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ORIGINAL ARTICLE – OPEN ACCESS

Are Red Blood Cell Distribution Width and RDW/Hemoglobin Ratio Predictable in Mortality Among Patients with Chronic Obstructive Pulmonary Disease?

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ABSTRACT

Objective: Chronic obstructive pulmonary disease (COPD), the third most common cause of death in the world, is a multicomponent disease with pulmonary and extrapulmonary manifestations. The red blood cell distribution width (RDW) conveys important information for short- and long-term prognosis through a variety of medical conditions. Anemia can be seen in patients with COPD due to systemic inflammation and malnutrition. The aim of this study was to evaluate the role of RDW and RDW/Hgb in the prediction of mortality in patients with exacerbated COPD.

Materials and Methods: Between December 2015 and December 2017, 97 patients admitted to the Department of Chest Diseases at the Ufuk University Medical Faculty, with a diagnosis of COPD exacerbation were evaluated retrospectively. The demographic, clinical, laboratory characteristics, pulmonary functional tests, and arterial blood gases were noted. The RDW values and RDW/Hgb ratios were compared between patients who had died and those who were still alive.

Results: About 79.4% of the patients (n=77) were male and the rest of them 20 (20.6%) were female. The mean age was 73.01±9.54 years. The RDW values of patients with mortality were higher than the living COPD patients (p<0.001). The RDW/Hgb ratio was found to be higher in patients who had died than those who were living (p<0.001). The levels of C-Reactive protein were significantly higher in patients with COPD with mortality (p=0.034).

Conclusion: The elevated RDW levels and the RDW/Hgb ratio were associated with an increased annual number of attacks, comorbidities, and an increased PO_2 and PCO_2 mortality risk in patients with COPD.

Keywords: Chronic obstructive pulmonary disease, red cell distribution width, RDW/Hb ratio, mortality

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) ranks the third among the causes of death worldwide and has a mortality rate ranging from 15% to 54% (1–3). A study performed in our country found the mortality rate for COPD to be 17.3% and reported that fatalities occurred most frequently due to pulmonary causes (4).

The red blood cell distribution width (RDW), which is easy and inexpensive to evaluate, shows variations in circulating erythrocytes and is used for assessing the differential diagnosis of anemia. It also shows that anisocytosis is common in other circumstances such as cardiopulmonary diseases, venous thromboembolism, malignancies, diabetes mellitus, pulmonary infections, and hepatic and renal failure (5, 6). The elevated RDW has a high negative predictive value for diagnosing a number of disorders, and also provides important information for making a prognosis. The RDW elevation reflects the dysregulation of hemostasis in the face of some conditions including oxidative stress, inflammation, malnutrition, dyslipidemia, and hypertension (7). RDW may have a potential role in affecting systemic factors that alter the erythrocyte hemostasis leading to anisocytosis such as inflammation and oxidative stress (8). Both the reduced serum antioxidant levels (selenium, carotenoids, and vitamin E) and the elevated inflammatory mediators (IL-6, C-Reactive Protein (CRP), and soluble TNF receptors I and II) are associated with an elevated RDW. The underlying mechanism of the relationship with a mortality risk in COPD and the elevated RDW is not clear, and chronic inflammation has been suggested as the cause (6, 9).

The aim of this study was to evaluate the effect of RDW in the prognosis of patients with COPD and its role in predicting mortality.

MATERIALS and METHODS

The present study was planned as a retrospective cohort study based on the data of patients admitted for inpatient care at the Department of Chest Diseases at the Medical Faculty of Ufuk University for COPD exacerbation between December 2015 and December 2017. Ninety-seven patients aged above 40 years diagnosed with COPD according to the GOLD criteria were included in the study. Subjects with a history of blood transfusion or treatment

with any anti-inflammatory or immunosuppressive agents, cancer, connective tissue disorders, inflammatory bowel disease, or hematologic disorder were excluded. Demographic and clinical characteristics and comorbidities were recorded. Total leukocyte count, hemoglobin (Hgb), RDW, mean corpuscular volume (MCV), RDW/Hgb, creatinine, and blood urea nitrogen (BUN) were measured by an automatic hematology and biochemistry analyzer (Abbott Cell-Dyn 3700; Abbott Laboratories, Abbott Park, Illinois, USA). Pulmonary function tests (PFT) were performed using the Core-Encore system (Germany) "VMAX." During the PFTs, post-bronchodilator forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and FEV1/FVC according to GOLD criteria were recorded. For COPD staging, FEV1 values above 80%, values between 80 and 50, values between 50 and 30, and values below 30% were classified as mild, moderate, severe, and very severe COPD, respectively. Arterial blood pressure analysis was performed using Instrumentation Laboratory-Synthesis 25 version 2001. The pH, partial oxygen pressure (PaO_2), partial carbon dioxide pressure ($PaCO_2$), and arterial oxygen saturation (SaO_2) readings were recorded.

Statistical Analysis

Statistical evaluation was carried out with the Statistical Package for the Social Sciences software for Windows Version 20.0 (SPSS Inc., Chicago, IL, USA). The distribution status of continuous variables was evaluated by the Kolmogorov-Smirnov test. Categorical variables were outlined as numbers and percentages [n (%)]. The group ratios were compared by the Chi-square test. Continuous variables were outlined as median (minimum-maximum) values if they were not normally distributed, and were outlined as mean±standard deviation if they were normally distributed. The Student's t-test or the Mann-Whitney U test were used to compare the two groups according to their respective distribution statuses. The statistical significance level was set at $p<0.05$.

Table 1. Demographic data

Features	n	%
Sex		
Male	77	79.4
Female	20	20.6
Age (year)	73.01±9.54	
Smoking status		
Non-smoker	15	15.5
Active smoker	3	3.1
Ex-smoker	79	81.4
Smoking package/year (p/y)	40.87±26.85	
mMRC	2.0	1.0–4.0
Exacerbation per year	2.0	0–7.0
COPD Group		
A	11	11.3
B	21	21.6
C	9	9.3
D	56	57.7
Comorbidity	79	81.4
Hypertension	51	52.4
Diabetes mellitus	24	24.7
Heart failure	17	17.5
Coronary artery disease	34	35.1
Kidney failure	10	10.3
Malignency	11	11.3

mMRC: Medical research council; COPD: Chronic obstructive pulmonary disease

RESULTS

The study included 97 patients, out of whom 20 were women (20.6%). Their mean age was 73.01±9.54 years. The patients' smoked 40.87±26.85 packs per year on average. Their median number of attacks per year was 2. About 67% of the patients who were diagnosed with advanced COPD (groups C and D) and 79 (81.4%) had comorbidities. The most common comorbid conditions were hypertension (n=51) and coronary artery disease (n=34). The more detailed demographical data of the patients were provided in Table 1. Forty-four (45.36%) of the patients with COPD died during monitoring and 53 (54.64%) patients were discharged. The deceased and surviving patients were comparable with respect to gender (p=0.640). Mean age of the deceased patients was 75.04±7.85 years compared with 71.32±10.52 years for the survivors (p=0.055). The perception of dyspnea (mMRC) was 2 (median) for the survivors compared with 3 for the deceased patients (p=0.091). The deceased patients had had more frequent attacks (p=0.040). Disease stages were similar in both groups (p=0.472). The deceased patients had had more comorbidities as compared to the surviving patients (p=0.015) (Table 2). The Respiratory Function Test and Arterial Blood Gas results of the deceased and surviving patients with COPD are provided in more detail in Table 3. Complete blood count results of the deceased and surviving patients with COPD show higher leukocyte (WBC) and neutrophil counts for the former group. The neutrophil to lymphocyte ratio was similar in both groups (p=0.974). The deceased patients with COPD had statistically significantly lower hemoglobin levels than the surviving patients with COPD ($p<0.001$). The deceased patients also had higher MPV and RDW values compared with the surviving patients. RDW/Hgb ratio was higher in the deceased patients ($p<0.001$). Level of CRP was significantly higher for the deceased patients (p=0.034). Blood serum biochemistry and complete blood count results of the two groups are provided in Table 4.

DISCUSSION

Patients with COPD had a 45.36% mortality rate in our study. The factors associated with mortality were: the number of attacks per year, number of comorbid conditions, FEV1 severity, PO_2, and PCO_2. The mortality varies between 15% and 54% in studies reporting a 3–5-year mortality rates. RDW was significantly higher among the deceased patients with COPD as compared to the surviving patients with COPD. First, in our study, the RDW/Hb rates were compared in the two groups and were significantly higher in the deceased COPD patient group.

Recent studies have suggested that elevated RDW level was associated with severity of the diseases and long-term mortality in patients with COPD and that it can be used as a biomarker for

Table 2. Demographic characteristics of living and deceased patients with COPD

Features	Surviving COPD		Deceased COPD		p
	n	%	n	%	
Sex					
Male	43	81.1	34	77.3	0.640
Female	10	18.9	10	22.7	
Age, year	71.32±10.52		75.04±7.85		0.055
Smoking status					
None-smoker	6	11.3	9	20.5	
Active smoker	3	5.7	0	0	0.148
Ex-smoker	44	83.0	35	79.5	
Smoking package/year (p/y)	42.96±27.52		38.41±26.11		0.402
mMRC	2.0	1.0–4.0	3.0	1.0–4.0	0.091
Exacerbation per year	2.0	0–7.0	3.0	0–5.0	**0.040**
COPD stage					
A	7	13.2	4	9.1	
B	14	26.4	7	15.9	0.472
C	5	9.4	4	9.1	
D	27	50.9	29	57.7	
Comorbities	39	73.6	40	90.9	**0.029**
Hypertension	25	47.2	26	59.1	0.242
Diabetes mellitus	13	24.5	11	25.0	0.957
Heart failure	4	7.5	13	29.5	**0.005**
Coronary artery disease	17	32.1	17	38.6	0.500
Kidney failure	3	5.7	7	15.9	0.098
Malignency	6	11.3	5	11.4	0.095
Number of comorbidities, n	1	0–4.0	2	0–4.0	**0.015**

mMRC: Medical research council; COPD: Chronic obstructive pulmonary disease

assessing the COPD severity (10–12). Seyhan et al. described that RDW levels were associated with increased mortality in 270 stable patients with COPD (10). The underlying cause may be that an inflammation-like response in the lungs may cause anisocytosis through erythropoiesis and may have an effect on the half-life of circulating erythrocytes, leading to increased RDW. In addition, we believe that our patients' advanced ages may have contributed to RDW elevations. A positive correlation between the aging and RDW have been demonstrated in previous studies (7).

In a study investigating the relationship between anemia and mortality in patients with COPD, the median life expectancy was 49 months in patients with anemia versus 74 months in patients without anemia (13). In a study by Metan et al., anemia was noted in 32.1% of patients with COPD, and these patients had a higher mortality rate as compared with patients with polycythemia and patients with normal hemoglobin levels (14). Fidan et al. found that rates of anemia due to COPD were correlated with COPD severity (15). In another study, Kollert et al. showed that high Hb levels with COPD patients have better long-term survival. (16). It has been suggested that oxygen supply to tissues was probably adversely affected when COPD was accompanied by increased systemic inflammation (17), and that erythropoietin resistance had also increased (18). This is supported by the significant relationship between the RDW/Hb ratio and mortality in our study.

The nutritional deficit resulting from impaired oral intake and/or potential disturbance in absorbance seen in advanced COPD may be another cause (19, 20). Iron, folate, and vitamin B12 levels of our patients were not available, but the group of deceased patients had lower Hb levels.

Positive correlations were found between the RDW values and inflammatory markers, CRP, and erythrocyte sedimentation rate, regardless of anemic status of the patients (21, 22), and another study reported further positive correlation between CRP and albumin levels (10). As a parameter that is commonly used for monitoring infection in clinical practice, CRP is very useful in assessing treatment response and mortality in COPD exacerbations (23). A study by Diaz et al. demonstrated a negative relationship between serum CRP elevation and FEV1 and PaO_2 values in patients with COPD independent of smoking status (24). In our study, we also demonstrated a positive correlation between CRP and RDW in deceased patients with COPD.

Table 3. Pulmonary function test and arterial blood gas results of living patients with COPD and deceased patients with COPD

Test results	Surviving COPD	Deceased COPD	p
Pulmonary function test			
FVC, liter	2.18±0.73	1.79±0.55	**0.004**
FVC, %	62.92±17.34	58.14±15.56	0.160
FEV1, liter	1.32±0.54	1.02±0.43	**0.005**
FEV1, %	50.02±18.14	43.39±17.87	0.074
FEV1/FVC	57.24±10.33	54.77±11.37	0.265
Arterial blood gas			
PaO_2, mmHg	60.82±13.90	54.82±11.91	**0.006**
$PaCO_2$, mmHg	39.01±7.40	57.36±8.24	**0.005**
pH	7.41±0.04	7.38±0.07	**0.007**
SaO_2, %	90.47±6.54	82.37±12.43	**<0.001**

FVC: Forced vital capacity; FEV1: Forced expiratory volume in 1 second; PaO_2: Partial oxygen pressure; $PaCO_2$: Partial carbon dioxide pressure, SaO_2: Arterial oxygen saturation

Table 4. Complete blood count, serum biochemical analysis, and C–reactive protein (CRP) results of living and deceased patients

Laboratory parameters	Surviving COPD	Deceased COPD	p
WBC, 10^3/uL	9.28 (3.77–20.90)	11.40 (6.10–29.30)	**0.008**
Lymphocyte, 1000/µL	1.86 (0.38–4.98)	2.08 (0.89–6.18)	0.076
Neutrophil, 1000/µL	6.35 (2.60–16.67)	7.43 (2.80–21.55)	**0.036**
Neutrophil lymphocyte ratio (NLR)	3.68 (0.71–17.43)	4.12 (1.64–19.66)	0.974
Hemoglobin, g/dL	14.41 (9.26–18.18)	11.45 (6.50–17.10)	**<0.001**
MCV, fL	88.13 (64.01–97.55)	85.72 (61.91–10.00)	0.225
RDW, %	12.70 (10.25–26.28)	15.90 (11.03–29.90)	**<0.001**
RDW/Hgb	0.90 (0.63–2.84)	1.31 (0.076–3.17)	**<0.001**
BUN,mg/dL	19.00 (9.00–50.00)	23.50 (8.97–91.00)	0.051
Cr, mg/dL	0.92 (0.57–2.25)	0.94 (0.47–3.25)	0.876
CRP, mg/dL	8.60 (0.01–84.10)	24.75 (0.01–226.98)	**0.034**

WBC: White blood cell; MCV: Mean corpuscular volume; RDW: Red blood cell distribution width; BUN: Blood urea nitrogen; CRP: C- reactive protein; Cr: Creatinin

A study investigating the relationship between respiratory functions and RDW determined that a negative correlation between FEV1 and FVC and RDW, independent of smoking consumption, ethnicity of subjects, and known important micronutrients (including vitamin E, vitamin C, retinol, and kriptoksin) (25). In their study, the authors observed a relationship between RDW and severity of air flow limitations, BODE index, and survival in patients with COPD. In another study, Tertemiz et al. showed a higher mortality rate in patients with higher RDW level (12). They also reported a negative correlation between pulmonary functions (FEV1 and FVC values) and RDW level. Current research has shown that increased RDW is an independent negative prognostic factor associated with severity of COPD (11, 26).

The limitations of this study were its retrospective design, limited study population, and unavailability of iron, folate, and vitamin B12 measurements which may lead to the increase in RDW.

To conclude, there are multiple factors that may affect the mortality in COPD. Increased RDW and RDW/Hb values were identified as poor prognostic factors in patients with COPD. Larger and randomized studies are needed to elucidate the value of these inexpensive and readily-available parameters in investigating the pathogenesis and predicting mortality.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ufuk University Medical Faculty Ethics Institution (No: 21080613/1).

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