ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Prognostic Value of the Red Cell Distribution Width to Platelet Count Ratio in Patients with Breast Cancer

Meme Kanserli Hastalarda Kırmızı Küre Dağılım Genişliğinin Trombosit Sayısına Oranının Prognostik Değeri

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ABSTRACT Objective: The prognostic value of red cell distribution width to platelet count ratio (RPR) in patients with breast cancer is not clear. This study aims to evaluate the prognostic significance of red cell distribution width to platelet count ratio in breast cancer patients. **Material and Methods:** A retrospective analysis was performed on 150 patients with non-metastatic breast cancer between January 2014-December 2018. The optimal cut off value of RPR was 0.54 for disease-free survival (DFS). The chi-square test or Fisher's exact test was used to evaluate relationships between the RPR and other clinicopathological variables. Kaplan-Meier log-rank test was used to determine the effect of variables on DFS. Cox's proportional hazards model was used for multivariate analysis. **Results:** Median follow-up period was 39±1.174 (13-66) months and 5-year survival was 96.60%. There was no relationships between the RPR and clinicopathological variables. Kaplan-Meier analysis showed significant correlation between elevated RPR level (p=0.001) and high MPV(mean platelet volume)/Platelet(P) ratio (p=0.006) and DFS. DFS was found to be short in patients with high RPR and high MPV/P ratio. When multivariate analysis was performed with cox regression analysis, RPR level (p=0.025) and tumor size (p=0.047) were found to be independent prognostic factors . RPR was found to be a more valuable prognostic marker than mean platelet volume to platelet ratio (MPV/P). **Conclusion:** We found that high RPR levels before adjuvant treatment were associated with poor DFS in patients with curative resected breast cancer. Accordingly, the RPR level can be used as a prognostic marker in non-metastatic breast cancer. However, further studies conducted with a larger number of patients are needed.

Keywords: Breast cancer; red cell distribution width; platelet; prognosis

ÖZET Amaç: Meme kanserli hastalarda kırmızı küre dağılım genişliğinin trombosit sayısına oranı (RPR)'nın prognostik değeri net olarak bilinmemektedir. Bu çalışmada amacımız kırmızı küre dağılım genişliğinin trombosit sayısına oranının meme kanserli hastalarda prognostik önemini değerlendirmektir. **Gereç ve Yöntemler:** Bu retrospektif çalışmaya Ocak 2014-Aralık 2018 tarihleri arasında opere olmuş 150 metastatik olmayan meme kanserli hasta dahil edildi. RPR düzeyinin hastalıksız sağkalım (HSK) için optimum cutoff değeri 0,54 olarak alındı. RPR ve klinikopatolojik değişkenler arasındaki ilişkiyi değerlendirmek için ki kare ve Fisher exact testleri kullanıldı. Değişkenlerin HSK etkisini saptamak için Kaplan-Meier log-rank testi kullanıldı. Multivariate analiz için Cox oransal hazards modeli kullanıldı. **Bulgular:** Hastaların median takip süresi 39±1,174 (13-66) ay idi. 5 yıllık sağkalım %96,60 idi. RPR ile klinikopatalojik değişkenler arasında ilişki saptanmadı. Kaplan-Meier analizinde yüksek RPR düzeyi (p<0,001) ve yüksek ortalama trombosit hacminin trombositlere oranı (MPV/P) (p=0,006) ile HSK arasında anlamlı ilişki saptandı. Yüksek RPR düzeyi ve yüksek MPV/P oranı olan hastalarda HSK kısa saptandı. Cox regresyon analizi ile multivariate analiz yapıldığında RPR (p=0,025) ve tümör çapı (p=0,047) bağımsız prognostik faktörler olarak tespit edildi. RPR'nin, MPV/P oranına göre daha değerli bir prognostik belirteç olduğu saptandı. **Sonuç:** Bu çalışmada, küratif rezeksiyon yapılmış meme kanserli hastalarda adjuvan tedavi öncesi yüksek RPR düzeylerinin kötü HSK ile ilişkili olduğu saptanmıştır. Metastatik olmayan meme kanserli hastalarda , RPR düzeyi prognostik bir marker olarak kullanılabilir, ancak daha fazla hasta sayısı ile yapılacak çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Meme kanseri; kırmızı küre dağılım genişliği; trombosit; prognoz

Breast cancer is the most common cancer among women and the leading cause of death for women.[1] Breast cancer is multifactorial.[2] Mortality rate decreases with screening methods and improvements in adjuvant therapy. However, survival rates are still not at the expected level. Prognostic factors

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help the doctors to choose the appropriate treatment for breast cancer patients. The choice of local and systemic therapies depends on prognostic and predictive factors. These factors can be listed as follows: tumor histology, axillary lymph node involvement, tumor hormone receptor level, tumor human epidermal growth factor receptor 2 (HER2)-status, patient age, comorbidity, menopausal status, and multigen tests.[3,4] Oncotype DX and Mammaprint are reliable molecular diagnostic tests that guide the selection of adjuvant therapy. However, these tests are not available in most countries due to the high cost. Therefore, there is a need for precise, inexpensive and easily accessible biomarkers for treatment selection. The red blood cell distribution width (RDW) is a low cost parameter that shows the distribution width of the erythrocyte size and is reported by routine laboratory test.[5,6] Latest studies have shown that high RDW levels reliably reflect the degree of systemic inflammation. Previous studies have shown that RDW is a poor prognostic factor in some cancers.[7-9] High RDW level is a prognostic indicator especially in patients with lung, colon, ovarian and breast cancer.[10,11] In another study, it was shown that high RDW level could be used as a marker of breast cancer activation. As RDW reflects chronic inflammation, it may also be affected by non-inflammatory conditions such as malnutrition, anemia and bone marrow disease.[12] Red cell distribution width to platelet count ratio (RPR) is a biomarker that reflects chronic inflammation and is theoretically thought to be less affected by noninflammatory conditions than RDW. There are limited number of previous studies investigating the prognostic effect of RPR in breast cancer patients.[13] The prognostic effect of RPR on breast cancer is not clear. Our aim was identify the prognostic and predictive value of RPR in breast cancer patients.

MATERIAL AND METHODS

We reviewed retrospectively the files of operated non-metastatic breast cancer patients diagnosed in our center between January 2014-December 2018. A hundred and fifty patients were included in the study. The exclusion criteria were as follows: carcinoma in situ, bilateral breast cancer, male breast cancer, cardiovascular disease, autoimmune disease and metastatic breast cancer.

Estrogen receptor (ER) and progesterone receptor (PR) were evaluated by immunohistochemistry (IHC). At least 1 percent positive staining for the IHC test ER was accepted. HER2 status was assessed by IHC or fluorescence in situ hybridization. IHC score of 3 or at least a 2.2-fold stronger HER2 signal relative to the CEP-17 signal in the tumor cells was accepted as positive.

Adjuvant treatment was given according to National Comprehensive Cancer Network (NCCN) guidelines. HER2-positive patients were treated with chemotherapy and transtuzumab if the tumor was >0.5 cm in diameter. Blood samples were obtained via peripheral venous puncture after the operation before the initiation of any adjuvant treatment. Peripheral venous blood was collected into sterile EDTA tubes. The RPR was calculated by dividing the RDW by the platelet count ($x10^4/\mu L$).

This study was conducted in accordance with the ethical standars of the World Medical Association's Declaration of Helsinki. Ethics committee approval was obtained from Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital (decision data: 23.09.2019 and number: 72/12).

STATISTICAL ANALYSIS

Mean and median values of numerical data were given based on their conformity to the normal distribution. The normality of the distribution was assessed using the Kolmogorov- Smirnov/Shapiro-Wilk test. Descriptive statistics of the data are presented with n (%), if the variable is normally distributed with mean±standart deviation, and if not normally distributed, with median (minimum-maximum). We used a Chi-square test or Fisher's exact test to determine the relationship between RPR and variables. Receiver Operating Characteristics (ROC) curve analysis by identifying the highest Youden index (sensitivity+specificity-1) was performed to establish the best cut-off value of RPR, MPV/P and PDW/P for disease-free survival (DFS). The primary outcome of the study was disease-free survival, which was accepted as the period between the initial diagnosis and first relapse. The Kaplan-Meier method and log-rank test

were used to estimate and compare the DFS rate. All variables that may affect DFS were assessed using a Cox proportional hazards model to identify any independent variables associated with DFS. Hazard ratios (HRs) estimated using Cox analysis were reported as relative risks with their corresponding 95% confidence intervals (Cls). Statistically, the significant p value was <0.05. SPSS 20.0 (Chicago, IL, USA) program was used for analysis.

RESULTS

Table 1 shows the prominent characteristics of the patients. The median age was 55 (26-88) years. The median follow-up was 39±1.174 months (13-66). Estimated 5-year median survival was 96.60%. Recurrence occurred in 18 (12%) patients during follow-up.

ROC analysis for optimal DFS cutoff values for RDW/P, were calculated as 0.54 (Area under the curve [AUC] 0.668, 95% CI: 0.521-0.815, p=0.021), for MPV/P 0.34 (AUC 0.686, 95% CI: 0.548-0.834, p=0.011) and for PDW/P 0.60 (AUC 0.642, 95% CI: 0.481-0.803, p=0.051). The specifity and sensitivity rates were 84.80% and 44%, 86.40% and 44%, 72.70% and 50% for RDW/P, MPV/P and PDW/P respectively (Figure 1).

RPR was categorized into two groups (≤0.54 vs. >0.54). The number of patients with low RPR level was 115 (76.70%) and the number of patients with high RPR level was 35 (23.30%). There was no relationship between RPR level and clinicopathological variables (Table 2). The univariate analysis revealed significant impacts of MPV/P level (p=0.006) and RPR level (p=0.001) on DFS. DFS was significantly shorter in the group with high RPR level. The 5-year DFS was 62.80% in the high RPR group and 85.60% in the low RPR group (Figure 2). There was no significant relationship between age, ER status, PR status, HER2 status, grade, lymph node metastasis status, PDW/P and DFS (Table 3). The compatibility of the model for Cox regression analysis was statistically significant (p=0.019). On multivariate analysis, RPR level and tumor size were significantly correlated with poor prognosis for DFS (Table 4). With multivariate analysis with Cox regression, DFS was found to be worse in the high RPR group than in the low RPR group (p=0.025) (Table 4).

TABLE 1: Main features of breast cancer patients.

Characteristics	n (%)
Age	
≤50	59 (39.3)
>50	91 (60.7)
Estrogen receptor	
Negative	23 (15.3)
Positive	127 (84.7)
Progesterone receptor	
Negative	30 (20)
Positive	120 (80)
Tumour size (cm)	
≤2	48 (32)
>2	102 (68)
Nuclear grade	
1	21 (14)
2,3	129 (86)
HER2	
Positive	46 (30.7)
Negative	104 (69.3)
Lymph node status	
Positive	69 (46)
Negative	81 (54)
PDW/P	
≤0.60	105 (70)
>0.60	45 (30)
MPV/P	
≤0.34	122 (81.3)
>0.34	28 (18.7)
RPR	
≤0.54	120 (80)
>0.54	30 (20)
RDW	
≤14	75 (50)
>14	75 (50)

PDW/P: Platelet distribution width to platelet count ratio; MPV/P: Mean platelet volume to platelet count ratio; RPR: Red cell distribution width to platelet count ratio; RDW: Red cell distribution.

When we subdivided 150 patients into hormone receptor positive, HER2-positive and triple negative patients, there was no difference between the groups in terms of DFS (p=0.665). When we evaluated the prognostic effect of RPR level among molecular subtypes, prognostic significance was found in hormone receptor positive (HR+) breast cancer patients (p=0.003). However, there was no prognostic effect of RPR on

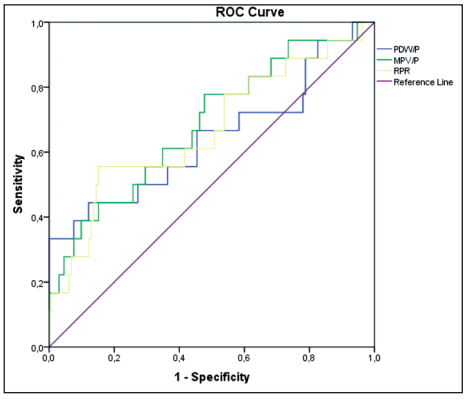

FIGURE 1: ROC curve analysis of DFS for RPR and PDW/P and MPV/P.

HER + breast cancer patients (p=0.058) and triple negative breast cancer patients (p=0.731) (Figure 3).

DISCUSSION

Our study has shown that high RPR is an independent prognostic factor for non-metastatic breast cancer patients as well as a stronger prognostic factor than MPV/P ratio.Complete Blood Counts (CBC) are routinely checked in cancer patients.Recently, prognostic significance of parameters has been shown, such as MPV, platelet-lymphocyte ratio, neutrophil-lymphocyte ratio which have been evaluated as complete blood parameters.[14] Another CBC parameter is RDW, which indicates the diameter of the red cell distribution. Studies have shown that RDW value is closely associated with chronic inflammation, cardiovascular disease, pulmonary disease, and hepatic disease. RDW has been shown to be a poor prognostic factor in the disease mentioned.[15-17] The relationship between RDW level and inflammation is not clearly understood. However, in chronic inflammation, RDW is thought to increase due to impaired iron metabolism caused by increased inflammatory cytokines, inhibition of erythropoietic response, and reduced survival of red cell cells.[9]

Inflammatory cells around of the tumor induce angiogenesis. As a result, tumor develops and metastases.[12,18] Increased RDW level in the case of chronic inflammation may be a potential biomarker in cancer

TABLE 2: Association between RPR and clinicopathological factors in patients with breast cancer.

Variables	Low RPR n (%)	High RPR n (%)	p-value
Age			
≤50	45 (37.50)	14 (46.70)	0.358
>50	75 (62.50)	16 (53.30)	
Tumor Size			
≤2 cm	38 (31.70)	10 (33.30)	0.861
>2 cm	82 (68.30)	20 (66.70)	
Grade			
1	16 (13.30)	5 (16.70)	1.000
2,3	99 (86.10)	30 (85.70)	
Estrogen receptor			
Negative	17 (14.8)	6 (16.70)	0.734
Positive	98 (85.2)	29 (83.30)	
Progesterone receptor			
Negative	21 (18.30)	9 (25.70)	0.334
Positive	94 (81.70)	26 (74.30)	
Her 2			
Negative	82 (68.30)	22 (73.30)	0.595
Positive	38 (31.70)	8 (26.70)	
Lymph node metastasis			
Negative	64 (53.30)	17 (56.70)	0.743
Positive	56 (46.70)	13 (43.30)	

HER2: Human epidermal growth factor receptor 2.

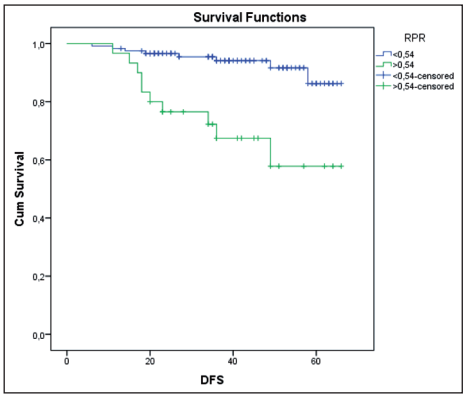

FIGURE 2: Kaplan-Meier curve for disease-free survival of low RPR and high RPR group.

development and growth. For patients with lung, colon, renal and breast cancer, high RDW level indicated a poor prognostic factor.[9,19,20]

The relationship between thrombocytosis and cancer has long been known. Platelets have an essential role in tumor growth, formation, and metastasis.[21] Platelets also inhibit the antitumor effects of natural killer (NK) cells, causing tumor cells grow and spread. High platelet count has been shown to cause short survival in many cancer types.Tumor cells stimulate platelet production by releasing various cytokines.[22,23]

Systemic inflammatory response is significant

TABLE 3: Univariate analysis of disease-free survival in breast cancer patients.

Variables	Mean DFS (months)±SE (95% CI)	p value (log- rank)
Age		
≤50	59.25±2.19 (54.95-63.56)	0.724
>50	59.57±1.61 (56.41-62.73)	
Estrogen receptor		
Negative	59.32±3.62 (52.23-66.42)	0.921
Positive	60.02±1.43 (57.22-62.83)	
Progesterone receptor		
Negative	57.46±3.50 (50.58-64.34)	0.504
Positive	60.39±1.44 (57.57-63.22)	
HER2		
(-)	59.63±1.63 (56.43-62.83)	0.701
(+)	60.37±2.36 (55.73-65.01)	
Tumor size		
≤2	62.84±1.52 (59.86-65.82)	0.282
>2 cm	57.99±1.93 (54.20-61.79)	
Lymph node involvement		
Negative	61.59±1.58 (58.48-64.70)	0.202
Positive	57.85±2.21 (53.51-62.19)	
Nuclear grade		
Grade 1	59.95±3.61 (50.87-65.03)	0.725
Grade 2,3	60.07±1.43 (57.27-62.87)	
RDW		
≤14	60.93±1.66 (57.66-64.20)	0.503
>14	58.93±2.07 (54.87-62.99)	
PDW/P		
≤0.60	60.18±1.43 (57.36-63.00)	0.077
>0.60	57.11±2.81 (51.59-62.62)	
RPR		
≤0.54	62.33±1.24 (59.90-64.76)	0.001
>0.54	52.18±3.65 (45.03-59.34)	
MPV/P		
≤0.34	61.08±1.32 (58.50-63.67)	0.006
>0.34	56.42±2.83 (50.86-61.98)	

HER2: Human epidermal growth factor receptor; RDW: Red cell distribution width; PDW/P: Platelet distribution width to platelet count ratio; RPR: Red cell distribution width to platelet count ratio; MPV/P: Mean platelet volume to platelet count ratio; CI: Confidence interval; DFS: Disease free survival; SE: Std. error.

TABLE 4: Multivariate analysis of disease-free survival in breast cancer patients.

Variables	p value	df	HR	95,0% CI for HR	
				Lower	Upper
Tumor size	0.047	1	3.902	1.019	14.937
Grade	0.190	1	0.382	0.091	1.609
Estrogen receptor	0.416	1	0.581	0.157	2.150
HER2	0.208	1	0.464	0.140	1.533
RPR	0.025	1	3.594	1.177	10.967
MPV/P	0.240	1	1.965	0.636	6.065
Lymph node involvement	0.166	1	2.073	0.739	5.814

RPR: Red cell distribution width to platelet count ratio; MPV/P: Mean platelet volume to platelet count ratio; CI: Confidence interval; HR: Hazard ratio; df: Reference category.

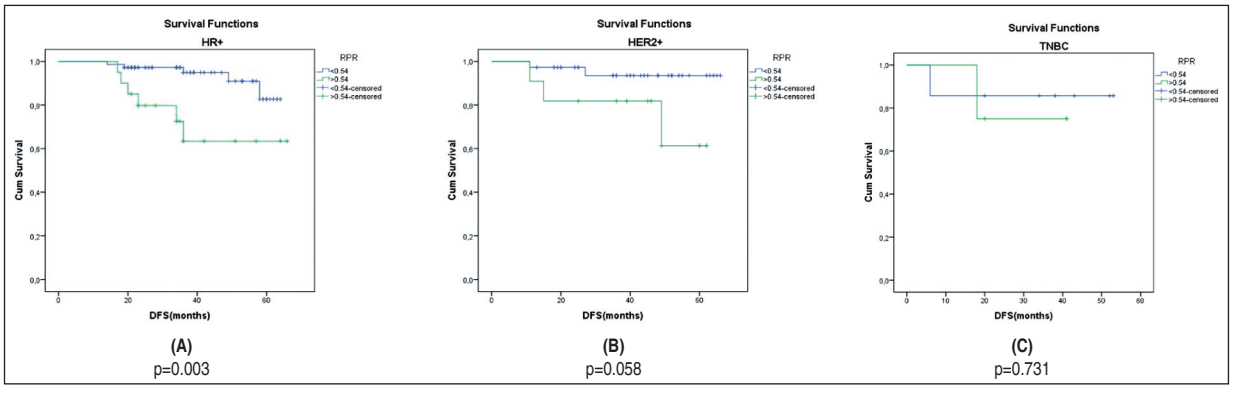

FIGURE 3: Prognostic value of RPR for DFS of hormone receptor positive (HR+) breast cancer patients **(A)**, HER2 -positive(HER2 +) breast cancer patients **(B)**, triple negative breast cancer (TNBC, **C**).

in cancer development and progression. Research has shown that RPR is an important prognostic marker for fibrosis in patients with chronic hepatitis.[24] Besides, prognostic significance has also been shown in acute pancreatitis and myocardial infarction (MI).[25,26] Based on these results, RPR can be used as a marker of inflammatory response. Moreover, it is thought that malnutrition, which is one of the non-inflammatory conditions in which RDW is affected, will be less affected than RDW. RPR is an easily accessible and inexpensive marker.

Takeuchi et al. showed the prognostic significance of RPR level in breast cancer patients.[13] In the study conducted by Takeuchi et al., the estimated value for RPR performed by ROC analysis was reported as 0.71. In our study, the best-predicted value by ROC analysis was 0.54. Future studies are needed to identify a standard cut off value.Takeuchi et al. did not perform subgroup analysis according to the molecular types of patients. We performed subgroup analysis of patients according to their molecular types. In our study, we found a significant prognostic effect of RPR level in breast cancer patients with HR+. We did not see any prognostic effect of RPR level in patients with HER2-positive breast cancer and in patients with triple negative breast cancer. The data may not be statistically significant due to the small number of HER2 positive breast cancer patients and TNBC patients. Takeuchi et al. found a significant relationship between RPR and patient age and HER2 status. However, in our study, no significant relationship was found between RPR and clinicopathological characteristics. This may be due to the short follow-up period and the fact that HER-positive breast cancer patients received the necessary adjuvant therapy.

Our study has some limitations. The number of patients is not very high and the follow-up time is not long. As the study was retrospective, blood parameters for iron deficiency were not examined.

Since RPR is not a standard cut-off value, it is considered the best predicted value by ROC analysis. However, this value may be different in other studies.

CONCLUSION

In patients with non-metastatic breast cancer, RPR level may indicate poor prognosis.When we performed subgroup analysis according to molecular types, we found that RPR level has a significant prognostic effect in patients with HR + breast cancer. We believe that RPR level will be helpful when deciding adjuvant therapy, especially for HR+ breast cancer patients. RPR is a inexpensive and easily accessible test and can help in selection of postoperative treatment in breast cancer patients. This should be supported by studies with more patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hayriye Şahinli;* ***Design:*** *Hayriye Şahinli, Esra Zeynelgil, Sema Türker;* ***Control/Supervision:*** *Hayriye Şahinli;* ***Data Collection and/or Processing:*** *Esra Zeynelgil;* ***Analysis and/or Interpretation:*** *Hayriye Şahinli;* ***Literature Review:*** *Hayriye Şahinli, Sema Türker;* ***Writing the Article:*** *Hayriye Şahinli;* ***Critical Review:*** *Hayriye Şahinli, Sema Türker;* ***References and Fundings:*** *Hayriye Şahinli, Esra Zeynelgil, Sema Türker.*

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