ORIGINAL ARTICLE

Relationship between hematological parameters and severity of chronic obstructive pulmonary disease

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KEY WORDS

chronic obstructive pulmonary disease, mean platelet volume, platelet-to-lymphocyte ratio, plateletcrit, platelet distribution width

ABSTRACT

INTRODUCTION Chronic obstructive pulmonary disease (COPD) is the most important lung disease leading to disability and even death. Recent studies have shown that platelet indices are associated with several cardiovascular diseases; however, data on COPD are scarce.

OBJECTIVES We aimed to investigate the relation between the severity of COPD and platelet indices, including the platelet-to-lymphocyte ratio (PLR), white blood cell count to mean platelet volume ratio (WMR), and red cell distribution width (RDW).

PATIENTS AND METHODS This retrospective study was based on data collected from 153 patients with COPD admitted to our outpatient clinic between March 2014 and March 2015. All participants underwent pulmonary function tests, and forced expiratory volume in 1 second, forced vital capacity (FVC), and percentage of FVC expelled in the first second of forced expiration were measured. The population was divided into 4 subgroups according to the severity of COPD: mild, mild to moderate, moderate to severe, and severe.

RESULTS We observed a significant increase in platelet distribution width (PDW), mean platelet volume, plateletcrit, PLR, and RDW, and a decrease in WMR with increasing severity of COPD. In a multiple logistic regression analysis, PDW and RDW were independently associated with severe COPD. A receiver operating characteristic curve analysis showed that a PDW exceeding 14.85 was associated with severe COPD with a sensitivity of 85% and a specificity of 86%, while an RDW exceeding 14.45 was associated with severe COPD with a sensitivity of 90% and a specificity of 87%.

CONCLUSIONS The PDW and RDW are independently associated with disease severity, which may indicate hypoxemia, underlying inflammation, and oxidative stress in COPD.

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INTRODUCTION Chronic obstructive pulmonary disease (COPD) is related to extreme inflammatory response of the airways when exposed to harmful gases or particles. COPD is the third leading cause of death in the world today.[1] Recently, it has been emphasized that COPD is a component of systemic inflammatory syndrome and that the mortality rate due to respiratory failure is higher than that resulting from cardiovascular diseases. Systemic inflammation leads to skeletal muscular atrophy, which further aggravates respiratory failure. It can even trigger or increase the severity of comorbidities such as ischemic vascular diseases, heart failure, osteoporosis, metabolic syndrome, and depression.[2]

According to several studies, platelets and their indices may be used as inflammatory markers for cardiovascular, inflammatory, and thromboembolic diseases.[3] The parameters related to the platelet size reflect platelet activity and

are termed the platelet indices. These include the mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT).[4] A number of previous studies have shown that high MPV, PDW, and PCT are associated with increased inflammatory state in the body, as well as with the severity and acute exacerbation of COPD.[5-7] Platelets interact with leukocytes and secrete a number of mediators that are involved in immune modulation. Therefore, novel platelet indices reflecting platelet activity may provide information on the inflammatory status in certain diseases. The lymphocyte count in peripheral blood has been shown to inversely correlate with inflammation. The platelet-to-lymphocyte ratio (PLR) is an index calculated through dividing platelet count by lymphocyte count in the peripheral blood; it has been shown to be associated with poor outcome in patients with COPD.[6,8,9] The neutrophil-to-lymphocyte ratio (NLR) is a similar simple hematological parameter, which has been shown to be related with pulmonary function, acute exacerbations, and poor outcome in COPD.[9-16]

The red blood cell distribution width (RDW) is a numerical measure of the size variability of circulating erythrocytes and is routinely reported as a component of complete blood count in the differential diagnosis of anemia. Disorders related to systemic inflammation, ineffective erythropoiesis, nutritional deficiencies, bone marrow dysfunction, or increased red blood cell destruction can result in higher RDW than the reference range observed in healthy individuals.[17] Recent studies have reported that RDW increases as the severity of COPD progresses and suggested that RDW might be used as a biomarker in the evaluation of the disease severity.[18] Moreover, elevated RDW levels were found to be associated with increased mortality risk in patients with COPD.[18,19]

The aim of our study was to investigate the relationship of platelet parameters including the MPV, PDW, PCT, PLR, white blood cell count to mean platelet volume ratio (WMR), and RDW with the severity of COPD.

PATIENTS AND METHODS

This was a retrospective cohort study based on the data collected from patients admitted to our outpatient clinic for pulmonary diseases between March 2014 and March 2015. A total of 153 patients with COPD, diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, were included in the study. Patients were divided into 4 groups according to the severity of COPD: group A (mild), group B (mild to moderate), group C (moderate to severe), and group D (severe). The exclusion criteria were as follows: previous hospitalization, use of emergency services, blood transfusions, use of any anti-inflammatory medications in the preceding 2 months (systemic steroids, immunosuppressive drugs, etc), history of cancer, connective tissue diseases, inflammatory bowel disorders, or hematological disorders. Demographic characteristics and medical histories, including comorbid diseases, were recorded. All patients were active smokers.

Peripheral venous blood samples were drawn from the antecubital veins of patients after an overnight fasting. The blood samples were put into lithium heparin–containing tubes to avoid pseudothrombocytopenia. Total and differential leukocyte counts, platelet counts, and other platelet indices were measured by an automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois, United States). Absolute cell counts were used in the analyses. The PLR was calculated as the platelet count divided by the lymphocyte count.

Pulmonary function tests

All participants underwent pulmonary function tests between March 2014 and March 2015, which were performed by the same technician using the Jaeger Master Screen Pneumo V452I device (Care Fusion, Höechberg, Germany). The best test result of the 3 consecutive measurements was recorded. Forced expiratory volume in 1 second, forced vital capacity (FVC), and percentage of FVC expelled in the first second of forced expiration were measured according to the American Thoracic Society guidelines.[20]

The disease severity staging was conducted according to the 2017 GOLD guidelines.[7]

Since this was a retrospective study, the participants did not sign an informed consent from. The study protocol was approved by the local ethics committee.

Statistical analyses

All analyses were performed using SPSS 16.0 for Windows (SPSS, Chicago, Illinois, United States). Continuous variables were presented as means (SD), and categorical variables, as numbers (percentages). The Shapiro–Wilk test was used to verify the normality of the distribution of continuous variables. The comparison of hematological parameters (RDW, MPV, PCT, WMR, PLR, and PDW) among the study subgroups was performed by the one-way analysis of variance test or the Kruskal–Wallis test; the χ^2 test or the Fisher exact test was used for categorical variables as appropriate. For the post hoc analysis, the Scheffe test or the Mann–Whitney test was performed. A P value of less than 0.0083, which was obtained by dividing 0.05 by 6 (total pairwise comparisons), was considered as significant in pairwise comparisons of the groups in the post hoc analysis due to the Bonferroni correction.

We further categorized patients into 2 subgroups: with mild COPD (groups A and B) and severe COPD (groups C and D). All possible (clinically important) determinants of severe COPD were analyzed in a univariate analysis. Variables for which the P value was lower than 0.10 in the univariate analysis were assessed by

TABLE 1 Baseline clinical and laboratory characteristics of patients with chronic obstructive pulmonary disease according to disease severity

Parameter	COPD				*P* value
	Mild (n = 39)	Mild to moderate (n = 46)	Moderate to severe (n = 38)	Severe (n = 30)	
Age, y	57.1 (11)	58.7 (12)	65.4 (11)	73.8 (10)	<0.001
Male sex, n (%)	23 (58.9)	30 (65.2)	30 (78.9)	25 (83.3)	0.08
Hypertension, n (%)	2 (5)	9 (20)	6 (16)	12 (40)	0.003
Diabetes, n (%)	1 (3)	2 (4)	3 (8)	4 (13)	0.29
Hemoglobin, g/dl	14.3 (1.4)	13.9 (1.7)	13.6 (1.7)	13.8 (1.6)	0.014
WBC, 10^9/l	6.9 (1.5)	7.1(1.6)	7 (1.5)	6.3 (1.9)	0.18
Platelets, 10^9/l	239 (42)	245 (65)	264 (97)	267 (70)	0.06[a]
RDW	13.6 (0.4)	14.1 (0.7)	15.4 (1.1)	16.8 (1.5)	<0.001
PDW	13.5 (0.5)	14.4 (1.7)	15.7 (1)	17.5 (1.6)	<0.001
MPV, fl	7.6 (0.4)	8 (0.6)	8.8 (0.4)	9.6 (0.4)	<0.001
PCT, %	0.190 (0.04)	0.227 (0.153)	0.254 (0.076)	0.292 (0.054)	<0.001[a]
Neutrophils, 10^9/l	3.9 (1)	4.3 (1.6)	4.4 (1.3)	4.2 (1.6)	0.48
Lymphocytes, 10^9/l	2.1 (0.6)	1.7 (0.5)	1.6 (0.6)	1.4 (0.5)	<0.001
NLR	2.1 (1)	3 (2.7)	3.4 (2.7)	3.7 (3.5)	0.048[a]
WMR	0.9 (0.2)	0.9 (0.2)	0.79 (0.2)	0.65 (0.2)	<0.001
PLR	129 (52)	157 (67)	193 (138)	210 (86)	0.001[a]
FEV_1, lt	2.05 (0.43)	1.91 (0.40)	1.52 (0.35)	1.19 (0.31)	<0.001
FVC, lt	3.80 (0.65)	3.79 (0.76	3.22 (0.62)	2.93 (0.60)	<0.001
FEV_1/FVC	0.51 (0.35)	0.47 (0.38)	0.45 (0.29)	0.39 (0.33)	<0.001[a]

a Kruskall–Wallis test

Data are presented as mean (SD) unless otherwise stated.

Abbreviations: FEV_1, forced expiratory volume in 1 second; FEV_1/FVC, percentage of forced vital capacity expelled in the first second of forced expiration; FVC, forced vital capacity; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PCT, plateletcrit; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; RDW, red cell distribution width; WBC, white blood cell; WMR, white blood cell count to mean platelet volume ratio

a multiple logistic regression analysis to evaluate the independent variables associated with severe COPD. After adjusting for the demographic covariates including age, male sex, and hypertension, we searched for the adjusted odds ratios (ORs) for RDW and PDW with 95% confidence intervals (CIs). In addition, a receiver operating characteristic (ROC) curve analysis was constructed to determine the predictive value of RDW and PDW for severe COPD. A *P* value of less than 0.05 for the final model was considered significant.

RESULTS A total of 153 patients with COPD were included in the study. The distribution of the COPD groups was as follows: group A, n = 39; group B, n = 46; group C, n = 38; and group D, n = 30. Baseline clinical and laboratory characteristics of the groups are presented in TABLE 1. There was an increase in PDW, MPV, PCT, and RDW values and a decrease in WMR and PLR values with an increase in the severity of COPD (from A to D). Patients in the severe COPD group were older, more often were male, had higher RDW, PDW, MPV, PCT, PLR, and NLR values but had lower hemoglobin levels, lymphocyte count, and WMR compared with the mild COPD group (TABLE 2). In the post hoc analysis, the PDW was significantly higher in each COPD group in an increasing manner from group A to group D. The RDW values of groups also significantly increased from group A to group D, except for the difference between groups A and B (TABLE 3).

We conducted the multiple logistic regression analysis to find independent variables associated with severe COPD (groups C and D). After adjusting for the demographic covariates including age, male sex, and hypertension, we found that the RDW (adjusted OR, 3.668; 95% CI, 1.234–11.75, *P* <0.001) and the PDW (adjusted OR, 2.454; 95% CI, 1.036–5.811, *P* <0.001) were independently associated with the presence of severe COPD (groups C and D) (TABLE 4).

The ROC curve analysis was conducted to determine the cut-off values for the RDW and PDW for severe COPD. Using a cut-off level of 14.85, the PDW was associated with the presence of severe COPD with a sensitivity of 85% and specificity of 86%, while an RDW above 14.45 was found to have a sensitivity of 90% and a specificity of 87% for severe COPD (FIGURE 1).

DISCUSSION In our study, we found that platelet indices including MPV, PDW, PCT, PLR, together with RDW and NLR increased, while the lymphocyte count and WMR decreased as

TABLE 2 Comparison of patients with mild (groups A and B) and severe chronic obstructive pulmonary disease (groups C and D)

Parameter	Mild COPD (n = 85)	Severe COPD (n = 68)	*P* value
Age, y	58.0 (11.7)	69.1 (11.0)	<0.001
Male sex, n (%)	53 (62.3)	55 (80.8)	0.012
Hypertension, n (%)	11 (12.9)	18 (26.4)	0.06
Diabetes, n (%)	3 (3.5)	7 (10.2)	0.19
Hemoglobin, g/dl	14.2 (1.6)	13.5 (1.6)	0.006
WBC, 10^9/l	7.05 (1.61)	6.70 (1.77)	0.21
Platelets, 10^9/l	243 (56)	266 (86)	0.058
RDW	13.86 (0.65)	16.00 (1.48)	<0.001
PDW	14.07 (0.95)	16.55 (1.39)	<0.001
MPV, fl	7.84 (0.59)	9.18 (0.59)	<0.001
PCT, %	0.210 (0.118)	0.271 (0.070)	<0.001
Neutrophils, 10^9/l	4.16 (1.38)	4.35 (1.46)	0.41
Lymphocytes, 10^9/l	1.90 (0.63)	1.56 (0.60)	0.001
NLR, median (IQR)	2.02 (1.60–2.72)	2.70 (1.88–4.14)	0.004[a]
WMR	0.90 (0.22)	0.73 (0.20)	<0.001
PLR, median (IQR)	130 (96–189)	182 (132–229)	0.001[a]

a Mann–Whitney test

Data are presented as mean (SD) unless otherwise stated.

Abbreviations: IQR, interquartile range; others, see TABLE 1

TABLE 3 Pairwise comparisons of the study groups in terms of variables that differed between the groups

Groups	*P* value									
	Age	Hemoglobin	RDW	PDW	PCT	MPV	Lymphocyte count	NLR	WBC/MPV ratio	PLR
A–B	0.94	0.735	0.08	0.001	0.97	0.016	0.11	0.38	0.99	0.47
A–C	0.016	0.28	<0.001	<0.001	<0.001	<0.001	0.03	0.024	0.17	0.10
A–D	<0.001	0.02	<0.001	<0.001	<0.001	<0.001	<0.001	0.014	<0.001	<0.001
B–C	0.059	0.85	<0.001	<0.001	0.009	<0.001	0.93	0.999	0.16	0.99
B–D	<0.001	0.18	<0.001	<0.001	<0.001	<0.001	0.17	0.95	<0.001	0.027
C–D	0.028	0.62	<0.001	<0.001	0.18	<0.001	0.48	0.99	0.042	0.21

Pairwise comparisons of the groups were performed with the Scheffe test, except for PCT, NLR, and PLR for which the Mann–Whitney test was used.

A *P* value of less than 0.0083 was considered significant in pairwise comparisons of the groups according to the Bonferroni correction.

Abbreviations: see TABLE 1

the severity of COPD increased. In addition, we determined that the RDW and PDW were independently associated with severe COPD.

Platelets play an important role in numerous inflammatory conditions. They contribute to the immune modulation by secreting a number of mediators that promote mutual cell activation, so they interact with leukocytes. Platelets and endothelial cell interactions facilitate the secondary capture of neutrophils and other leukocytes, which triggers an interaction between different immune cells and the endothelium.[21,22] PDW is the standard deviation of the logarithmic transformation of platelets. It is an index that provides information about the viability of the platelets to be used in transfusions; an increase in PDW indicates that abnormally large and small platelets are in circulation. Wang et al[23] reported that a significant increase in PDW is related with COPD and pulmonary embolisms. However, they did not observe a relationship between the PDW and disease severity.

We did not identify any study that indicated a relationship between the severity of COPD and PDW. In our study groups, we observed an increase in PDW as the severity of COPD increased. We believe that this increase could be related to an elevation in the thrombosis load and/or increased inflammation that occurs as the disease becomes more severe. Although the age of patients increased as the severity of COPD increased, we conducted a multiple logistic regression analysis to identify the variables that are independently associated with severe COPD.

TABLE 4 Significant predictors of severe chronic obstructive pulmonary disease (groups C and D) in univariate and multivariable logistic regression analyses

Variable	Univariate analysis			Multivariable analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.092	1.056–1.132	<0.001	1.006	0.942–1.074	0.863
Male sex	2.708	1.272–5.726	0.009	2.012	0.458–8.840	0.354
Hypertension	2.324	1.010–5.342	0.047	0.559	0.116–2.695	0.468
Hemoglobin	0.748	0.604–0.925	0.007	1.131	0.979–1.883	0.636
MPV	3.093	1.701–8.961	<0.001	3.95	0.891–17.648	0.071
PDW	6.904	3.764–12.879	<0.001	2.454	1.036–5.811	0.041
RDW	11.901	5.468–25.894	<0.001	3.688	1.234–11.795	0.020
NLR	1.177	1.007–1.378	0.041	0.945	0.397–2.264	0.899
PLR	1.008	1.003–1.013	0.001	1.001	0.978–1.025	0.931
WMR	0.022	0.004–0.123	<0.001	0.869	0.04–200.7	0.960

Abbreviations: CI, confidence interval; OR, odds ratio; others, see **TABLE 1**

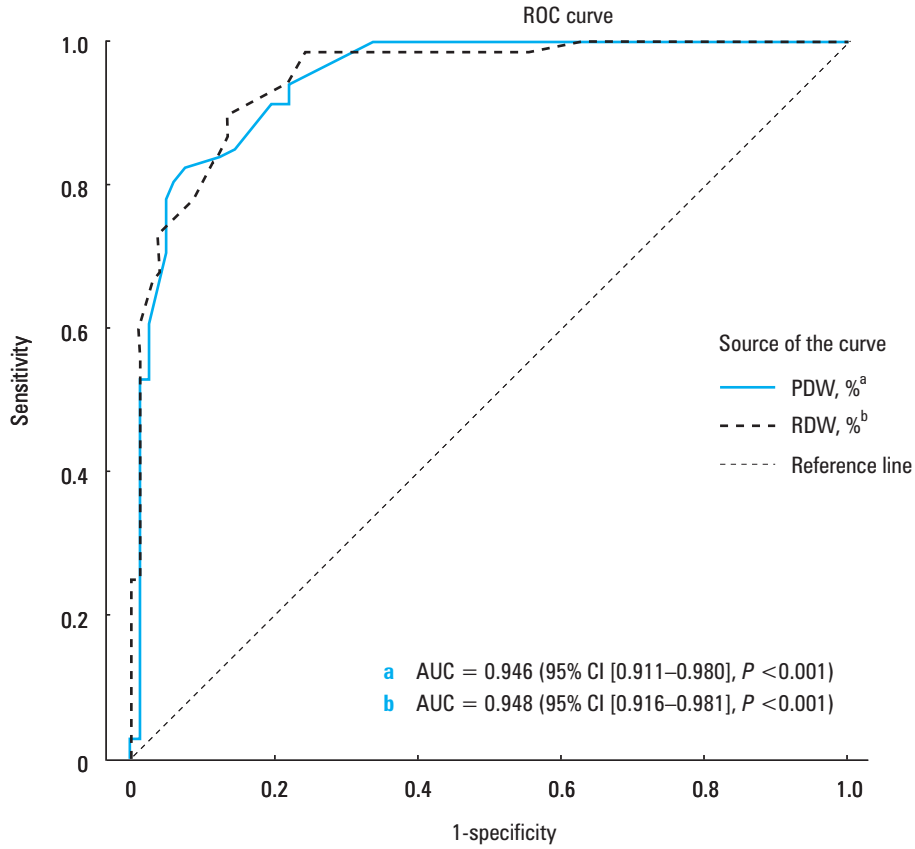

FIGURE 1 Receiver operating characteristic curves for platelet distribution width and red cell distribution wdith to predict severe chronic obstructive pulmonary disease
Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic; others, see **TABLE 4**

We found that the PDW and RDW were independently associated with the presence of severe COPD irrespective of the effect of age. Our results were consistent with the previous studies showing an increased PDW in patients with COPD. Also, PDW was shown to increase in various pulmonary diseases other than COPD such as obstructive sleep apnea syndrome,[24] pulmonary tuberculosis,[25-27] pulmonary embolism,[23,28] and pulmonary hypertension.[29]

The MPV is an automatically calculated measurement of the average size of platelets found in circulating blood and is typically included in complete blood count tests. Increased MPV is a marker of platelet activation. The MPV acts as an acute-phase reactant in inflammatory conditions depending on the severity of systemic inflammation. It has been shown to increase in low-grade inflammations but to decrease due to intensive degradation of platelets in inflammatory regions in severe inflammatory conditions. Previous studies reported conflicting results on the MPV in patients with COPD. Some of them found that the parameter is significantly higher in this patient group.[5,30,31] In a study by Zhang et al,[32] the MPV was higher in patients with COPD compared with controls, and even higher in patients during acute exacerbations compared with

those in the convalescence period. On the other hand, some other studies suggested that the MPV decreases in patients with inflammatory disorders including COPD even during acute exacerbations, so it may be used as a negative acute-phase reactant. Our study is consistent with the results of previous studies.[6,30,31] According to our results, patients with more severe COPD had higher MPV values.

PCT reflects the platelet count in blood, which is important for inflammatory processes, thrombosis, and cardiovascular physiopathology. Previous studies have indicated an association between PCT and various cardiovascular events, such as a worse outcome in acute coronary syndrome[33,34] and presence of cardiac syndrome X,[35] and various pulmonary diseases such as pulmonary tuberculosis[25,26] and coal workers' pneumoconiosis.[36] Makhlouf et al[5] showed that PCT is higher in diabetic or nondiabetic patients with COPD compared with healthy controls, which is consistent with our results.

Low lymphocyte count is related with increased inflammation. Combined with the platelet count, the PLR reflects the inflammatory status in the body more accurately. A number of previous studies have shown the association between the PLR and various pulmonary diseases such as obstructive sleep apnea syndrome,[37,38] pulmonary tuberculosis,[39] and COPD.[6-8,11] Karadeniz et al[7] found that the PLR was higher in patients with COPD during acute exacerbation compared with stable ones and healthy controls, and they concluded that the PLR might be a useful and easily accessible tool for evaluating the ongoing inflammation during the stable period and the disease severity during acute exacerbations in patients with COPD. Our results were in line with those findings in terms of high PLR values in patients with more severe COPD.

The NLR has been widely studied in various cardiovascular conditions and pulmonary diseases. Since a decrease in lymphocyte count and an increase in neutrophil count is expected in inflammatory conditions, the assessment of the NLR would provide a more precise indicator of the inflammatory state in patients with COPD. Furutate et al[15] explored the relation of the NLR with the severity and exacerbation of COPD. They found an increased NLR in patients with COPD during exacerbation compared with those during stable period. Moreover, they found a positive correlation of the NLR with the body mass, airflow obstruction, dyspnea, and exercise capacity (BODE) index, extent of emphysema, and the modified Medical Research Council dyspnea score, and a negative correlation with the 6-minute walking test result. They concluded that the NLR is associated with disease severity and exacerbation in patients with COPD. Our results were in line with their findings. We found higher NLR values in patients as the severity of COPD increased.

The RDW is a quantitative measure of anisocytosis. It is routinely measured by automated hematology analyzers and has been reported to be a component of the complete blood count. The RDW is typically elevated in conditions of ineffective red cell production and increased red cell destruction.[40] Our literature search revealed a limited number of studies analyzing the relationship between the RDW and COPD. Seyhan et al[19] observed a relationship between the RDW and increased mortality of patients with stable COPD. After eliminating the effects of potential confounders, a recent population-based study has reported an independent negative association between the RDW and lung function. One of the most important changes in the GOLD 2017 report was that the evaluation of COPD was refined by the separation of the spirometric assessment from symptom evaluation.[41]

To the best of our knowledge, there have been no studies in the English literature investigating the relationship between the RDW and severity of COPD. An increased RDW reflects a profound deregulation of erythrocyte homeostasis involving both impaired erythropoiesis and abnormal red blood cell survival, which may be attributed to a variety of underlying metabolic abnormalities such as shortening of telomere length, oxidative stress, inflammation, poor nutritional status, dyslipidemia, hypertension, erythrocyte fragmentation, and alteration of erythropoietin function.[42] Celik et al[43] reported that the RDW value on admission was significantly higher in the pulmonary embolism group among patients with suspicion of pulmonary embolism on admission to the emergency department, and they concluded that the RDW might be considered as a useful diagnostic tool for patients with suspected acute pulmonary embolism. In our study, we found that the RDW significantly increased with an increase in the severity of COPD. Moreover, it was independently associated with severe COPD. Our results were consistent with previous studies reporting a correlation between RDW and severity of COPD.

Since severe COPD is an inflammatory condition characterized by frequent exacerbations that require hospitalizations,[41] patients with high PDW and RDW values are at high risk of frequent flare-ups. Therefore, these patients need close clinical monitoring and their need for hospitalization should be evaluated more carefully.

Our study has several limitations, such as a retrospective, single-center design and the lack of a healthy control group.

In conclusion, we demonstrated that the PDW and RDW are associated with disease severity in patients with COPD. The PDW and RDW could be indicators of hypoxemia, underlying inflammation, and oxidative stress.

CONTRIBUTION STATEMENT SK and CS designed the study. FA analyzed the data. AS, AZ, and NY

interpreted the data. SK, FA, and AY revised the manuscript and approved the final version.

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