ORIGINAL ARTICLE

Serum Red Blood Cell Distribution Width Level of Chronic Obstructive Pulmonary Disease Patients and the Characteristics of the Exacerbation

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ABSTRACT

Objective: *Red blood cell distribution width (RDW) is a measure of red blood cell size heterogeneity. The aim of this study is to evaluate the relationship between the RDW level and the characteristics of the chronic obstructive pulmonary disease (COPD) exacerbations.*

Methods: *The records of the hospitalised COPD patients were evaluated retrospectively. The demographic characteristics, duration of follow-up and the numbers of exacerbations and hospitalisations, duration of the hospital stay, need of non-invasive mechanic ventilation (NIMV) or intensive care unit (ICU) and laboratory findings were recorded.*

Results: *There were 35 women (18.5%), 154 men (81.5%), Totaling 189 patients whose mean age was 67.4 ± 10.6 years. The mean durations of follow-up and hospitalisation were, respectively, 2.85 ± 2.5 years and 8.5 ± 5.4 days. Forty-one of the patients (22%) were current smokers and 115 of them (61.8%) were ex-smokers. Nearly one-third of the patients (34.9%) had increased RDW levels. When the patients with an increased RDW level compared to normal ones, no statistically significant difference was found with respect to the gender, smoking history, smoking pack-years, numbers of the exacerbation and hospitalisation, duration of hospital stay and need of NIMV or ICU. However, it was found that the presence of exitus was significantly higher in patients with an increased RDW level (*p = *0.02).*

Conclusion: *This study suggested that an increased level of RDW might be related with increased mortality in COPD patients. Further long-term prospective studies with healthy controls and COPD patients in both stable and exacerbation periods are needed in order to evaluate clinical significance of these findings.*

Keywords: COPD, RDW, exacerbation, hospitalisation, mortality

INTRODUCTION

Red blood cell distribution width (RDW) is a measure of red blood cell size heterogeneity and it reflects the erythrocyte morphology (1). It is a component of complete blood count and it is used in the differential diagnosis of anaemia (2). Furthermore, systemic inflammation, ineffective erythropoiesis, nutritional deficiencies, bone marrow dysfunction or increased destruction can also cause a higher RDW. Recent evidence reports that acute or chronic disorders such as cardiovascular diseases (CVD), cancer, sepsis, chronic obstructive pulmonary disease (COPD), pulmonary thromboembolism (PTE), diabetes mellitus, liver and kidney failure are related with increased RDW levels (1–4).

It is also reported that higher RDW levels may reflect underlying chronic inflammation, which can result in an increased mortality (3). There is an association between increased RDW levels and high mortality risk in both general population and some diseases including CVD and COPD (2, 3). COPD is a systemic disease and inflammation has an important role on development of COPD. COPD-related inflammation may also impair erythropoiesis and cause increased RDW levels, as do other chronic inflammatory processes. However,

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there are limited studies evaluating the relation among COPD, mortality and RDW levels (1, 3).

Chronic obstructive pulmonary disease is a treatable and preventable systemic disease, characterised by persistent airflow limitation that is usually progressive and associated with an increased inflammatory response to noxious particles and gases (5). It is the fifth leading cause of death and estimated to be the third in 2030 worldwide (6). Exacerbations are an important cause of mortality and morbidity in COPD patients (7, 8). The aim of this study is to evaluate the relationship between the RDW level and the characteristics of the COPD exacerbations.

SUBJECTS AND METHODS

The medical records of the hospitalised patients with COPD exacerbation in the Pulmonary Diseases Clinic were evaluated retrospectively. The exacerbation of the COPD was defined as an acute event characterised by a worsening of the respiratory symptoms that was beyond normal day-to-day variations and led to a change in medication (5).

The demographic characteristics, smoking history, duration of follow-up and the numbers of exacerbations and hospitalisations, duration of the hospital stay, need of non-invasive mechanic ventilation (NIMV) or intensive care unit (ICU) were recorded. Laboratory findings including haemogram and artery blood gas analysis that were taken on the first day of hospitalisation were also recorded.

Exclusion criteria

Patients with other lung diseases such as tuberculosis, bronchiectasis and interstitial lung disease were excluded. Patients with iron or vitamin deficiencies (such as B12 or folate) and recent transfusions were also excluded from the study.

Laboratory analysis

The red cell distribution width was assessed by flow cytometric analysers as the part of the routine full blood count. The red blood cell distribution width was calculated as (standard deviation of red cell volume/mean cell volume) × 100. The normal range was between 12.2% and 17.2% in our laboratory.

Statistical analysis

Statistical analyses of the study were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA). Categorical variables were expressed as counts (percentage). Numeric variables were expressed as mean and standard deviation. Comparisons of categorical variables between the groups were performed using the Chi-square test. A two-sided p-value < 0.05 was considered statistically significant.

RESULTS

There were 35 women (18.5%), 154 men (81.5%), totalling 189 patients. The mean age was 67.4 ± 10.6 years. The mean durations of follow-up and hospitalisation were, respectively, 2.85 ± 2.5 years and 8.5 ± 5.4 days. Forty-one of the patients (22%) were current smokers and 115 of them (61.8%) were ex-smokers. Respiratory infections (72%) were the most common causes of the exacerbations. Demographic data, the characteristics of exacerbation and laboratory findings of the patients are shown in Tables 1 and 2.

It was found that the level of RDW was increased in one-third of the patients (34.9%). Retrospective analyses of 189 COPD patients revealed that the RDW level had a mean value of 16.95 ± 2.2. The comparison of exacerbation characteristics and laboratory parameters according to the RDW levels are shown in Table 3.

When the patients with increased RDW level were compared to normal ones, no statistically significant difference was found with respect to the gender, smoking history, smoking pack-years, numbers of the exacerbation and hospitalisation, duration of hospital stay and need of NIMV or ICU (Table 4). However, it was found that the presence of exitus was significantly higher in patients with increased RDW level ($p = 0.02$) (Figure).

DISCUSSION

This study demonstrated that nearly one-third of the hospitalised COPD patients with the exacerbation had increased RDW levels. There were no statistically significant differences of gender, smoking history, smoking pack-years, numbers of the exacerbation and hospitalisation, duration of hospital stay and need of NIMV or ICU in patients with increased RDW level compared to normal ones. However, it was found that the presence of exitus was significantly higher in patients with increased RDW level.

The red blood cell distribution width (RDW) is a simple and cheap parameter, which is a component of the haemogram. It reflects the degree of heterogeneity of erythrocyte volume. It is also known as anisocytosis. The red blood cell distribution width is used for differential diagnosis of anaemias (2). Beside this, RDW is a recently recognised biomarker of adverse outcome in

Table 1: Demographic characteristics of the patients

		n	%
Gender	Female	35	18.5
	Male	154	81.5
Smoking history	Non-smoker	30	16.1
	Current smoker	41	22
	Ex-smoker	115	61.8
RDW	Normal RDW	123	65.1
	Increased RDW	66	34.9
NIMV	(–)	114	60.3
	(+)	75	39.7
ICU	(–)	175	92.6
	(+)	14	7.4
Exitus	(–)	177	93.7
	(+)	12	6.3

ICU = intensive care unit; NIMV = non-invasive mechanic ventilation; RDW = red blood cell distribution width.

Table 2: The characteristics of exacerbation and laboratory parameters

	Min	Max	Mean ± SD
Age, years	35	93	67.4 ± 10.6
Smoking pack/year	0	140	42.8 ± 29.9
The number of exacerbation, n	1	20	2.9 ± 3.4
The number of hospitalisation, n	1	12	2.1 ± 2.1
Duration of hospitalisation, day	1	34	8.5 ± 5.4
Haemoglobin g/dL	8.9	18.1	13.03 ± 1.7
Haematocrit, %	25.2	55.1	39.8 ± 5.3
RDW	13.4	27.1	16.95 ± 2.2
CRP, mg/dL	0.04	47.82	8.04 ± 10.1
$PaCO_2$, mmHg	22	92	48.7 ± 14.2
SO_2, %	65.6	99.1	90.1 ± 10.1

CRP = C-reactive protein; RDW = red blood cell distribution width; SD = standard deviation.

Table 3: The comparison of exacerbation characteristics and laboratory parameters according to RDW levels

	Normal RDW	Increased RDW	*p*-value
Age, years	66.8 ± 10.8	68.6 ± 9.97	0.15
Smoking pack/year	40.8 ± 28.6	46.3 ± 32	0.7
The number of exacerbation, n	2.9 ± 3.4	3.02 ± 3.4	0.1
The number of hospitalisation, n	2.05 ± 1.9	2.2 ± 2.3	0.7
Duration of hospitalisation, day	8.61 ± 5.8	8.4 ± 4.5	0.8
CRP, mg/L	8.6 ± 10.7	7.02 ± 8.9	0.42
PaO_2, mmHg	67.7 ± 18.9	66.3 ± 16.7	0.08
$PaCO_2$, mmHg	47.2 ± 13.6	51.03 ± 15.1	0.007
SO_2, %	90.7 ± 7.8	89.3 ± 7.6	0.47

CRP = C-reactive protein; RDW = red blood cell distribution width.

various acute and chronic conditions (9). An increased RDW is related with both impaired erythropoiesis and abnormal red blood cell survival, which may be attributed to a variety of underlying metabolic abnormalities

Table 4: Demographic characteristics of the patients according to RDW level

		Normal RDW		Increased RDW		*p*-value
		n	%	n	%	
Gender	Female	19	15.4	16	24.2	0.13
	Male	104	84.6	50	75.8	
Smoking history	Non-smoker	19	15.8	11	16.7	0.8
	Current smoker	25	20.8	16	24.2	
	Ex-smoker	76	63.3	39	59.1	
NIMV	(–)	80	65	34	51.5	0.07
	(+)	43	35	32	48.5	
ICU	(–)	116	94.3	59	89.4	0.07
	(+)	7	5.7	7	10.6	
Exitus	(–)	119	96.7	58	87.9	0.02
	(+)	4	3.3	8	12.1	

ICU = intensive care unit; NIMV = non-invasive mechanic ventilation; RDW = red blood cell distribution width.

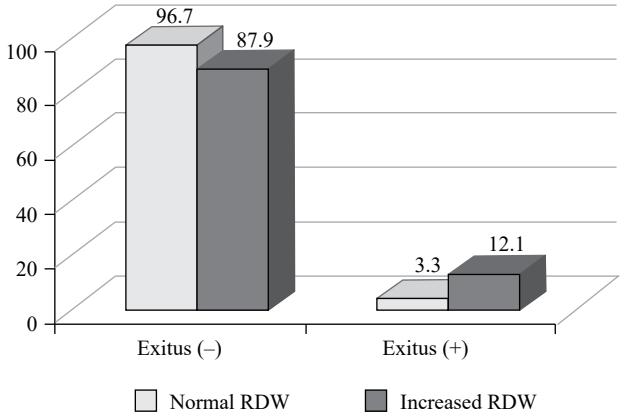

Figure: Comparison of RDW levels according to presence of exitus. RDW = red blood cell distribution width.

such as oxidative stress, inflammation, erythrocyte fragmentation and alteration of erythropoietin function (2).

Anisocytosis can also see in some disorders such as cardiovascular disease, cancer, sepsis, diabetes, liver/kidney failure and respiratory diseases including community acquired pneumonia (CAP), venous thromboembolism and COPD (2, 4, 10–12). The studies evaluating the relation between COPD and RDW levels are limited (1, 3). In a retrospective analysis of stable COPD patients, it was revealed that RDW is positively correlated with C-reactive protein (CRP), right ventricular dysfunction and pulmonary arterial hypertension (3). In a multivariable logistic regression analysis, the presence of high RDW was found to be only for independent parameter predicting right ventricle (RV) failure in COPD patients and it is suggested that RDW may be used to identify COPD patients with RV failure (13).

Chronic obstructive pulmonary disease is a treatable and preventable systemic disease characterised by persistent airflow limitation that is usually progressive (5). It is one of the most important causes of mortality and morbidity worldwide. Particularly in older-age groups in the United States, it is among the 10 most important disease-causing hospitalisations and death with increasing prevalence day-by-day (14). Exacerbations are the most frequent cause of morbidity, hospital admission and mortality in COPD (15). The exacerbation of the COPD is defined as an acute event characterised by worsening of the respiratory symptoms that was beyond normal day-to-day variations and led to a change in medication (5). Respiratory failure can be seen in the exacerbation of COPD. The arterial blood gas analysis is an important tool for defining respiratory failure and to start NIMV therapy in COPD patients. The relation between RDW and arterial blood gas analysis parameters of COPD patients was also investigated. It is reported that oxygen saturation is significantly lower for patients with an elevated RDW (1). In our study, it was also found that mean PaO_2 and oxygen saturation values were lower in patients with increased RDW levels compared to normal ones. However, the difference was not statistically significant. Beside this, mean $PaCO_2$ was significantly higher in patients with increased RDW level compared to normal ones (51.03 ± 15.1 *vs* 47.2 ± 13.6, $p = 0.007$). It suggests that RDW level may be useful for predicting hypercapnic COPD patients who needs NIMV therapy.

The stage of COPD is assessed by the pulmonary function test, health status and presence of exacerbation/hospitalisation (5). It reflects the severity of disease. There is a study evaluating the relation between RDW level and the stage of disease. The highest RDW is observed in the very severe stage ($p < 0.001$) of COPD patients in the study by Tertemiz *et al.* (1). In our study, it was not possible to compare the RDW levels according to stages of disease due to its retrospective design. There was a lack of data about health status assessed by modified Medical Research Council (mMRC) Questionnaire or COPD assessment test (CAT) due to the retrospective nature of this study. Furthermore, most of the patients were not able to perform the pulmonary function test since they had a severe dyspnoea due to exacerbation.

The association between RDW level and length of stay (LOS) in hospital is also investigated in recent studies (11, 16). The red blood cell distribution width (RDW) is associated with length of stay in hospital and use of vasopressors in hospitalised patients with CAP (11). Greater initial RDW and change of RDW during the heart failure hospitalisation are associated with longer LOS, suggesting that both initial RDW and change of RDW during the hospitalisation may be helpful in personalising prognosis and treatment (16). In contrast, there was no significant difference of LOS in the hospital between the groups in our study. It is thought that study populations including different diseases might be responsible for opposite results.

The baseline RDW and an increase in RDW during the hospitalisation are also compared in patients with sepsis and heart failure (16, 17). It is reported that there is an increase in RDW from baseline during the first 72 hours after the hospitalisation, and it is significantly associated with adverse clinical outcomes in sepsis. Therefore, it is suggested that a combination of baseline RDW value and an increase in RDW can be a promising independent prognostic marker in patients with severe sepsis or septic shock (17). It is also suggested that both initial RDW and change of RDW during the hospitalisation may be helpful in personalising prognosis and treatment of patients with heart failure (16). However, it was not possible to evaluate the role of RDW changes during the hospitalisation on adverse clinical outcomes due to retrospective design of this study.

A potential independent association is recently demonstrated between high RDW levels and the risk of all-cause mortality in critically ill patients, although the underlying mechanism is still unclear (17). An elevated RDW has been associated with adverse outcomes of heart failure, infective endocarditis, VTE and idiopathic pulmonary hypertension (9,18). The RDW is recognised as a mortality marker in patients with CVD (3). It is also reported that baseline RDW is significantly associated with incidence of fatal cardiac events (19). An increased RDW conveys an important information for both short- and long-term prognosis (3). Greater initial RDW and change of RDW during the heart failure hospitalisation are associated with 30-day mortality (16). The RDW is found to be associated with 30-day mortality in hospitalised patients with CAP (11). Even more importantly, the value of RDW is now being regarded as a strong and independent risk factor for death in the general population (2). Furthermore, the studies evaluating the role of RDW on mortality in COPD patients are also support these findings (1, 3). Elevated RDW levels are associated with an increased mortality risk in stable COPD patients (3). It is suggested that there is a correlation between survival of COPD patients and RDW levels (1). Also, the presence of exitus was significantly higher in patients with an increased RDW level in our study as similar to the literature.

There were several limitations of this study that should be considered. Firstly, it was a retrospective investigation, and data collection was based on medical records. Secondly, it reflected the RDW levels of only hospitalised patients with COPD exacerbation. So, the study group did not include outpatients and study population was relatively small. Furthermore, it was not possible to compare the RDW results of the patients in stable or exacerbation periods. Thirdly, only baseline RDW levels of the patient were recorded, so comparing the role of changes of RDW levels during the hospitalisation on adverse clinical outcomes was not possible. Fourthly, it was not possible to assess the patient's health status by modified Medical Research Council (mMRC) Questionnaire or COPD assessment test (CAT) and to evaluate the new classification of COPD because of its retrospective nature. So, the severity of the disease was not classified.

CONCLUSION

Early detection and effective treatment of exacerbations are key factors that may reduce in hospital admissions. The RDW is a simple, easy to perform and cheap parameter. It might be useful for predicting hypercapnic COPD patients who needs NIMV therapy in the exacerbation period. Also, it is suggested that an increased level of RDW might be related with increased mortality in COPD patients. Further long-term prospective studies with healthy controls and COPD patients in both stable and exacerbation periods are needed in order to evaluate clinical significance of these findings.

AUTHORS' NOTE

SAB conceived paper, oversaw data collection, conducted data analysis, wrote manuscript and approved final version. T Onyilmaz participated in study design, data collection, wrote manuscript and approved final version. EKU participated in study design, data collection, and revision of manuscript and approved final version. I Basyigit participated in study design, interpretation of data and revision of manuscript and approved final version. HB and FY participated in study design and interpretation of data, critically revised manuscript and approved final version. The authors declare that they have no conflicts of interest.

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