Original Article

The usefulness of red blood cell distribution width and its ratio with platelet count in breast cancer after surgery and adjuvant treatment: a retrospective study

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Background: To date, red blood cell distribution width (RDW) and RDW-to-platelet count ratio (RPR) have been investigated for their association with cancer. This study aimed to investigate the prognostic value of RDW and RPR in breast cancer before and after treatment.

Methods: We retrospectively enrolled 395 patients with breast cancer, who were diagnosed between December 2009 and December 2015 and analyzed the association between RDW, RPR, and long-term prognosis. We also compared the RDW and RPR values with the pathologic parameters of breast cancer. The cutoff values for before-treatment RDW, RPR value, after-treatment RDW, and RPR were determined using receiver operating characteristic (ROC) curve analysis by identifying the highest Youden index.

Results: In the before-treatment state, no significant disease-free survival (DFS) or overall survival (OS) was found in the RPR and RDW values. However, we found that elevated after-treatment RPR and RDW were significant prognostic factors for DFS, with hazard ratios (HRs) of 2.233 [95% confidence interval (CI): 1.073–4.649; P=0.032] and 2.067 (95% CI: 1.085–3.937; P=0.027). Kaplan-Meier analysis indicated that the after-treatment RPR and RDW groups had poor OS (HR =30.461; 95% CI: 5.138–180.575; P<0.001) compared with the lower after-treatment RPR and RDW groups. In particular, when the RPR and RDW were in the lower group before the treatment and became elevated after the treatment, it showed a remarkably significant result for OS, with HR 132.6 (95% CI: 3.689–4,767.341; P=0.007) and 10.119 (95% CI: 1.853–55.249; P=0.008).

Conclusions: Thus, after-treatment RPR and RDW could have prognostic value for breast cancer after surgery and adjuvant treatment.

Keywords: Breast cancer; red blood cell distribution width (RDW); red blood cell distribution width to platelet count ratio (RDW-to-RPR)

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Introduction

Breast cancer is one of the most commonly diagnosed cancers worldwide and is one of the most frequent causes of cancer-related deaths (1). Furthermore, in breast cancer, local relapse and distant metastasis are important for clinical management. In breast cancer patients, assessment of the patient's prognosis is very important because of clinical decision-making in care and treatment after surgery. Several molecular diagnostic tests have been applied to obtain reliable prognostic information, such as Oncotype Dx. However, its clinical use is still limited owing to its uncertain role and high cost (2). Therefore, an indicator that is simple, convenient, and inexpensive to administer should be helpful for early recurrence detection and for guiding treatment decisions.

Recently, red blood cell distribution width (RDW) has been investigated for its association with cancer (3). RDW is a widely used laboratory parameter reported in complete blood count tests, and it reflects the heterogeneity in the size of circulating erythrocytes (4). Higher RDW values indicate greater variation in the size of red blood cells. Platelets play an important role in cancer progression and metastasis (5,6). Elevated platelets are associated with poor prognosis in cancers, such as colorectal cancer, endometrial cancer, gastric cancer, ovarian cancer, and pancreatic cancer (7-11). Furthermore, the RDW-to-platelet count to ratio (RPR) reflects the severity of inflammation and is used to predict fibrosis in chronic hepatitis (12). Furthermore, RPR is increasingly being recognized to have an important role and a potential biomarker in breast cancer patients (13). However, there are no reports on the prognostic value of RPR in breast cancer before and after treatment. Therefore, in this study, we aimed to investigate the prognostic value of RDW and RPR in breast cancer before and after treatment. We present the following article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-410/rc).

Highlight box

Key findings

- Elevated red blood cell distribution width (RDW) and RDW-to-platelet count to ratio (RPR) levels after surgery and adjuvant therapy are associated with poor disease-free survival and overall survival in patients with breast cancer.

What is known and what is new?

- When the RDW and RPR groups had lower levels before treatment and then increased to a higher level after treatment, the prognostic value was more significantly associated with poor survival.

What is the implication, and what should change now?

- As RDW and RPR are simple and cost-effective, they are useful biomarkers for improved risk assessment in breast cancer.

Methods

Patients selection and data extraction

We retrospectively reviewed 411 patients diagnosed with primary breast cancer at Gyeongsang National University Changwon Hospital between December 2009 and December 2015. The exclusion criteria were as follows: age <19 years; noninvasive breast cancer or stage IV breast cancer; preoperative treatment such as neoadjuvant chemotherapy; insufficient information on laboratory data or pathologic results; and other diseases such as hematological disorders, liver cirrhosis, and heart failure. Ultimately, 395 patients with breast cancer were enrolled and analyzed in this study. All information, such as pathological results and, laboratory data, was obtained from medical records. The baseline characteristics of the enrolled patients are summarized in *Table 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Review Board of the Gyeongsang National University Changwon Hospital (No. GNUCH 2021-11-013) and the requirement for informed consent was waived because it was a retrospective study.

Clinical assessment

All patients underwent surgical resection including breast-conserving surgery or total mastectomy. Subsequently, adjuvant treatment, such as chemotherapy, radiotherapy, and endocrine therapy, was administered. After surgery, all patient received adjuvant chemotherapy followed by four cycles of doxorubicin (60 mg/m^2)/cyclophosphamide (600 mg/m^2) chemotherapy every 21 days and received four cycles of docetaxel (75 mg/m^2) chemotherapy every 21 days in patient who have metastatic axillary lymph node or high-risk patients. Radiotherapy following breast-conserving surgery and total mastectomy in high-risk patients. And estrogen-receptor positive patient started endocrine therapy as like tamoxifen (in pre-menopausal woman) or aromatase-inhibitor (in post-menopausal woman). A regular follow-up

Table 1 Characteristics of breast cancer patients

Factors	Total number =395, n (%)
Age (years)	
<48.5	145 (36.7)
≥48.5	250 (63.3)
Histology	
IDC	338 (85.6)
ILC	16 (4.1)
Mucinous	12 (3.0)
Medullary	6 (1.5)
Other	23 (5.8)
Surgery	
Mastectomy	156 (39.5)
BCS	236 (59.7)
Others	3 (0.8)
Tumor size	
≤2.0 cm	249 (63.0)
>2.0 cm	146 (27.0)
Node	
N0	251 (63.5)
N1–3	144 (36.5)
HG	
1–2	238 (60.2)
3	127 (32.2)
Unknown	30 (7.6)
ER status	
Negative	131 (33.2)
Positive	264 (66.8)
PR status	
Negative	176 (44.6)
Positive	219 (55.4)
HER2 status	
Negative	312 (79.0)
Positive	83 (21.0)
Subtype	
Luminal A	251 (63.5)
Luminal B	35 (8.9)
HER2	38 (9.6)
Triple negative	71 (18.0)
LV invasion	
Negative	339 (85.5)
Positive	56 (14.5)
Recurrence	
No	347 (87.8)
Yes	48 (12.2)
Death	
No	381 (96.5)
Yes	14 (3.5)

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; BCS, breast-conserving surgery; HG, histologic grade; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; LV, lymphovascular.

evaluation was performed at 6-month intervals for during 1–5 years and at 1-year intervals for during 5–10 years after treatment. Follow-up investigations included physical examinations, laboratory analysis (complete blood count and carbohydrate-anti-gene 15-3 levels), and radiological assessment (mammography, ultrasonography, and bone scan).

Biochemical measurements

Venous blood samples were obtained via peripheral venous puncture before treatment. After treatment, venous blood samples were obtained after surgery, adjuvant chemotherapy, and radiotherapy, before and after the median time of blood sampling was 29 months. RDW and platelet counts were measured using a hematology analyzer (XN-10; Sysmex Corporation, Kobe, Japan). According to the manufacturer's instructions, the normal range of RDW is 11.5–14.5%, and platelet is 13–40 ($\times 10^4$/μL). The RPR was calculated by dividing the RDW by the platelet count ($\times 10^4$/μL).

Statistical analysis

Statistical analysis was performed using the SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA). The distribution of RDW and RPR are in *Figure 1*. The optimal cut-off values for RDW and PRP were determined by receiver operating characteristic (ROC) curve analysis by identifying the highest Youden index (sensitivity + specificity − 1)

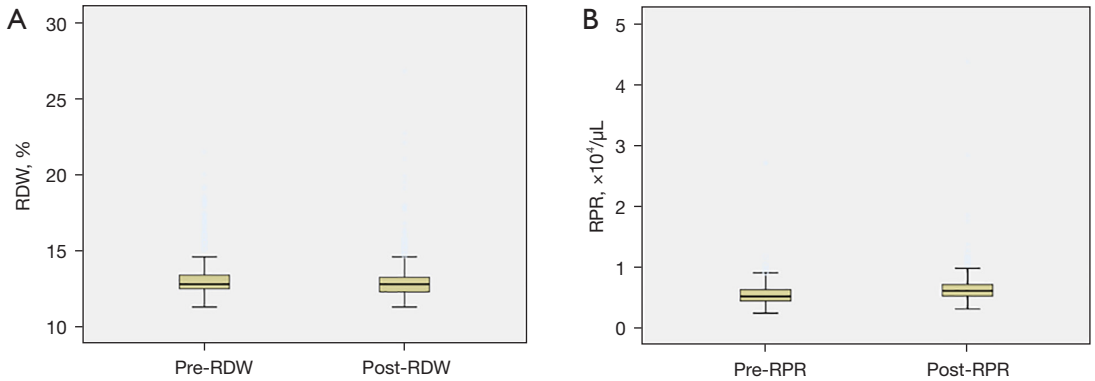

Figure 1 The distribution of (A) RDW and (B) RPR. RDW, red blood cell distribution width; RPR, red blood cell distribution width to platelet count ratio.

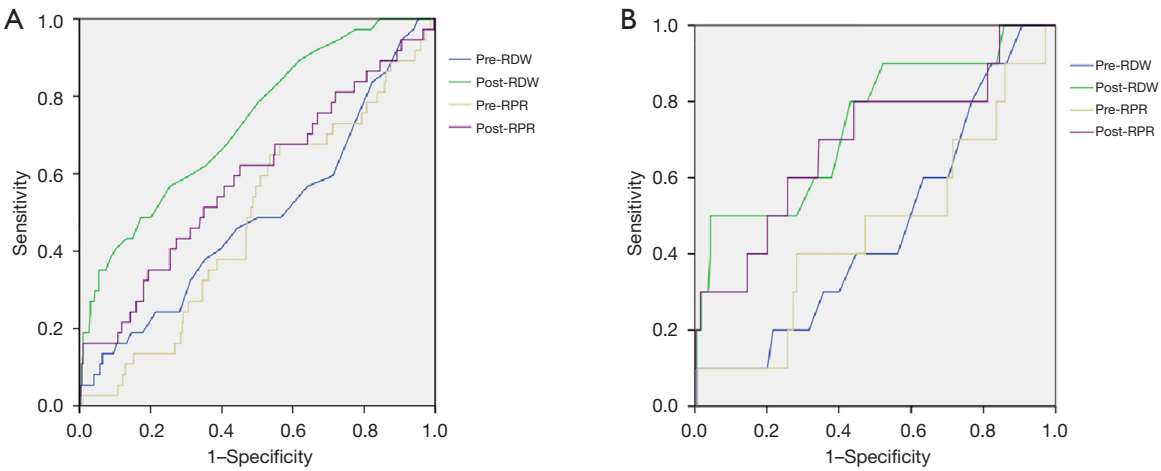

Figure 2 ROC curve analysis based on RDW and RPR for (A) DFS and (B) OS. RDW, red blood cell distribution width; RPR, red blood cell distribution width to platelet count ratio; ROC, receiver operating characteristic; DFS, disease-free survival; OS, overall survival.

before and after treatment. As shown in *Figure 2A* and *Table 2* for DFS, the area under the ROC curve (AUC) for pre-RDW, post-RDW, pre-RPR and post-RPR was 0.474 (P=0.872), 0.697 (P<0.000), 0.481 (P=0.718), and 0.592 (P=0.081), respectively. ROC analysis based on RDW, RPR for OS, as shown in *Figure 2B* and *Table 3*, the area under the ROC curve (AUC) for pre-RDW, post-RDW, pre-RPR and post-RPR was 0.457 (P=0.729), 0.736 (P=0.009), 0.486 (P=0.686), and 0.693 (P=0.037), respectively.

Survival curves were estimated using the high RDW group (≥ cutoff value)/high RPR group (≥ cutoff value) and low RDW group (< cutoff value)/RPR group (< cutoff value) before and after treatment. Kaplan-Meier curve analysis and log-rank tests were used to compare patient survival rate. Independent prognostic factors were identified via univariate analysis using the Cox proportional hazards model to identify the independent variables associated with survival. Hazard ratios (HRs) estimated using Cox regression were reported as relative risks with corresponding 95% confidence intervals (CIs). Multivariate Cox regression analysis was performed for parameters found to be significant in the univariate analysis. Statistically significant was set at P value <0.05.

Results

Patient's characteristics

A total of 395 patients with breast cancer enrolled in this study. The median age was 48.5 years old (range, 24–

Table 2 Optimal cut-off value of RDW, RPR before and after breast cancer treatment for DFS

Characteristics	Cut-off value	Specificity	Sensitivity	AUC (95% CI)	Treatment
RDW	12.75	0.444	0.478	0.474 (0.383–0.566)	Before
RDW	12.85	0.571	0.625	0.697 (0.613–0.780)	After
RPR	0.517	0.524	0.50	0.481 (0.394–0.569)	Before
RPR	0.631	0.590	0.579	0.592 (0.490–0.694)	After

RDW, red blood cell distribution width; RPR, red blood cell distribution width to platelet count ratio; DFS, disease-free survival; AUC, area under the curve; CI, confidence interval.

Table 3 Optimal cut-off value for of RDW, RPR before and after breast cancer treatment for OS

Characteristics	Cut-off value	Specificity	Sensitivity	AUC (95% CI)	Treatment
RDW	12.75	0.449	0.429	0.457 (0.304–0.610)	Before
RDW	13.05	0.655	0.643	0.736 (0.579–0.892)	After
RPR	0.510	0.501	0.500	0.486 (0.319–0.653)	Before
RPR	0.660	0.656	0.600	0.693 (0.508–0.879)	After

RDW, red blood cell distribution width; RPR, red blood cell distribution width to platelet count ratio; OS, overall survival; AUC, area under the curve; CI, confidence interval.

89 years). The median follow-up period was 84 months. After follow-up, 48 patients (12.2%) experienced recurrence and death of patients were 14 (3.5%) died. The study population was divided into four groups (high RDW, low RDW, high PRP, and low PRP) after treatment according to the optimized cut-off values determined by ROC analysis (*Figure 3*). The optimal cutoff values for disease-free survival (DFS) and, overall survival (OS) before and after treatment are shown in *Tables 2*,*3*.

Survival

There was no significant difference in DFS and OS between the high and low RDW groups before treatments. Likewise, no DFS or OS differences were found between the high and low RPR groups in before treatment. However, after treatment, the univariate analysis showed that the DFS and OS rates of the high RDW group were significantly lower than those of low RDW group (P=0.015 and P=0.016, respectively; *Figure 3A*,*3B*). In addition, multivariate Cox regression analysis indicated that elevated RDW was positively associated with DFS (HR =2.067; 95% CI: 1.085–3.937; P=0.027) and OS (HR =3.272; 95% CI: 0.832–12.866; P=0.05) (*Tables 4*,*5*). Although not P<0.05, the univariate analysis showed that the DFS and OS rates in the high RPR group were significantly lower than those in the low RPR group after treatment (P=0.053 and P=0.043, respectively; *Figure 3C*,*3D*). We analyzed two groups: a high RDW/high RPR group that satisfied both the high RDW and high RPR groups and a low RDW/low RPR group that satisfied both the low RDW and low RPR groups. As shown in *Figure 4*, patients with high RDW/high RPR had significantly lower DFS and OS rates than those with low RDW/low RPR (P=0.008 and P<0.001, respectively). Furthermore, Cox regression multivariate analysis revealed that high RDW/high RPR was associated with poor DFS (HR =10.467; 95% CI: 4.863–22.527; P<0.001) and OS (HR =30.461; 95% CI: 5.138–180.575; P<0.001) (*Tables 4*,*5*). Finally, we examined the effects of RDW and RPR changes after the initial treatment between the lower and higher group. Kaplan-Meier analysis revealed that patients with changed value of lower RDW and RPR before treatment and higher RDW and RPR after treatment had significantly poorer DFS (P=0.005 and P=0.02, respectively) and OS (P=0.004 and P<0.001, respectively) (*Figure 5*). In addition, Cox regression multivariable analysis showed that changing the lower group to the higher group was associated with poor DFS [HR(RDW) =4.947; 95% CI: 2.068–11.834; P<0.001 and HR(RPR) =6.548; 95% CI: 2.360–18.168; P<0.001] and OS [HR(RDW) =10.119; 95% CI: 1.853–55.249; P=0.008 and HR(RPR) =132.6; 95% CI: 3.689–4,767.341; P=0.007] (*Tables 4*,*5*).

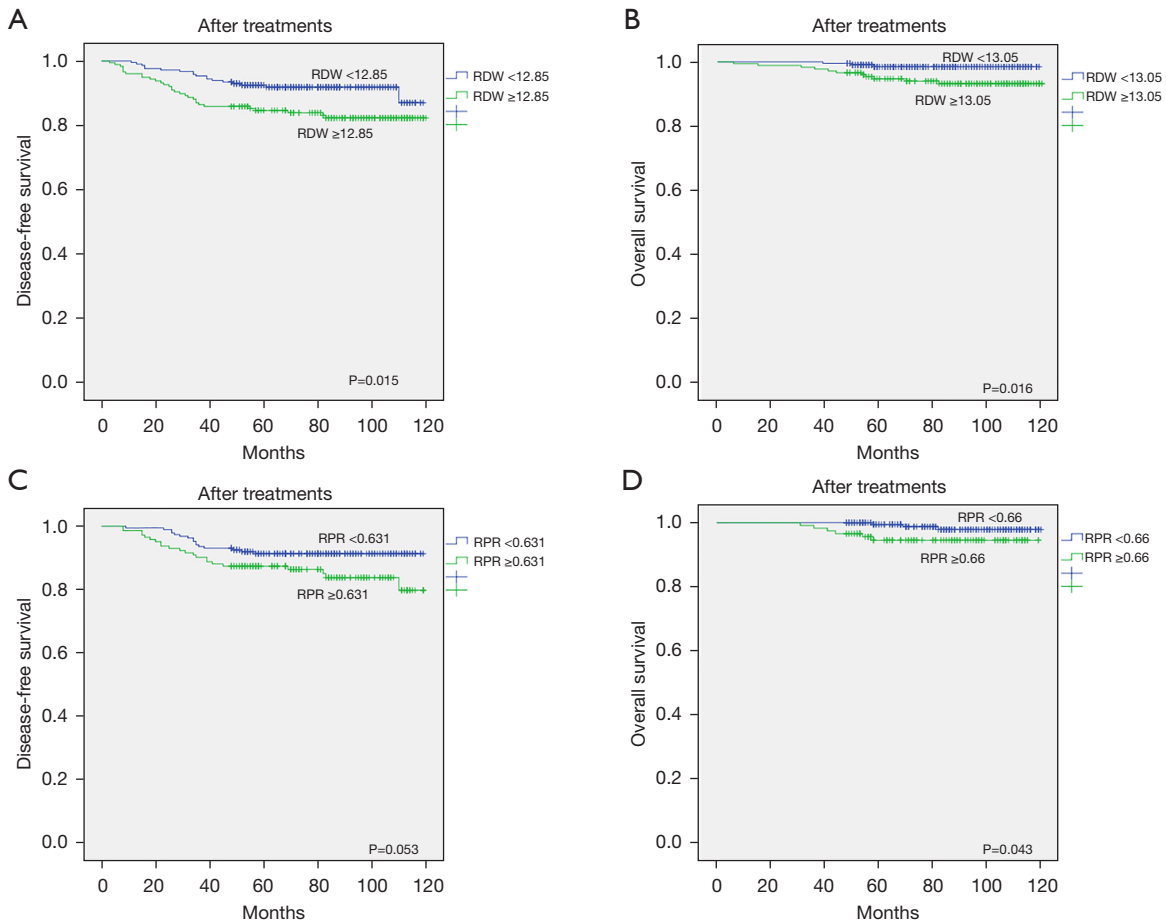

Figure 3 Kaplan-Meier analysis of (A) disease-free survival and (B) overall survival stratified by the RDW in breast cancer patients after treatments and (C) disease-free survival and (D) overall survival stratified by the RPR in breast cancer patients after treatments. RDW, red blood cell distribution width; RPR, red blood cell distribution width to platelet count ratio.

Discussion

In our study, we suggested that elevated post-treatment RDW and RPR were associated with poor prognosis in patients with breast cancer, and these may be used as prognostic factors in cases of both high RDW and high RPR. To the best of our knowledge, this is the first study to evaluate the effects of RDW with RPR before and after treatment. In particular, our results demonstrated that elevate RDW and RPR values before and after treatments were independent factors for poor survival in breast cancer patients.

In cancer microenvironment, inflammation promotes tumor growth, invasion, angiogenesis, and eventually metastasis (14,15). During inflammation, red blood cell maturation disturbs the red blood cell membrane, leading to increased RDW (16). The mechanism underlying the relationship between RDW and survival or disease activity is not clear. However, high RDW thought to be caused by chronic inflammation, age-related diseases, and oxidative stress, which lead to changes in erythropoiesis (4,17). Because a malignant tumor may extend the inflammatory response in the process of its progression and increase circulation levels, RDW may be a potential biomarker of cancer growth and metastatic activity (18). In addition, RDW is an easily available and inexpensive parameter in blood samples and reflects the size heterogeneity of circuiting erythrocytes. Therefore, preoperative RDW was suggested as an independent predictor of breast cancer in a recent retrospective study (18).

Platelet count is a parameter that is measured in the complete blood count and is affected by systemic

Table 4 Multivariable logistic regression and Cox analysis of breast cancer disease-free survival

Characteristic	HR	95% CI	P value
Age (years)			
<50	1		
≥50	1.261	0.695–2.286	0.444
T stage			
T1	1		
T2	1.260	0.651–2.438	0.493
T3	2.016	0.703–5.778	0.192
N stage			
N0	1		
N1	2.530	1.068–5.993	0.035
N2	6.266	2.413–16.274	<0.001
N3	8.642	3.391–22.028	<0.001
LV invasion			
Negative	1		
Positive	7.905	0.745–83.870	0.086
Subtype			
Luminal A	1		
Luminal B	1.823	0.734–4.530	0.196
HER2	2.741	1.131–6.646	0.026
Triple negative	1.459	0.570–3.739	0.431
RDW after treatment			
< COV	1		
≥ COV	2.067	1.085–3.937	0.027
RPR after treatment			
< COV	1		
≥ COV	2.233	1.073–4.649	0.032
RDW & RPR after treatment			
Low-low	1		
High-high	10.467	4.863–22.527	<0.001
RDW before to after treatment			
Low to low	1		
Low to high	4.947	2.068–11.834	<0.001
RPR before to after treatment			
Low to low	1		
Low to high	6.548	2.360–18.168	<0.001

HR, hazard ratio; CI, confidence interval; LV, lymphovascular; HER2, human epidermal growth factor receptor 2; RDW, red blood cell distribution width; COV, cut-off value; RPR, red blood cell distribution width to platelet count ratio.

Table 5 Multivariable logistic regression and Cox analysis of breast cancer overall survival

Characteristic	HR	95% CI	P value
Age (years)			
<50	1		
≥50	0.870	0.290–2.607	0.803
T stage			
T1	1		
T2	0.216	0.042–1.100	0.065
T3	1.422	0.150–13.498	0.759
N stage			
N0	1		
N1	3.546	0.572–21.967	0.064
N2	30.055	3.446–262.099	0.002
N3	15.530	2.792–86.387	0.002
LV invasion			
Negative	1		
Positive	13.092	0.401–426.990	0.148
Subtype			
Luminal A	1		
Luminal B	–	–	–
HER2	20.379	3.557–116.751	0.001
Triple negative	5.076	0.738–34.898	0.099
RDW after treatment			
< COV	1		
≥ COV	3.272	0.832–12.866	0.05
RPR after treatment			
< COV	1		
≥ COV	2.510	0.407–15.489	0.322
RDW & RPR after treatment			
Low-low	1		
High-high	30.461	5.138–180.575	<0.001
RDW before to after treatment			
Low to low	1		
Low to high	10.119	1.853–55.249	0.008
RPR before to after treatment			
Low to low	1		
Low to high	132.6	3.689–4,767.341	0.007

HR, hazard ratio; CI, confidence interval; LV, lymphovascular; HER2, human epidermal growth factor receptor 2; RDW, red blood cell distribution width; COV, cut-off value; RPR, red blood cell distribution width to platelet count ratio.

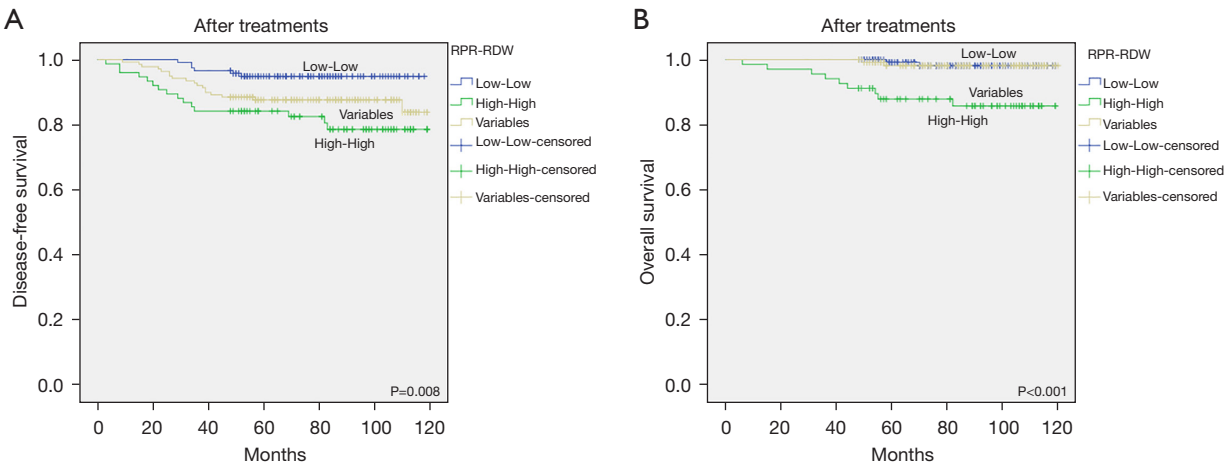

Figure 4 Kaplan-Meier analysis of (A) disease-free survival and (B) overall survival stratified by the RDW and RPR in breast cancer patients after treatments. RDW, red blood cell distribution width; RPR, red blood cell distribution width to platelet count ratio.

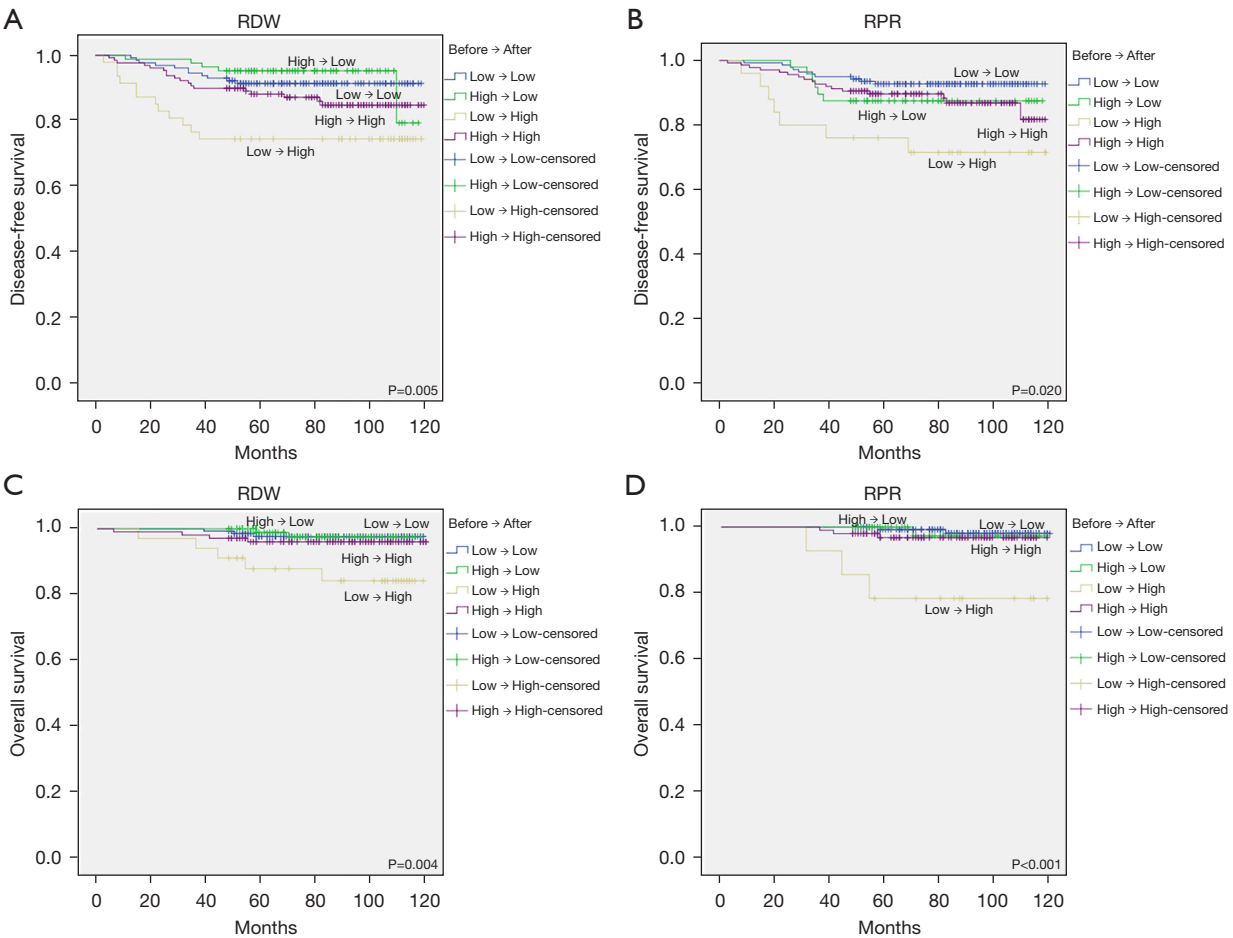

Figure 5 Kaplan-Meier analysis of disease-free survival (A,B) and overall survival (C,D) stratified by the RDW and RPR changes in breast cancer patients before and after treatments. RDW, red blood cell distribution width; RPR, red blood cell distribution width to platelet count ratio.

inflammation. A study showed that elevated platelet levels can be seen in many cancers, and that platelet count is inversely correlated with survival (19). Platelets are rich in growth factors such as platelet-derived growth factor-receptor (PDGF), transforming growth factor-beta. The PDGF-receptor is involved in cancer invasion and metastasis (20). In breast cancer, PDGF beta receptor expression is correlated with unfavorable pathological characteristics and survival (20).

In several studies, elevated RPR levels have been associated with poor prognosis in chronic hepatitis, pancreatitis, and acute myocardial infarction (12,21,22). Although the reason for this is uncertain, the imbalance between RDW and platelet count could be a significant prognostic factor for the poor prognosis of breast cancer patients with elevated RPR (13). Most of the aforementioned studies used preoperative RDW and PRP values, and significant values were obtained. However, in our study, there was no significant difference before treatment with RDW and RPR. Rather, only the after-treatment RDW and RPR values were significantly associated with survival. Therefore, we analyzed two points. One is that dividing different subgroups that one is high RDW/high RPR group which satisfies both high RDW and high RPR group and another is low RDW/low RPR group which satisfies both low RDW and low RPR group. Another point is that the RDW and RPR changed after initial treatments between the lower and higher groups. In this analysis, we revealed that when a lower value before treatment became higher after treatment, survival was very poor.

There are limitations in our study that were conducted in a single center, and it was performed retrospectively with a limited number of patients. In particular, in OS, it can be very difficult to conclude as the final death is only 14. Although the absolute values of RDW and RPR are currently difficult to determine, the overall elevated values are meaningfully available for each hospital. In addition, it is necessary to investigate patients with breast cancer who undergo neoadjuvant chemotherapy.

Recently, various blood cell markers have been reported to be prognostic factors. So, further study on details including mechanism or intervention should be carried out.

To our knowledge, the present study is the first to reveal a relationship between RDW, RPR levels in before and after treatment, and survival. The results of our study confirmed that observing the RDW, RPR levels in before-after treatment, and the process of continuous change can be important indicators for predicting the prognosis of breast cancer patients.

Conclusions

Elevated RDW and RPR levels after surgery and adjuvant therapy are associated with poor DFS and OS in patients with breast cancer. Particularly, when both the high RDW and high RPR groups were satisfied, the prognostic value was significantly associated with poor survival. Furthermore, when the RDW and RPR groups had lower levels before treatment and then increased to a higher level after treatment, the prognostic value was more significantly associated with poor survival. As RDW and RPR are simple and cost-effective, they are useful biomarkers for improved risk assessment in breast cancer.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-410/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-410/dss

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-410/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-410/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Gyeongsang National University Changwon Hospital (No. GNUCH 2021-11-013) and individual consent for this retrospective analysis was waived.

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