

# The role of serum red blood cell distribution width level in predicting the short term mortality of community-acquired pneumonia, acute attack chronic pulmonary disease, and acute pulmonary thromboembolism

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## ABSTRACT

**Background:** There is a growing concern in inflammatory parameters that are commonly used in routine practice and can be measured cost-effectively for predicting mortality community-acquired pneumonia (CAP), acute-attack chronic obstructive pulmonary disease (COPD), and acute pulmonary thromboembolism (PTE). Red blood cell distribution width (RDW) is a significant parameter indicating the heterogeneity of the size of red blood cells (RBCs). The present study was designed to compare RDW levels among patients that were hospitalized due to CAP, acute PTE, and acute-attack COPD, all of which are characterized by persistent inflammation, and to investigate the role of RDW in predicting 30-day mortality.

**Material and Method:** The RDW levels measured on admission in all three groups were evaluated retrospectively.

**Results:** The 554 patients comprised 320 (57.76%) men and 234 (42.24%) women with a mean age of  $67.074 \pm 14.73$  years. The patients comprised 92 (16.6%) CAP, 265 (47.8%) acute PTE, and 197 (35.6%) acute-attack COPD patients. Mean RDW was  $14.42\% \pm 2.73\%$  (range, 3.77-28%) while it was  $14.88\% \pm 3.30\%$  in the CAP group,  $13.21\% \pm 2.77\%$  in the COPD group, and  $15.15\% \pm 2.12\%$  in the PTE group. In the COPD, CAP, and PTE groups, RDW levels were significantly higher in patients with 30-day mortality compared to those without mortality ( $p=0.008$ ,  $p=0.020$ , and  $p<0.05$ , respectively).

**Conclusion:** RDW is a practical, inexpensive and automatically reported blood test parameter which can be used along with scoring systems in the prediction of prognosis and ICU requirement and also in the follow-up of patients with diseases that are characterized by persistent inflammation in their pathophysiology.

**Keywords:** Red blood cell distribution width, community acquired pneumonia, pulmonary thromboembolism

## INTRODUCTION

Community-acquired pneumonia (CAP) is an inflammatory disease caused by bacteriologic infection of the lung parenchyma, and pulmonary thromboembolism (PTE) is a disease characterized by clinical manifestations of the blockage of the pulmonary artery (1-3). Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation caused by airway and/or alveolar abnormalities arising from significant exposure to harmful particles or gases. Acute exacerbations of COPD are diagnosed when specific symptoms including increased sputum volume and dyspnea worsen beyond day-to-day variability. In these diseases, early diagnosis and treatment are

of paramount importance for reducing mortality and morbidity. Recently, there is a growing concern in inflammatory parameters that are commonly used in routine practice and can be measured cost-effectively for predicting mortality in CAP, acute PTE, and acute-attack COPD (4).

Red blood cell distribution width (RDW) is a significant parameter indicating the heterogeneity of the size of red blood cells (RBCs) as well as their morphology. RDW is a simple, cost-effective, routinely measured, and automatically reported blood test parameter. RDW elevation has been shown to be associated with the increase in oxidative stress and other inflammatory markers such as C-reactive protein (CRP). Moreover,

in acute PTE, elevated RDW has been associated with mortality and this association has been attributed to acute inflammation and also to alterations in blood viscosity (5). Han et al. (6) evaluated the RDW levels measured on admission and at 24 h after presentation in patients with acute PTE and reported that the group with elevated RDW levels had higher mortality rates. In the CAP requiring hospitalization, RDW levels have been shown to vary significantly among patients and these variations have been associated with prognosis, mortality, and severity of clinical profile. In a retrospective study, the elevated RDW level in CAP was found to be a predictor of intensive care unit (ICU) requirement and mortality (7). Another retrospective study evaluated 442 patients with acute-attack COPD and revealed that increased RDW was independently associated with in-hospital and one-year mortality (8). Another study evaluated a total of 36,532 patients hospitalized in ICU and reported that an elevated RDW level measured on admission was a significant independent risk factor for in-hospital and 4-year mortality (6-9).

The present study was designed to compare RDW levels among patients that were hospitalized due to CAP, acute PTE, and acute-attack COPD, all of which are characterized by persistent inflammation, and to investigate the role of RDW in predicting 30-day mortality.

## MATERIAL AND METHOD

Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Ankara Chest Diseases and Chest Surgery Education and Research Hospital (Date:19.12.2019, Decision No:654). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The retrospective study included a total of 554 patients that were hospitalized in our Chest Diseases outpatient clinic and ICU due to CAP, acute-attack COPD or acute PTE within 24 h after admission to emergency service. The 554 patients comprised 92 (16.6%) CAP and 265 (47.8%) PTE patients who were diagnosed and treated based on international guidelines and 197 (35.6%) stable COPD patients who were diagnosed, graded, and treated based on GOLD (Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease) guidelines (1-4). Exclusion criteria were as follows: age below 18 years, pregnancy, a diagnosis of diseases other than COPD, PTE, and CAP, history of blood transfusion, intradermal or oral iron, vitamin B12, and folic acid use. The APACHE II (Acute Physiology and Chronic Health Evaluation II) scores of the patients hospitalized in ICU were retrieved from patient records. All the patients included in the study had undergone a complete blood count (CBC) examination within the

first 4 h after admission to the clinic or ICU and had been followed up for 30-day mortality. CBC examination was performed photo metrically using a BC-6800 auto analyzer. Normal reference ranges for hemoglobin (HGB), hematocrit (HCT), platelet (PLT) count, and RDW were accepted as 12-16 g/dL, 40-54%, 142-424 103/ $\mu$ L, and 11.6-17.2%, respectively.

## Statistical Analysis

Statistical analyses were performed using SPSS version 15.0 (SPSS, Inc.; Chicago, IL, USA). Demographic data related to patients and control subjects were expressed as numbers, percentages, median values, and min-max values. Data were presented as mean  $\pm$  standard deviation (SD) and median (range) for continuous variables and as frequencies (percentiles) for categorical variables. The Shapiro-Wilk test was used to assess the normal distribution of the variables. Nonparametric categorical parameters were analyzed using the Chi-square test, and nonparametric dependent ordinal parameters were analyzed using the Wilcoxon test. Independent nonparametric or parametric values were analyzed using the Mann-Whitney U test or student t test. RDW level affecting the 30-day mortality was determined using logistic regression analyses. ROC curves analysis was used to determine cut-off values in relation to mortality of RDW levels. p value 0.05 was considered statistically significant.

## RESULTS

The 554 patients comprised 320 (57.76%) men and 234 (42.24%) women with a mean age of  $67.074 \pm 14.73$  years. The patients comprised 92 (16.6%) CAP, 265 (47.8%) acute PTE, and 197 (35.6%) acute-attack COPD patients. Mean age was  $69.63 \pm 15.44$ ,  $71.57 \pm 10.54$ , and  $62.79 \pm 15.95$  years in CAP, COPD, and PTE patients, respectively, and no significant difference was found among the three groups with regard to mean age ( $p=0.831$ ). Of all patients, 133 (24%) patients were hospitalized in ICU and had a mean APACHE II score of  $23.79 \pm 7.26$  (range, 8-44). The median APACHE II score in the CAP group was 29.00 and was significantly higher than the scores in COPD and PTE groups ( $p<0.001$ ). Thirty-day mortality occurred in 49 (8.84%) patients and the mortality rate in the CAP group ( $n=36$ ; 6.50%) was significantly higher than that of other groups ( $p<0.001$ ). **Table 1** presents the demographic characteristics, mortality rates, clinical and ICU hospitalization rates, CURB-65 scores in CAP patients, and GOLD stages in COPD patients. In the CAP group, the 30-day mortality rate increased as the CURB-65 (Confusion Urea Respiratory Rate Blood Pressure-65) score increased ( $p<0.001$ ). The use of LTOT and NIMV at home and the grading of patients with the new combined GOLD staging had no significant effect on 30-day mortality ( $p=0.366$ ,  $p=0.968$ , and  $p=0.520$ , respectively).

**Table 1. Demographic and clinical characteristics**

	Groups	Mean±SD	Median
Age (years)	CAP	69.63±15.44	73.00
	Acute-attack COPD	71.57±10.54	71.00
	AcutePTE	62.79±15.95	63.00
	Total	67.07±14.73	69.00
<b>Variables</b>		<b>n(%)</b>	
Groups	CAP	92 (16.6)	
	Acute-attack COPD	197 (35.6)	
	AcutePTE	265 (47.8)	
	Total	554 (100)	
Gender	CAP	Male	55 (59.8)
		Female	37 (40.2)
	Acute-attack COPD	Male	147 (74.6)
		Female	50 (25.4)
	Acute PTE	Male	118 (44.5)
		Female	147 (55.5)
Total	Male	320 (57.8)	
Female	234 (42.2)		
Outpatient hospitalization	CAP	43 (46.7)	
	Acute-attack COPD	188 (95.4)	
	Acute PTE	190 (71.7)	
Comorbidities	CAP	55 (59.7)	
	Acute-attack COPD	111 (56.3)	
	Acute PTE	70 (26.4)	
	Total	236 (42.5)	
ICU hospitalization	CAP	49 (53.3)	
	Acute-attack COPD	9 (4.6)	
	Acute PTE	75 (28.3)	
	Total	133 (24)	
Mortality	CAP	36 (39.1)	
	Acute-attack COPD	5 (2.5)	
	Acute PTE	8 (3)	
	Total	49 (8.84)	
Pneumonia	CURB-65 score	2	22 (23.9)
		3	30 (32.6)
		4	23 (25.0)
		5	17 (18.5)
COPD	GOLD stage	A	33 (16.8)
		B	71 (36.0)
		C	43 (21.8)
		D	50 (25.4)

CAP: Community-acquired pneumonia, COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism, ICU: Intensive care unit, CURB-65: Confusion Urea Respiratory Rate Blood Pressure-65, GOLD:Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, SD: Standard deviation

**Table 2. Red blood cell distribution width levels**

Groups	RDW		
	Mean±SD	Median	Min-Max
CAP	14.88±3.30	14.65	10.18-28.00
COPD	13.21±2.77	12.48	3.77-23.10
PTE	15.15±2.12	14.60	9.70-23.50
Total	14.42± 2.73	14.00	3.77-28

RDW: Red blood cell distribution width, CAP: Community-acquired pneumonia, COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism

**Table 3. Correlation between GOLD stages, use of LTOT and NIMV and RDW**

Variables	n	%	RDW (%)	p
GOLD stages	A	33	25	10.86
			50	11.78
			75	12.85
	B	71	25	11.19
			50	12.49
			75	14.44
	C	43	25	12.61
			50	11.56
			75	12.61
	D	50	25	11.76
			50	12.78
			75	15.12
LTOT	Yes	38	25	11.93
			50	13.43
			75	15.11
	No	159	25	11.19
			50	12.17
			75	14.44
NIMV	Yes	17	25	12.05
			50	13.61
			75	15.47
	No	180	25	11.22
			50	12.24
			75	14.50

GOLD: Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, LTOT: Long-term oxygen therapy (LTOT), NIMV: noninvasive mechanical ventilation (NIMV) at home

In the CBC examination performed within the first 4 h after admission, the PLT counts and HGB, HCT levels were normal in 90.8%, 65.16%, and 60.64% patients in the CAP, COPD, and PTE groups, respectively. **Table 2** presents the laboratory parameters of the CAP, COPD and PTE group. RDW was significantly higher in the PTE group compared to other groups (p<0.001). In the CAP group, mortality-associated RDW increased as the CURB-65 score increased (p<0.05). In the COPD group, no significant difference was found between the patients using and not using NIMV at home with regard to RDW (p=0.067), whereas RDW was significantly higher in patients using LTOT at home compared to patients not using it (p=0.007). No significant relationship was found between the new combined GOLD staging and RDW (p=0.061) (**Table 3**).

In the COPD, CAP, and PTE groups, RDW levels were significantly higher in patients with 30-day mortality compared to those without mortality (p=0.008, p=0.020, and p<0.05, respectively) (**Table 4**). When the RDW levels relationship with mortality was evaluated by logistic regression analysis, it was determined that it increased 0.530 times in CAP, 0.731 times in COPD and 0.759 PTE groups (**Table 5**). In the ROC analysis, a RDW value below 15.45 % predicted independent mortality with a sensitivity of 75.5% and specificity of 74.1% (**Table 6, Figure 1**).

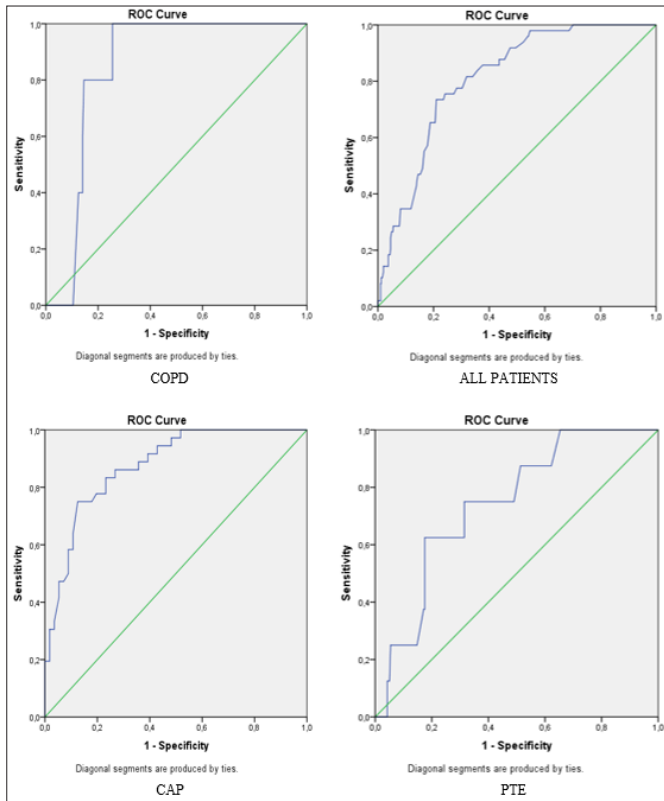


Figure 1. Effect of RDW in predicting 30-day mortality

Variables	n	%	RDW (%)	p	
Acute-attack COPD Mortality	Yes	5	25	15.27	0.008
		50	16.36		
		75	17.00		
	No	192	25	12.32	
		50	11.27		
		75	12.32		
Acute PTE Mortality	Yes	8	25	14.85	0.020
		50	16.80		
		75	18.57		
	No	257	25	13.60	
		50	14.60		
		75	16.20		
CAP Mortality	Yes	36	25	15.47	<0.05
		50	16.55		
		75	19.00		
	No	56	25	11.25	
		50	12.99		
		75	14.95		
Total Mortality	Yes	49	25	15.45	<0.05
		50	16.60		
		75	18.95		
	No	505	25	12.32	
		50	13.80		
		75	15.50		

COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism, CAP: Community-acquired pneumonia

## DISCUSSION

Community-acquired pneumonia (CAP), acute PTE, and COPD area leading cause of mortality and morbidity in clinical practice of chest diseases. In patients with acute PTE, 1- to 3-month mortality rates range between 5.4-15% and these rates may reach up to 50% in the presence of hypotensive shock (10). Repeated acute exacerbations of COPD lead to reduced lung function as well as repeated hospitalization, and increased mortality and morbidity (11). In-hospital mortality rate has been reported as 6.7% while short-term mortality rates vary between 1.8% and 20.4% (12). In CAP, however, short-term mortality rates vary between 2.4% and 34.6% and may reach up to 30% in patients requiring ICU and in patients with increased CURB-65 scores Scoring systems such as CURB-65 and pneumonia severity index (PSI) are commonly used for assessing disease severity and requirement of hospitalization and ICU admission (13,14). In our study, the overall mortality rate was 8.84% and the CAP group had the highest mortality rate (39.1%) among others. This high rate could be attributed to the high ICU admission rate (53.3%) and the high mean age among our patients. Due to the retrospective nature of our study, only CURB-65 scores were available for our CAP patients. It is commonly known that the severity of CAP increases as the CURB-65 scores increase. In our study, we also found that the mortality rate increased as the CURB-65 scores increased. Nevertheless, the mortality rate in our COPD patients (2.5%) was remarkably lower than those reported in the literature, which could be associated with the lower ICU admission rate in this group as well as the lower prevalence of GOLD C and D stages and the lower rate of patients using LTOT and NIMV at home. However, unlike in other studies, the 30-day mortality in our PTE patients (3%) was remarkably lower than those reported in the literature.

	WALD	p	OR	95% CI for EXP(B)	
				Lower	Upper
CAP	22.057	<0.001	0.530	0.406	0.691
COPD	5.074	0.024	0.731	0.557	0.960
PTE	4.131	0.042	0.759	0.582	0.990

RDW: Red blood cell distribution width, CAP: Community-acquired pneumonia, COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism

	AUC	p	95% CI	Cut off	Sensitivity %	Specificity %	
CAP	0.885	<0.001	0.819	0.951	15.25	77.8%	76.6%
COPD	0.836	0.010	0.768	0.904	15.00	80.0%	78.8%
PTE	0.746	0.018	0.604	0.887	15.55	75.0%	69.5%
All patients	0.810	0.026	0.759	0.862	15.45	75.5%	74,1%

RDW: Red blood cell distribution width, CAP: Community-acquired pneumonia, COPD: Chronic obstructive pulmonary disease, PTE: Pulmonary thromboembolism

Studies investigating systemic inflammatory diseases have shown elevated RDW levels, which are known to indicate dysregulation of erythrocyte homeostasis and abnormal erythrocyte survival and to occur in response to the underlying mechanism of telomere shortening, oxidative stress, and inflammation (15,16). Recently, there has been a growing interest in the role of RDW in predicting short- and long-term mortality in patients with CAP, acute-attack COPD, acute PTE, and sepsis, all of which have persistent inflammation in their pathophysiology (6,17,18). Studies evaluating CAP patients have shown that RDW is associated with the severity of clinical profile and could be an independent risk factor for predicting the prognosis, short-term mortality, and ICU requirement. RDW shows time-dependent variation due to the fact that each RBC circulates for 100-120 days due to in these patients groups, in particular, it has been suggested that repeated measurement of RDW during hospitalization (7,19,20). A previous study evaluated patients with acute-attack COPD and reported that on-admission RDW levels were significantly higher in patients receiving LTOT and NIMV at home (21). Another study evaluated patients with acute-attack COPD and revealed that increased RDW was a significant independent risk factor for COPD at a cut off value of  $\geq 13.75\%$  (9). Tertemiz et al. (22) revealed that increased RDW levels established a positive correlation with the severity of clinical profile and a negative correlation with pulmonary function tests. A retrospective study evaluated 309 patients with acute PTE and found increased RDW levels in the mortality group. In all the studies abovementioned, the physiology of increased RDW has not been elucidated. Nevertheless, in some studies, this increase has been attributed to neutrophil activation induced by increased oxidative stress in CAP, to intermittent hypoxemia in PTE, and to hypoxemia and reduced lung function in COPD (23,24). In the present study, we aimed to compare RDW levels among patients that were hospitalized due to CAP, acute PTE, and acute-attack COPD, all of which are characterized by persistent inflammation. The results indicated that the RDW levels were significantly higher in PTE patients compared to other patients (Table 2). The incidence of alterations in blood viscosity and intermittent hypoxemia is higher in acute PTE compared to CAP and acute-attack COPD, which is associated with the physiology of the disease and explains the high mean RDW level. In our COPD patients, RDW was significantly higher in patients using LTOT at home compared to patients not using it ( $p=0.007$ ) and this finding was considered to be associated with increased erythropoietin secondary to hypoxia and also with oxidative stress (16,21,25). On the other hand, in our study, only a small proportion of our

COPD patients (8.6%) were using NIMV at home and no significant difference was found between the patients using and not using NIMV at home with regard to RDW ( $p=0.067$ ). The absence of a significant difference could be attributed to the fact that patients with hypoxemic or hypercapnic respiratory failure could not be identified since no evaluation could be performed on the arterial blood gas parameters that were measured simultaneously with RDW due to the retrospective nature of our study. In our study, unlike in other studies in the literature, no significant relationship was found between the new combined GOLD staging and RDW in patients with stable COPD ( $p=0.061$ ). Although the staging procedure was performed in the patients within the last one year, no standardization could be achieved due to the retrospective nature of the study and the absence of standardization was considered to affect the results of the study.

Our study was limited in several ways. First, the study was a single-center and retrospective study. Second, RDW levels were only measured during hospital admission and these measurements were not standardized, baseline RDW levels (i.e. pre-admission levels) were not measured in the patients, and no serial measurement was performed. Third, prediction of mortality was limited to 30 days and no data could be retrieved regarding specific causes of death due to the retrospective nature of the study.

## CONCLUSION

Red blood cell distribution width is a practical, inexpensive and automatically reported blood test parameter which can be used along with scoring systems in the prediction of prognosis and ICU requirement and also in the follow-up of patients with diseases that are characterized by persistent inflammation in their pathophysiology.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Clinical Trials Ethics Committee of Ankara Chest Diseases and Chest Surgery Education and Research Hospital (Date:19.12.2019, Decision No:654).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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