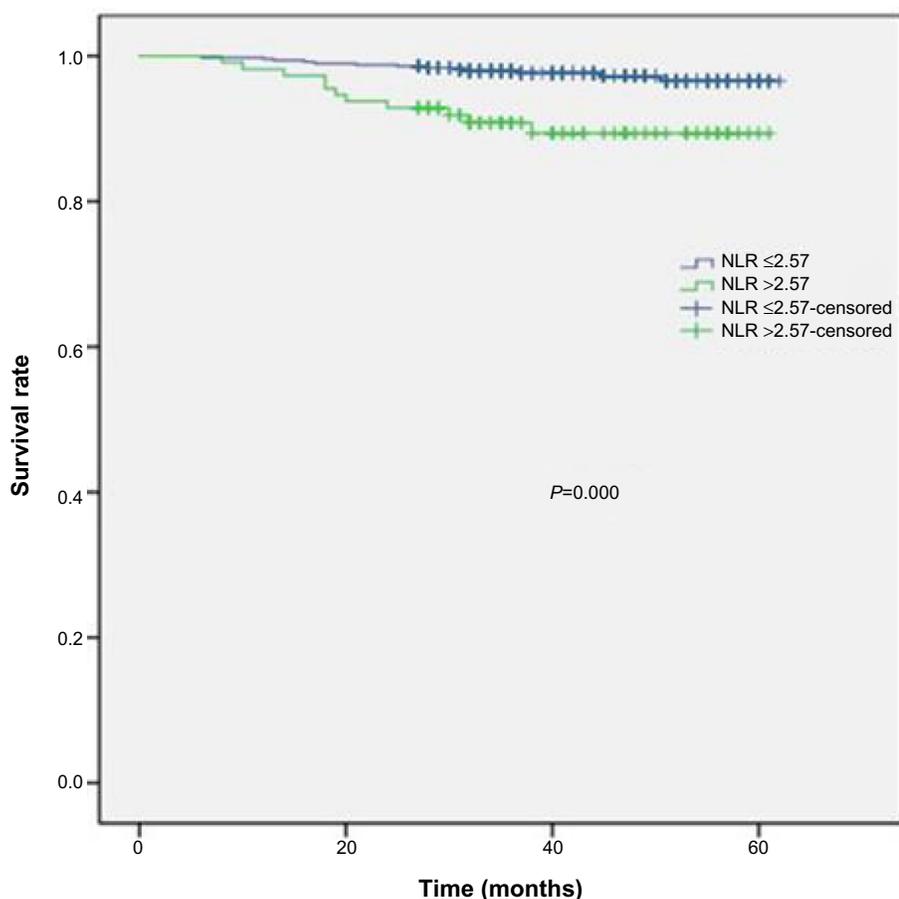
Abbreviations: CI, confidence interval; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; RDW, red cell distribution width; T stage, tumor stage.

To identify factors for breast cancer DFS and OS, 15 potential variables of interest were analyzed by univariate analysis, as listed in Table 1. T (tumor) stage, node stage, ER status, PR status, and molecular subtype were significantly associated with DFS and OS. HER2 status was

only significantly associated with DFS. We found that none of NLR, PLR, RDW, or MPV were associated with DFS. However, NLR and RDW were significantly associated with OS, and PLR might be associated with OS. Patients with an NLR higher than 2.57 showed a significantly lower 5-year OS rate than did patients with an $NLR \leq 2.57$ (90.2% versus 97.4%, respectively) (Figure 1). Patients with a RDW higher than 13.45% showed significantly lower 5-year OS rate than did patients with $RDW \leq 13.45\%$ (93.3% versus 97.5%, respectively) (Figure 2).

Next, a Cox proportional multivariate hazard model for OS was performed. We found that NLR and RDW, along with node stage and molecular subtype, were independent prognostic factors (Table 2). The hazard ratios for NLR and RDW were 3.628 and 2.341, respectively.

The ROC curve for OS prediction revealed an area under the curve of 0.643 (95% confidence interval [CI]: 0.518–0.767, $P=0.018$) for NLR and 0.624 (95% CI: 0.507–0.740, $P=0.040$) for RDW. Therefore, NLR was superior to RDW as a predictive factor in patients with breast cancer (Figure 3).

**Figure 1** Kaplan–Meier survival curves according to NLR.

Notes: Patients with an NLR higher than 2.57 showed a significantly lower 5-year overall survival rate than did patients with an $NLR \leq 2.57$ (90.2% versus 97.4%, respectively).

Abbreviation: NLR, neutrophil–lymphocyte ratio.

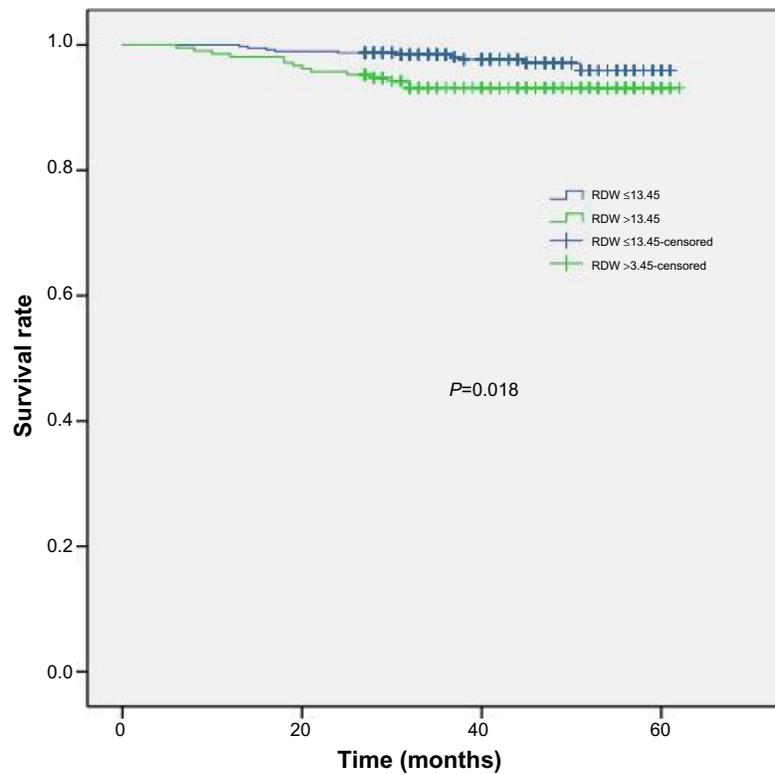


Figure 2 Kaplan–Meier survival curves according to RDW.

Notes: Patients with an RDW higher than 13.45% showed significantly lower 5-year overall survival rate than did patients with RDW \leq 13.45% (93.3% versus 97.5%, respectively).

Abbreviation: RDW, red cell distribution width.

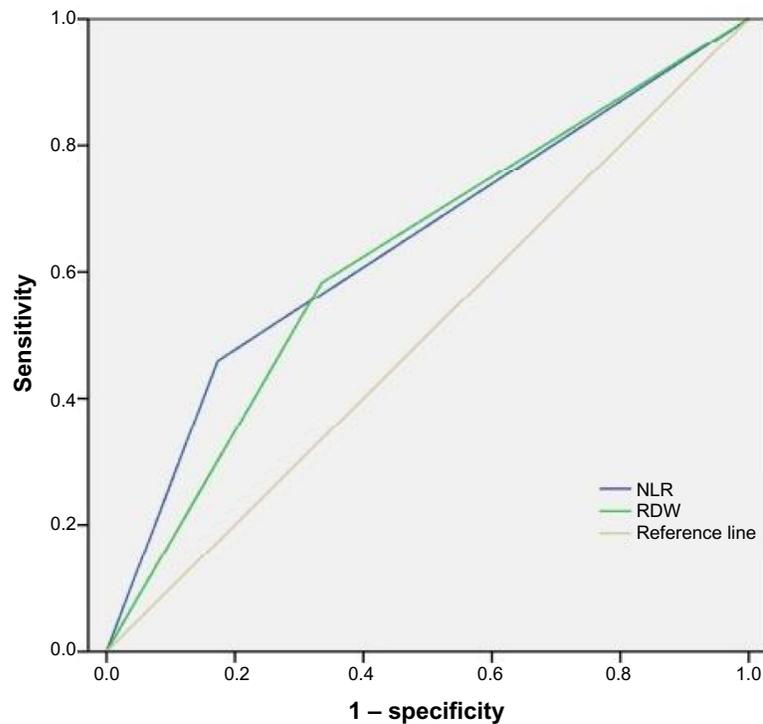


Figure 3 The ROC curves grouped by NLR and RDW.

Notes: The ROC for NLR is represented by the blue line with an AUC of 64.3% with a sensitivity of 45.8 and a specificity of 17.3%, and the ROC for the PLR is represented by the green line with an AUC of 62.4% with a sensitivity of 58.3% and a specificity of 33.6%.

Abbreviations: AUC, area under the curve; NLR, neutrophil–lymphocyte ratio; PLR, platelet–lymphocyte ratio; RDW, red cell distribution width; ROC, receiver operating characteristic.

Table 3 shows that NLR >2.57 was associated with diabetes and infiltrative carcinoma, while RDW $>13.45\%$ was associated with increased T stage and premenopausal status.

OS stratified by molecular subtype according to NLR and RDW

Both luminal A and triple-negative subtypes in which the NLR was higher than 2.57 showed significantly lower 5-year survival rate than did those types with an NLR ≤ 2.57

(93.3% versus 99.3%, $P=0.001$; 68.8% versus 95.1%, $P=0.000$, respectively). There was no significant survival difference according to NLR in the luminal B and HER2-enriched subtypes (Figure 4).

The triple-negative subtype was the only subtype in which RDW $>13.45\%$ showed significantly lower 5-year survival rate than did an RDW $\leq 13.45\%$ (81.3% versus 95.5%, respectively, $P=0.025$); there was no significant survival difference according to RDW in the other subtypes (Figure 5).

Table 3 Baseline characteristics of the 608 patients grouped by NLR and RDW

Characteristic	NLR, n (%)		P-value	RDW, n (%)		P-value
	≤ 2.56	> 2.56		$\leq 13.45\%$	$> 13.45\%$	
Age (years)			0.066			0.404
≤ 35	25 (5.0)	1 (0.9)		19 (4.8)	7 (3.3)	
> 35	471 (95.0)	111 (99.1)		379 (95.2)	203 (96.7)	
Menopausal status			0.501			0.025
Premenopausal	235 (47.4)	57 (50.9)		178 (44.7)	114 (54.3)	
Postmenopausal	261 (52.6)	55 (49.1)		220 (55.3)	96 (45.7)	
Hypertension			0.752			0.875
Yes	95 (19.2)	20 (17.9)		76 (19.1)	39 (18.6)	
No	401 (80.8)	92 (82.1)		322 (80.9)	171 (81.4)	
Diabetes			0.001			0.694
Yes	17 (3.4)	12 (10.7)		18 (4.5)	11 (5.2)	
No	479 (96.6)	100 (89.3)		380 (95.5)	199 (94.8)	
Histology			0.024			0.854
CIS	63 (12.7)	9 (8.0)		48 (12.1)	24 (11.4)	
IDC	407 (82.1)	90 (80.4)		326 (81.9)	171 (81.4)	
Others	26 (5.2)	13 (11.6)		24 (6.0)	15 (7.1)	
T stage			0.070			0.038
Tis	63 (12.7)	9 (8.0)		48 (12.1)	24 (11.4)	
T1	252 (50.8)	70 (62.5)		224 (56.3)	98 (46.7)	
T2 + T3	181 (36.5)	33 (29.5)		126 (31.7)	88 (41.9)	
Node stage			0.458			0.345
N0	308 (62.1)	62 (55.4)		250 (62.8)	120 (57.1)	
N1	116 (23.4)	30 (26.8)		95 (23.9)	51 (24.3)	
N2	47 (9.5)	11 (9.8)		34 (8.50)	24 (11.4)	
N3	25 (5.0)	9 (8.0)		19 (4.8)	15 (7.1)	
ER status			0.341			0.294
Negative	171 (35.1)	34 (30.4)		142 (35.7)	66 (31.4)	
Positive	322 (64.9)	78 (69.6)		256 (64.3)	144 (68.6)	
PR status			0.645			0.158
Negative	220 (44.4)	47 (42.0)		183 (46.0)	84 (40.0)	
Positive	276 (55.6)	65 (58.0)		215 (54.0)	126 (60.0)	
HER2 (n=570)			0.736			0.564
Negative	352 (75.4)	76 (73.8)		278 (74.3)	150 (76.5)	
Positive	115 (24.6)	27 (26.2)		96 (25.7)	46 (23.5)	
Molecular subtype (n=570)			0.614			0.860
Luminal A	270 (57.8)	60 (58.3)		212 (56.7)	118 (60.2)	
Luminal B	45 (9.6)	14 (13.6)		39 (10.4)	20 (10.2)	
HER2 enriched	70 (15.0)	13 (12.6)		57 (15.2)	26 (13.3)	
Triple-negative	82 (17.6)	16 (15.5)		66 (17.6)	32 (16.3)	

Abbreviations: CIS, carcinoma in situ; ER, estrogen receptor; IDC, infiltrative ductal carcinoma; ILC, infiltrative lobular carcinoma; NLR, neutrophil-lymphocyte ratio; PR, progesterone receptor; RDW, red cell distribution width; T stage, tumor stage; Tis, tumor in situ; HER2, human epidermal growth factor receptor 2.

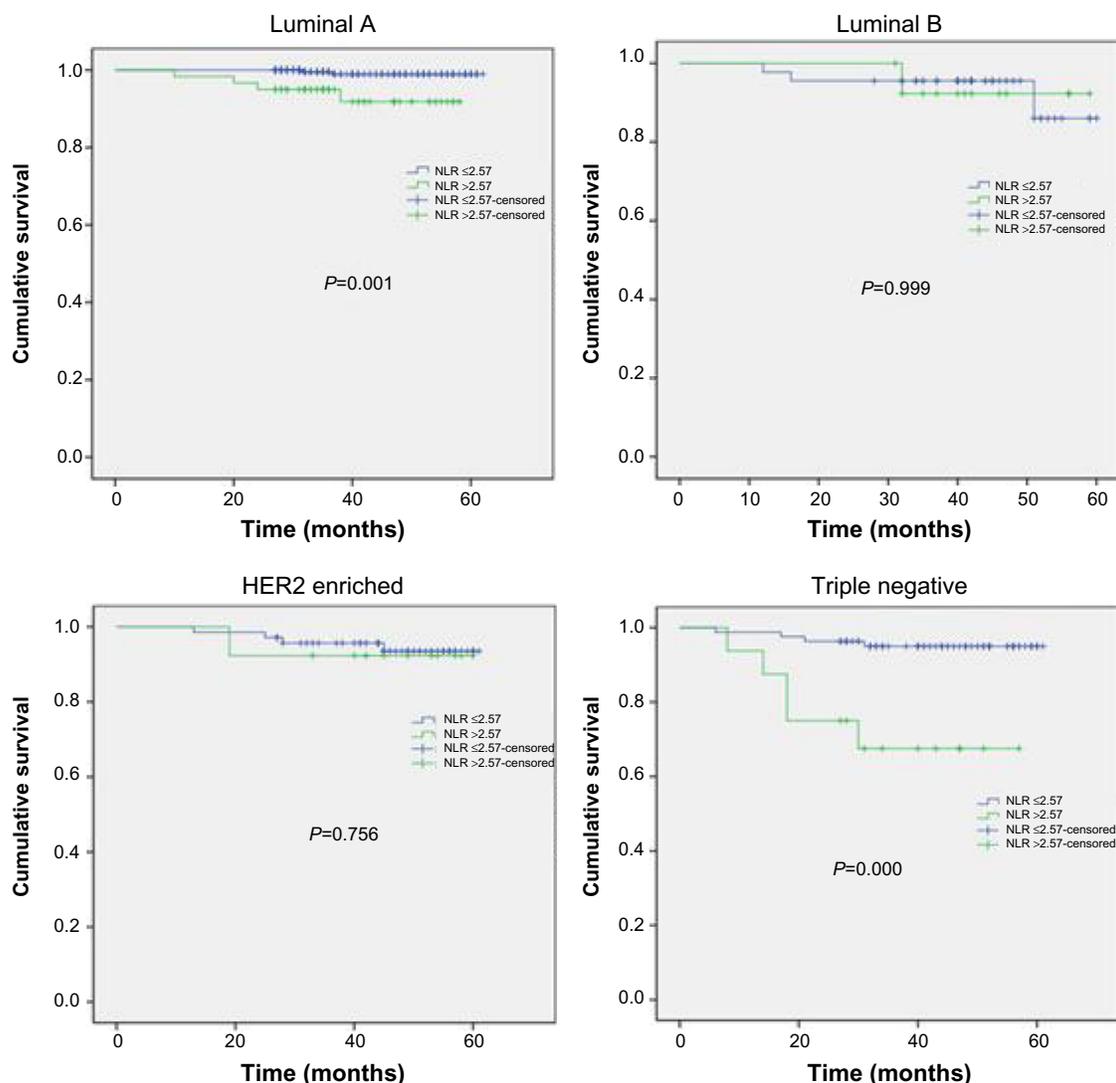


Figure 4 Overall survival curves stratified by NLR of four intrinsic subtypes.

Notes: Both luminal A and triple-negative subtypes in which the NLR was higher than 2.57 showed significantly lower 5-year survival rate than did those types with an NLR ≤ 2.57 (93.3% versus 99.3%, $P=0.001$; 68.8% versus 95.1%, $P=0.000$, respectively).

Abbreviation: NLR, neutrophil-lymphocyte ratio; HER2, human epidermal growth factor receptor 2.

Discussion

Our study demonstrated that an elevated NLR pre-operation was an independent factor of poor survival in breast cancer patients. This finding is consistent with those from previous reports regarding breast cancer.¹²⁻¹⁴ However, our results showed only a trend of higher mortality with elevated PLR ($P=0.051$). In this study, the cutoff value for NLR was 2.57, which is approximately equal to 2.5 in the Noh et al study¹³ and lower than 3.3 in the Azab et al studies.^{12,14} It is interesting to note that patients in Noh et al's study¹³ and our study were Asian, while in the Azab et al study,^{12,14} the subjects were American and the authors had divided patients into four groups; therefore, these differences might be attributed to population differences.

Although there are a great many studies showing an association between high NLR and poor prognosis in cancer, the exact mechanisms underlying this relationship are unclear. One possible hypothesis is that cancer-associated inflammation, as a chronic systemic inflammatory response, impacts patient survival.²¹ The inflammatory response involves systemic alterations triggered by circulating cytokines and chemokines, such as an increase in neutrophil and platelet counts, and a decline in lymphocyte counts. Tumor-related neutrophils play important roles in enhanced angiogenesis, tumor growth, and metastasis.⁸ Some studies have established systemic inflammation-based prognostic scores before surgery.^{22,23} For instance, a study by Proctor et al²³ showed that systemic inflammation-based scores, including the

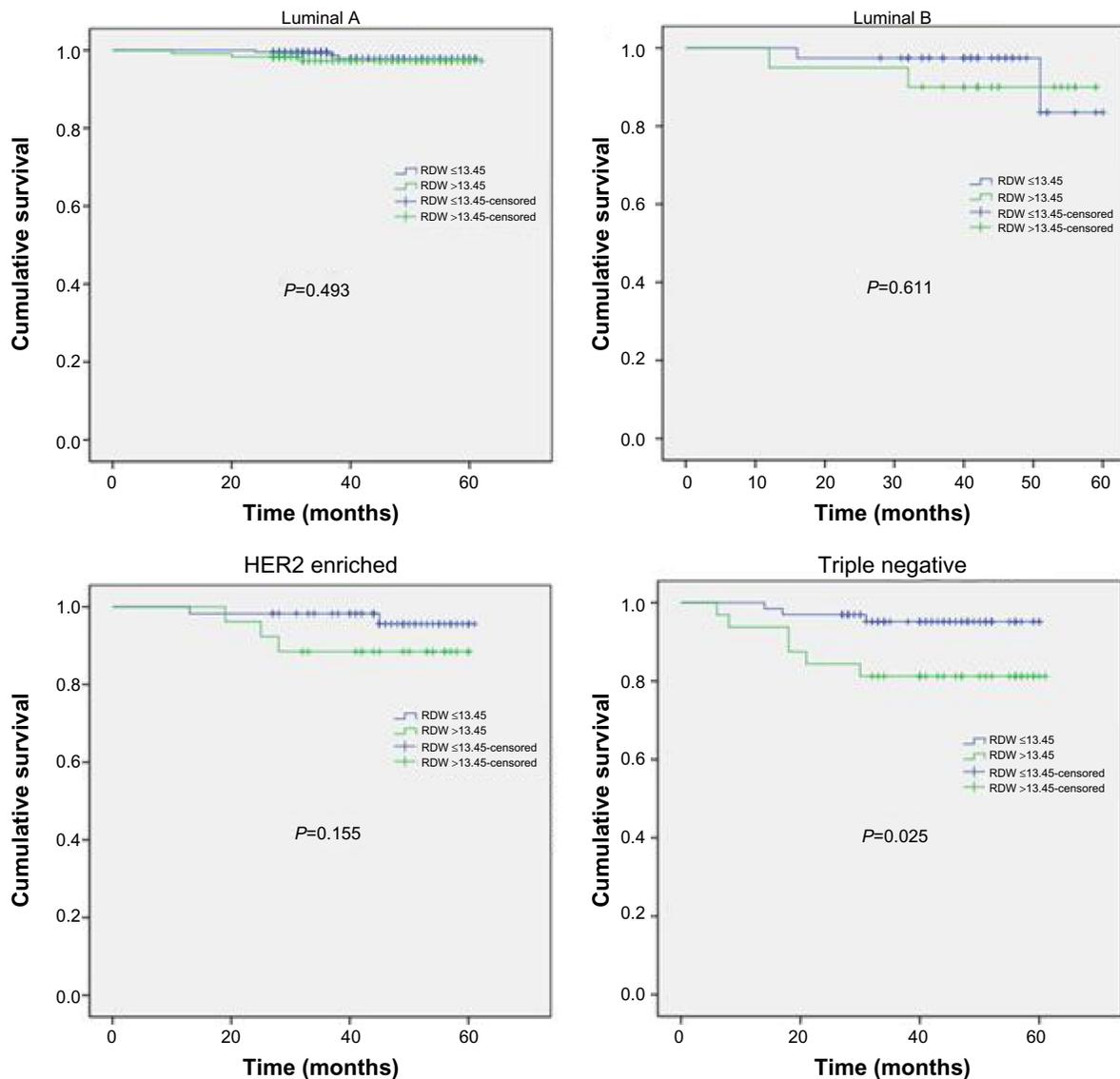


Figure 5 Overall survival curves stratified by RDW of four intrinsic subtypes.

Notes: The triple-negative subtype was the only subtype in which RDW >13.45% showed significantly lower 5-year survival rate than did an RDW ≤13.45% (81.3% versus 95.5%, respectively, $P=0.025$).

Abbreviation: RDW, red cell distribution width.

modified Glasgow Prognostic Score, NLR, PLR, Prognostic Index, and Prognostic Nutritional Index, have prognostic value for a variety of cancers. NLR without other inflammatory markers, on the other hand, may not provide clinicians with information about the inflammatory condition of the patient.²⁴ RDW and MPV are also routine inflammatory markers.¹¹

The exact mechanisms of how inflammation influences RDW levels are unknown, but potential mechanisms include impairing iron metabolism, inhibiting the response to erythropoietin, and decreasing red blood cell survival via the production of inflammatory markers.²⁵ A study by Seitanides et al²⁶ suggested that elevated RDW is significantly correlated

with disseminated solid malignancies to the bone marrow. Another study by Koma et al²⁷ indicated that high levels of RDW are associated with poor survival in lung cancer. A breast cancer study by Seretis et al²⁸ showed that elevated RDW could be a useful biomarker to distinguish between benign or malignant breast tumors, and elevated RDW is significantly correlated with primary tumor diameter and the absolute number of the infiltrated axillary lymph nodes.

To our knowledge, our study is the first to analyze the relationship between RDW or MPV and prognosis in breast cancer patients. We found a significant association between high RDW and poor breast cancer prognosis, and it was an independent factor of poor survival. However, compared

with NLR, ROC curves verified that NLR was superior to RDW as a predictive factor in patients with breast cancer.

We did not identify any predictive value for MPV. However, MPV measurements are complex, and the delay in time between sample collection and laboratory analysis might have affected our results.²⁹

In this study, we also focused on the relationship between NLR or RDW and the prognosis according to subtype. In contrast to the study by Noh et al,¹³ our results showed that elevated NLR was significantly associated with poor prognosis not only for luminal A, but for triple-negative subtypes. Moreover, it demonstrated a better discrimination for the triple-negative subtype in terms of *P*-value than did the luminal A subtype (*P*=0.001 versus *P*=0.000, respectively). Our results also showed that elevated RDW is significantly associated with poor prognosis for the triple-negative subtype only. Triple-negative breast cancer is well known to have a poor prognosis compared with other subtypes, which is a hot topic in breast cancer research. Thus, the triple-negative subtype may be more influenced by a chronic systemic inflammatory response. A prospective study by Retsky et al³⁰ showed that the nonsteroidal anti-inflammatory drug ketorolac used perioperatively suppresses early breast cancer relapse, which has particular relevance to the triple-negative subtype. On the other hand, inflammation may regulate the host's immune reaction. It is plausible that host cell-mediated immunity continues to exert important destructive effects on any residual tumor cells and micrometastases.¹² Engel et al³¹ found that triple-negative breast cancer cells stimulate a significantly stronger natural killer cell immune response than ER-positive breast cancer cells, and infiltration of immunosuppressive T-regs (CD4+ T-cells, CD8+ T-cells, and forkhead box P3-positive [Foxp3] regulatory T-cells) increased in human triple-negative breast cancer specimens. Many studies report that high levels of tumor-infiltrating lymphocytes are associated with a good outcome in patients with triple-negative breast cancer.^{32–34} The precise mechanism in which NLR and RDW exert their effect, especially in triple-negative subtypes, should be further studied. Our study had a short mean follow-up duration and was a single-center retrospective study. Results with longer follow-up should be performed in the future, and a multicentric perspective study is warranted.

Conclusion

Preoperative NLR and RDW is a convenient, easily measured prognostic indicator in patients with breast cancer, especially

those with the triple-negative subtype. These results suggest that cancer-associated inflammation in triple-negative breast cancer may play a greater role in promoting breast cancer progression than the other subtypes. However, further validation studies are required.

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Disclosure

The authors report no conflicts of interest in this work.

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