

# Is red blood cell distribution width an indicator of prognosis and mortality in respiratory intensive care unit?

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## ABSTRACT

**Objectives:** The range of variation of erythrocytes measured as Red blood cell distribution width (RDW). Mortality indicators in patients in intensive care depend on variation of physiological variables. High RDW rates have been commonly associated with heart disease, pulmonary embolism and pulmonary hypertension, peripheral artery disease, heart failure, liver disease and infectious diseases. We aimed in this study to determine the effect of RDW on prognosis and mortality in Chronic Obstructive Pulmonary Disease (COPD) patients in intensive care unit (ICU).

**Methods:** The cases who are treated for COPD in ICU between January 1, 2018 and December 31, 2019 reviewed. Demographic data, Charlson Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA) scores, procalcitonin, white blood cell, RDW, C-reactive protein, duration of mechanical ventilation, inotrope requirement, length of stay ICU, and 30-day mortality reviewed.

**Results:** Total number of 369 cases are included into the study and divided in two groups according to their RDW values (High RDW and normal RDW group). High RDW group had longer length of stay in ICU and hospital, mechanical ventilation duration, higher APACHE II, CCI, SOFA, white blood cell and procalcitonin values and lower C-reactive protein compared to normal RDW group. First outcome was hospital 30-day mortality in ICU. The age, RDW, inotrope use, MV duration, LOS H, APACHE II, CCI, SOFA, procalcitonin, CRP, HGB and HCT levels were found to be higher in patients with mortality compared those without. With the sensitivity value of 70.9% and the specificity of 47.7%, RDW the cut off value was found to be 16.5.

**Conclusions:** The risk of 30-day mortality, length of stay ICU and hospital and mechanical ventilation duration was higher in COPD patients with high RDW levels.

**Keywords:** RDW, ICU, COPD, mortality, indicator

The range in the volume and size of the red blood cells are measured with the test named red cell distribution width (RDW) [1]. RDW is always included in the complete blood count panel and inexpensive to do. The normal range is 11.6-17.2%. Although RDW is traditionally used to differentiate

the type of anemia, in recent studies, high RDW rates are found to be associated with heart disease, heart failure, acute pulmonary embolism and pulmonary hypertension, peripheral artery disease, liver disease, and infectious diseases [2-7]. Additionally, the RDW values have also been shown to be high in other critically

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ill patients with pneumonia, Gr (-) bacteriemia, and sepsis in intensive care unit (ICU) and it was a risk factor for hospital mortality [8-11].

Metabolic abnormalities like oxidative stress and inflammation in the cells are linked to high RDW levels and might be the main cause of the mortality in critically ill patients [12]. Mortality indicators in patients admitted to ICU depend on many physiological variables.

This research is aimed to determine the prognostic value of RDW and its relationship with mortality in patients with Chronic Obstructive Pulmonary Disease (COPD) in intensive care.

### METHODS

The retrospective study was initiated after approval from the Medical Specialization Training Board of Ataturk Chest Diseases and Thoracic Surgery Training and Research Hospital (approval date & number: 12/17/2020 & 705).

The cases who were admitted to ICU between January 1, 2018 and December 31, 2019 were reviewed retrospectively. The study included patients aged 18 years and older, admitted to ICU with a diagnosis of COPD between January 1, 2018 and December 31, 2019.

Exclusion criteria were as follows; cases with

**Table 1. Demographics and prognostic factors of the patients according to RDW distribution**

n =369		RDW (%)				p value
		Normal RDW (n = 216)		High RDW (n = 153)		
		$\bar{X} \pm SD$	Median (IQR)	$\bar{X} \pm SD$	Median (IQR)	
Gender	Female	84 (38.9%)		55 (35.9%)		0.566
	Male	132 (61.1%)		98 (64.1%)		
Age (year)		72.76 ± 11.45		71.14 ± 11.17		0.178
30 day mortality		68 (31.5%)		66 (43.1%)		<b>0.022</b>
Inotrope use		51 (23.6%)		37 (24.2%)		0.899
LOS H (day)		15 (15)		19 (16)		<b>0.009</b>
LOS ICU (day)		3(4)		4 (7)		<b>0.016</b>
MV duration (day)		0 (2)		0 (4)		<b>0.026</b>
APACHE II		20 (7)		20 (11)		<b>0.046</b>
CCI		6 (3)		6 (3)		<b>0.027</b>
SOFA		5 (2)		5 (4)		<b>0.021</b>
WBC (×10 <sup>3</sup> /ml)		11 (6.9)		12.4 (7.6)		<b>0.050</b>
Procalcitonin (ng/ml)		0.18 (0.64)		0.29 (2.8)		<b>0.037</b>
CRP (mg/l)		33.84 (54.12)		7.7 (21.83)		<b>0.015</b>
HGB (g/dl)		12.2 (3.35)		11.3 (4)		0.055
HCT (%)		38.6 (11)		37.7 (13.2)		0.471

Continuous variables are expressed as either the mean ± standard deviation (SD) or the median (IQR), and categorical variables are expressed as either frequency or percentage. Continuous variables were compared with a student t test or the mann whitney u test, and categorical variables were compared using Pearson’s chi-square test or fisher exact test. RDW = Red blood cell distribution width, LOS H = Length of stay Hospital, LOS ICU = Length of stay Intensive Care Unit, MV = Mechanical Ventilation, APACHE II = Acute Physiology and Chronic Health Evaluation II, CCI = Charlson Comorbidity Index, SOFA = Sequential Organ Failure Assessment, WBC = White blood cell, CRP = C-reactive protein, HGB = Hemoglobin, HCT = Hematocrit

known hematological malignancy, recent blood transfusion and anemia (hemoglobin < 13.5 g/dl in males, hemoglobin < 12.0 g/dl in females are accepted as anemia), cases who were stayed in ICU less than one day and cases who had a pathology or medical condition makes RDW lower than 11.6.

The normal range of RDW is 11.6-17.2, the cases with RDW  $\geq$  17.3 are included into the high RDW group.

Clinical data like demographics, Charlson Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, procalcitonin, white blood cell (WBC), C-reactive protein (CRP) values, length of stay ICU (LOS ICU), length of stay hospital (LOS H), mechanical ventilation (MV) duration, inotrope use, hemoglobin (HGB), hematocrit (HCT) and RDW values are noted. The mortality data has been taken from the Death Notification System.

### Statistical Analysis

The results were compared using Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Chicago, IL, United States). Whether the distribution of continuous variables was normal or not was determined by Kolmogorov Smirnov test. Continuous data were described as mean  $\pm$  SD and median (interquartile range) for skewed distributions. Categorical data presented as numbers and percentages. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Firstly, possible risk factors that thought to be related with mortality were analyzed in one variable multinomial logistic regression analyzed. Variables with  $p < 0.25$  in univariate logistic regression analysis were included in multivariate logistic regression analysis. The Backward Wald method was used for multivariate logistic regression analysis. ROC curve analysis was used to determine the cut off points. The  $p$ -value  $< 0.05$  is accepted as significant

**Table 2. The factors affecting mortality in COPD patients**

n = 369	Univariate Analysis					Multivariate Analysis (Backward wald 6 <sup>th</sup> step)				
	Wald	p value	OR	95% CI for EXP(B)		Wald	p value	OR	95% CI for EXP(B)	
				Lower	Upper				Lower	Upper
Age (year)	7.332	<b>0.007</b>	1.027	1.007	1.047					
Gender	0.306	<b>0.580</b>	1.132	0.729	1.758					
RDW (%)	5.822	<b>0.016</b>	1.076	1.014	1.141					
LOS H (day)	2.042	<b>0.153</b>	0.989	0.975	1.004	10.049	<b>0.002</b>	0.966	0.946	0.987
LOS ICU (day)	9.141	<b>0.002</b>	1.056	1.019	1.095					
MV duration (day)	20.847	<b>&lt; 0.001</b>	1.111	1.062	1.163	11.650	<b>0.001</b>	1.081	1.034	1.130
APACHE II	45.444	<b>&lt; 0.001</b>	1.130	1.090	1.170	10.350	<b>0.001</b>	1.073	1.028	1.121
CCI	19.046	<b>&lt; 0.001</b>	1.295	1.153	1.455					
SOFA	67.431	<b>&lt; 0.001</b>	1.751	1.532	2.001	30.189	<b>&lt; 0.001</b>	1.519	1.309	1.763
WBC( $\times 10^3$ /ml)	0.138	<b>0.710</b>	0.997	0.983	1.012					
Procalcitonin (ng/ml)	0.647	<b>0.421</b>	1.006	0.991	1.021					
CRP (mg/l)	7.780	<b>0.005</b>	1.005	1.001	1.008	4.232	<b>0.040</b>	1.005	1.000	1.009
HGB (g/dl)	5.109	<b>0.024</b>	0.903	0.827	0.987					
HCT (%)	7.299	<b>0.007</b>	0.965	0.940	0.990	7.175	<b>0.007</b>	0.957	0.927	0.988

OR = odds ratio. Multinomial Logistic Regression Nagelkerke  $R^2=0.512$  (Hosmer ve Lemeshow  $p > 0.05$ )

RDW = Red blood cell distribution width, LOS H = Length of stay Hospital, LOS ICU = Length of stay Intensive Care Unit, MV = Mechanical Ventilation, APACHE II = Acute Physiology and Chronic Health Evaluation II, CCI = Charlson Comorbidity Index, SOFA = Sequential Organ Failure Assessment, WBC = White blood cell, CRP = C-reactive protein, HGB = Hemoglobin, HCT = Hematocrit

**Table 3. The RDW cut-off value for mortality**

Test variables: RDW						
AUC	p value	95% Confidence Interval		Cut off	Sensitivity	Specificity
		Lower	Upper			
0.580	0.002	0.539	0.658	16.5	70.9%	47.7%

AUC = area under the curve

and p value between 0.05 and 0.10 are excepted borderline significant level on all statistical analysis.

**RESULTS**

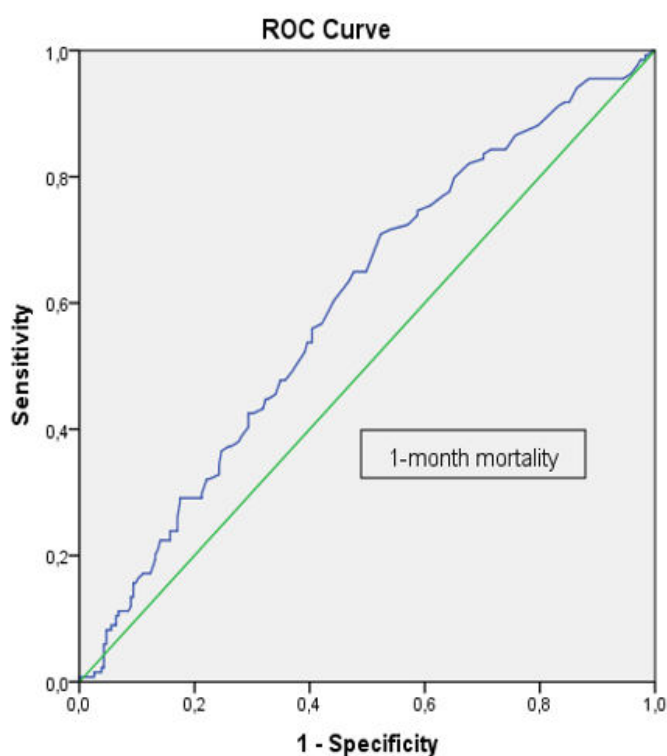
The comparison of the demographic, clinical and laboratory data of patients (n = 369) admitted to ICU with COPD, according to RDW groups are given in the Table 1. According to the results, 30-day mortality, LOS ICU, LOS H, MV duration, APACHE II, CCI, SOFA, WBC and procalcitonin values were found to be significantly higher and CRP levels were significantly lower in the group with high RDW values (Table 1).

Logistic regression analysis was done using the possible factors that might affect mortality in cases with COPD. After the last step of the analysis (6<sup>th</sup> step), six parameters (LOS H, MV duration, APACHE II, SOFA, CRP and HCT) were found to be the significant determinators for hospital mortality in cases with COPD, treated in ICU. The increase in MV duration, APACHE II scores, SOFA scores and CRP values and decrease in LOS H and HCT values are associated with increase hospital mortality in cases with COPD (Table 2).

A ROC curve analysis was applied to find the RDW cut off value in cases with COPD that determines the success of the RDW value in predicting mortality. It shows that RDW can differentiate in determining the mortality risk at COPD patients correctly at a rate of 58% (moderate). To answer the question of which value should be taken as the cut-off value for this test, the sensitivity value was 70.9% and the specificity value was 47.7%, the cut off value was found to be 16.5. The risk of mortality was found statistically higher in patients with RDW of 16.5 and above (Table 3) (Fig. 1).

The age, RDW, inotrope use, MV duration, LOS H, APACHE II, CCI, SOFA, procalcitonin, CRP, HGB and HCT levels were found to be higher in patients with mortality compared to those without mortality (Table 4).

Spearman correlation analysis was applied to determine the relationship between RDW values and other variables of patients with COPD in intensive care and the results are given in the Table 5. Accordingly, there is a low level positive correlation between RDW and LOS H, LOS ICU, MV duration, APACHE II, CCI, SOFA, and WBC. There is a low level negative relationship between RDW and CRP, and HGB (Table 5).



**Fig. 1. ROC Curve Analysis for RDW value in predicting mortality.**

**Table 4. Comparison between cases with and without mortality**

n = 369	Mortality (+) (n = 134)	Mortality (-) (n = 235)	p value
Sex, n (%)			0.580
Female	48 (35.8%)	91 (38.7%)	
Male	86 (64.2%)	144 (61.3%)	
Age (year)	75 (15)	71 (17)	<b>0.003</b>
RDW	17.2 (4.32)	16.2 (3.9)	<b>0.002</b>
Inotrope use. n (%)	70 (52.2%)	18 (7.7%)	<b>&lt; 0.001</b>
MV duration (day)	3 (6)	0 (0)	<b>&lt; 0.001</b>
LOS ICU (day)	4.5 (7)	3 (4)	<b>0.003</b>
LOS H (day)	17 (19)	16 (15)	0.235
APACHE II	24 (11)	19 (6)	<b>&lt; 0.001</b>
CCI	7 (3)	6 (3)	<b>&lt; 0.001</b>
SOFA	7 (4)	4(2)	<b>&lt; 0.001</b>
WBC ( $\times 10^3$ /ml)	12.05 (6.85)	11.5 (6.7)	0.616
Procalcitonin (ng/ml)	0.31 (2.2)	0.15 (0.71)	<b>0.002</b>
CRP (mg/l)	17.4 (54.55)	8 (25.79)	<b>0.002</b>
HGB (g/dl)	12.2 (3.8)	11.65 (3.4)	<b>0.039</b>
HCT (%)	38.7 (12.4)	37.1 (12)	<b>0.018</b>

Continuous variables are expressed as the median (IQR ) and categorical variables are expressed as either frequency or percentage. Continuous variables were compared with the mann whitney u test and categorical variables were compared using Pearson's chi-square test or fisher exact test. RDW = Red blood cell distribution width, LOS H = Length of stay Hospital, LOS ICU = Length of stay Intensive Care Unit, MV = Mechanical Ventilation, APACHE II = Acute Physiology and Chronic Health Evaluation II, CCI = Charlson Comorbidity Index, SOFA = Sequential Organ Failure Assessment, WBC = White blood cell, CRP = C-reactive protein, HGB = Hemoglobin, HCT = Hematocrit

## DISCUSSION

In this study, we detected an association between RDW values and prognosis-mortality of patients with COPD in ICU. Our findings are as follows; firstly; 30-day mortality, LOS H, LOS ICU and MV duration are higher in patients with high RDW values compared to those with normal RDW. Secondly; RDW is moderately successful in determining the mortality risk at COPD patients, with an accuracy of 58 percent. Thirdly; RDW is found to be one of the predictor for mortality. The other predictors of mortality was older age, inotrope use, MV duration, LOS H, APACHE II, CCI, SOFA, procalcitonin and CRP levels.

Similarly to our study, Osadnik *et al.* [13] also found an association between RDW and mortality. They thought that this association was due to the positive

correlation between RDW and inflammation [13].

In a study of Lorente *et al.* [14]; septic patients who died had higher RDW values compared to survivors in the the first week of ICU admission. They also found association between RDW and SOFA, COPD, ischemic heart disease [14]. In our study, we used CCI for defining comorbidities and found COPD patients with higher RDW levels had also higher 30-day mortality. Lorente *et al.* [14] showed that patients with RDW more than 15.5% had a 70% higher risk of death in the first 30 days than those with a lower RDW values.

Similar to our study, other researchers found that high RDW levels were a risk factor for mortality in patients with some certain medical conditions. RDW has been associated with increased mortality in inten-

**Table 5. The relation between RDW and other variables in COPD patients**

		RDW n = 369
Age	r	-0.041
	p	0.438
LOS H	r	0.162
	p	<b>0.002</b>
LOS ICU	r	0.144
	p	<b>0.005</b>
MV Duration	r	0.170
	p	<b>0.001</b>
APACHE II	r	0.191
	p	<b>&lt; 0.001</b>
	n	<b>368</b>
CCI	r	<b>0.159</b>
	p	<b>0.002</b>
SOFA	r	<b>0.133</b>
	p	<b>0.011</b>
WBC	r	0.114
	p	<b>0.028</b>
Procalcitonin	r	0.082
	p	0.118
CRP	r	-0.116
	p	<b>0.026</b>
HGB	r	-0.154
	p	<b>0.003</b>
HCT	r	-0.060
	p	0.251

RDW = Red blood cell distribution width, LOS H = Length of stay Hospital, LOS ICU = Length of stay Intensive Care Unit, MV = Mechanical Ventilation, APACHE II = Acute Physiology and Chronic Health Evaluation II, CCI = Charlson Comorbidity Index, SOFA = Sequential Organ Failure Assessment, WBC = White blood cell, CRP = C-reactive protein, HGB = Hemoglobin, HCT = Hematocrit

sive care patients [8, 9], patients with community acquired pneumonia [10], sepsis [15], gram-negative bacteremia [11]. Sadaka *et al.* [16] studied in patients with septic shock; they found that high RDW was associated with higher mortality. However, Budak *et al.* [17] did not find a relation between RDW and other inflammation markers like MPV, NRL and WBC count.

Zhang *et al.* [18] found that high RDW levels were associated with mortality on admission; however its

predictive performance was suboptimal. Similarly, this study showed that RDW might determine the mortality risk at COPD patients with an accuracy of 58%.

There are some studies in the literature about relation with RDW and sepsis-mortality, but there is not enough study on COPD patients. Although RDW is shown as mortality indicator COPD patients in ICU, multicenter randomized studies with large number of the patients with other respiratory disease are required to confirm the role of RDW in prognosis of the pa-

tients in ICU.

### Limitations

Our study's limitations are as follows; a single-center study and has retrospective design, we measured RDW only in admission into the ICU therefore we can not comment on the RDW change by time and we have only included the patients with COPD and we might not generalize our findings to all patients with other respiratory diseases.

### CONCLUSION

The risk of 30-day mortality, LOS H, LOS ICU and MV duration was higher in COPD patients with high RDW levels but there is a low level correlation.

#### Authors' Contribution

Study Conception: GED, MÖC; Study Design: GED, MÖC; Supervision: GED, MÖC; Funding: GED, MÖC; Materials: GED, MÖC; Data Collection and/or Processing: GED, MÖC; Statistical Analysis and/or Data Interpretation: GED, MÖC; Literature Review: GED, MÖC; Manuscript Preparation: GED and Critical Review: MÖC.

#### Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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