Original Article

ISSN: 1735-0344 *Tanaffos 2025; 24(4): 330-337*

TANAFFOS

Predicting COPD Severity by Red Cell Distribution Width as a Potential Marker

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Received: 20 May 2024
Accepted: 11 July 2025

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Background: Chronic obstructive pulmonary disease (COPD) is a condition of the lower airways and lungs with stable inflammation and alterations in the structure of small airways. There are some biomarkers linked to acute exacerbations of COPD (AECOPD). Red cell distribution width (RDW) is one of these biomarkers. To investigate the correlation between RDW and the severity of COPD, and to assess its relationship with the stage of airway obstruction in spirometry among COPD patients.

Materials and Methods: In an 18-month retrospective study, a total of 255 participants were enrolled, including 170 patients with COPD (85 with stable COPD and 85 with acute exacerbations of COPD) and 85 age- and sex-matched healthy individuals. Demographic factors and blood laboratory tests were conducted for each group. The COPD groups had their COPD severity, spirometry parameters, and inflammation indices recorded and then compared.

Results: RDW levels are increased in COPD patients ($p<0.001$). However, no statistically significant relationships between RDW values and CAT scores or mMRC grades were observed. Our analysis revealed that spirometry parameters and RDW levels are negatively correlated ($p<0.05$). Additionally, the RDW parameter has a positive and significant correlation with PCO_2 and a negative and significant relationship with pH ($p<0.05$), while no significant correlation exists between the RDW parameter and $PHCO_3$.

Conclusion: Our findings indicate that RDW could serve as a potential predictor of COPD conditions, especially in spirometry parameters.

Keywords: Chronic obstructive pulmonary disease (COPD); Red cell distribution width (RDW); Acute exacerbation; Biomarker

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a condition of the lower airways and lungs that is characterized by varying degrees of persistent inflammation and alterations in the structure of small airways (bronchiolitis) and weakening of the alveolar wall, which is called emphysema (1, 2). COPD is a common and heterogeneous disease and has substantial morbidity, disability, and mortality on a global scale, particularly affecting disadvantaged individuals (2).

COPD is thought to affect an estimated 384 million people globally, with a notable number of undetected cases. According to the World Health Organization (WHO), COPD is ranked as the third leading cause of death in the world (3).

Globally, there are many significant risk factors for COPD, including male sex, a body mass index (BMI) of less than 18 kg/m^2, smoking, exposure to biomass, and occupational exposure to dust or smoke (4).

Although it appears that, because of greatly multifaceted exacerbations, there is unlikely to recognize a universal indicator that can encompass all of them, some biomarkers, including increased C-reactive protein (CRP), eosinophils, neutrophils, fibrinogen, cytokines (such as interleukin-6, interleukin-8, and tumor necrosis factor-α (TNF-α)), troponin T, and N-terminal pro-brain natriuretic peptide (NT-proBNP), are linked to acute exacerbations of COPD (AECOPD) (5, 6).

Red cell distribution width (RDW), an index used in the evaluation of red blood cell morphology and anemias, is a routine hematological parameter currently being investigated as a potential biomarker of COPD. To calculate RDW, the standard deviation of red blood cell volumes is divided by the mean corpuscular volume of the erythrocytes, and then the result is multiplied by 100 (7). Ozgul et al. have shown that the RDW parameter is significantly increased in COPD patients compared to the control group (*P* value<0.05) (8). RDW parameter has been linked to COPD severity and the prognosis for acute exacerbations, according to certain research (8-11). We sought to find out the following: 1) The relationship between serum RDW levels and disease severity in stable COPD patients and those with acute exacerbations; and 2) The relationship between the RDW parameter in COPD patients and the stage of airway obstruction in spirometry.

MATERIALS AND METHODS

Study design

The study was conducted over 18 months between 2020 and 2021. The cases enrolled were patients with COPD who were admitted to two hospitals. Patients were diagnosed according to the criteria outlined in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline. Patients with end-stage renal failure (ESRD), a history of recent hospitalization (last two months) and active infections, cancer and hematological diseases, recent blood transfusions (last two months), a history of rheumatological diseases, and inability to perform spirometry test were excluded. 170 COPD Patients were divided into two subgroups: Acute exacerbations of COPD and stable COPD. There were also 85 age- and sex-matched individuals in the control group. The severity of patients' conditions was evaluated using the COPD Assessment Test (CAT) score and the modified Medical Research Council (mMRC) grading. There was no significant difference in the scores and grades between patients with AECOPD and those with stable COPD ($p > 0.05$).

Laboratory measurements and spirometry

We recorded blood index parameters in every group of the study, indices relating to inflammation, and also arterial blood gas in the AECOPD and stable COPD groups. Blood samples of AECOPD patients were collected immediately after admission. Spirometry was done by patients who were able to properly perform the test. In spirometry tests, parameters measured included: 1) Forced Expiratory Volume in one second (FEV1), 2) Forced Vital Capacity (FVC), and 3) FEV1/FVC. Spirometry in COPD patients showed no significance in the relation of spirometry parameters in both AECOPD and stable COPD groups.

Statistical analysis

The means with standard deviation were used to represent variables. Means were compared using the chi-squared test and one-way ANOVA test. For correlation analyses, Pearson's correlation tests were utilized.

Ethics approval and consent to participate

The protocol for conducting the present study was approved by the ethics committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1398.693). All experiments were performed in accordance with relevant guidelines and regulations, and written informed consent was obtained from all of the participants.

RESULTS

This study evaluated clinical scores, inflammatory markers, and blood gas parameters between the acute exacerbation of COPD and stable COPD groups to assess physiological and inflammatory differences. Results of clinical scores and laboratory tests are summarized in Tables 1 and 2.

Clinical scores

The CAT score did not differ significantly between the acute exacerbation and stable COPD groups (p=0.122), indicating a similar perceived symptom burden. Although the mMRC grades showed no significant difference (p=0.073), the higher proportion of patients with severe dyspnea (grades 2 and 3) in the acute exacerbation group suggests a trend toward more pronounced breathlessness during exacerbations.

Inflammatory markers

CRP levels were significantly higher in acute exacerbation than in stable COPD (p=0.025), reflecting increased systemic inflammation during exacerbations. In contrast, ESR values showed no significant difference (p=0.111), suggesting similar levels of chronic inflammation between groups. The higher CRP in acute exacerbation highlights the acute inflammatory response linked to disease exacerbation.

Table 1. Demographic factors, COPD severity, spirometry, and laboratory tests

	Acute exacerbation of COPD (n=85)	Stable COPD (n=85)	Healthy control groups (n=85)	P-value
Age (years), Mean±SD	64.49±11.9	62.75±7.72	62.39±12.09	<0.05
Gender: male/female	61/24	49/36	47/38	<0.05
CAT score (0-40)	19.79±6.38	18.29±6.14	-	0.122
mMRC grade:				
0	11	5	-	0.073
1	27	32		
2	33	42		
3	14	6		
Spirometry:				
FEV1 (%)	54.42±13.41	57.62±12.65	-	0.112
FVC (%)	63.31±9.95	64.59±10.83		0.423
FEV1/FVC (%)	61.64±11.39	64.61±10.95		0.84
ESR	20.96±24.99	16.20±9.97	-	0.111
CRP	46.65±60.41	8.23±8.87		0.025
pH	7.30±0.08	7.38±0.03		<0.001
HCO_3	30.81±6.43	26.91±3.21		<0.001
PCO_2	61.87±19.04	46.23±4.79		<0.001

Table 2. Blood parameters in study groups

Blood parameter	Acute exacerbation of COPD (n=85)	Stable COPD (n=85)	Healthy control groups (n=85)	P-value	Significance
RBC (×10^6/μL)	5.05±0.86	5.02±0.30	4.30±0.57	<0.001	Acute Exacerbation & Stable COPD > Healthy Control
Hb (g/dL)	14.90±2.76	14.06±1.65	12.84±1.46	<0.001	Acute Exacerbation & Stable COPD > Healthy Control
HCT (%)	46.51±8.61	42.46±4.52	38.3±3.83	<0.001	Acute Exacerbation > Stable COPD & Healthy Control
MCV (fL)	92.87±6.77	91.88±6.87	86.84±4.77	0.386	Acute Exacerbation & Stable COPD > Healthy Control
PLT (×10^3/μL)	202.13±83.26	262.11±94.58	254.95±72.04	<0.001	Acute Exacerbation < Stable COPD & Healthy Control
WBC (×10^3/μL)	9.68±4.66	7.35±1.86	8.06±1.75	<0.001	Acute Exacerbation > Stable COPD & Healthy Control
RDW (%)	15.19±2.59	13.74±1.90	13.59±1.04	<0.001	Acute Exacerbation > Stable COPD & Healthy Control

Arterial blood gases

Acute exacerbation was associated with significantly lower pH (p=0.001) and higher PCO_2 (p=0.001), indicative of more apparent respiratory acidosis. HCO_3 levels were elevated in acute exacerbation (p=0.001) as a compensation mechanism to manage acidosis.

Blood parameters

Blood parameters analysis among study groups revealed some significant results. RDW elevation was seen in acute exacerbation compared to the other groups (p< 0.001), suggesting an increased variability in RBC sizes. Other hematological markers (RBC, Hb, HCT, MCV) were elevated in both COPD groups compared to healthy controls (p<0.001). However, patients with acute exacerbation had slightly higher values than those with stable COPD, reflecting increased erythropoietic activity and oxygen transport demands during exacerbations. Hematological alterations, including increased WBC and RDW, reflect the acute systemic response during exacerbations.

WBC counts were significantly higher in acute exacerbation than in stable COPD and healthy controls (p< 0.001), indicating heightened inflammatory responses during exacerbations.

Platelet counts were significantly lower in acute exacerbation than in stable COPD and healthy controls (p=0.001), which may indicate platelet consumption related to inflammation and coagulation activity during exacerbations.

Although no significant associations were observed between spirometric parameters and RDW levels in patients with stable COPD or AECOPD (Table 1), our analysis suggested a potential inverse association between spirometric parameters and RDW levels (Table 3).

Additionally, the RDW parameter has a positive and significant correlation with PCO_2 and a negative and significant relationship with pH, while no significant correlation exists between the RDW parameter and $PHCO_3$ (Table 3).

It is worth noting that the relationship between RDW levels in COPD patients and mMRC grades was also analyzed. The RDW values were 15.30±2.99 for mMRC grade 0, 14.24±2.36 for grade 1, 14.46±2.32 for grade 2, and 14.48±1.78 for grade 3, with no statistically significant differences in RDW across the mMRC grades (Table 4).

In addition, the correlation between RDW and CAT scores was evaluated. This analysis revealed a correlation coefficient (r) of 0.120 with a p-value of 0.119, indicating a weak and statistically non-significant association (Table 5). These findings suggest that RDW is not significantly associated with either the mMRC grade or CAT score, indicating that RDW levels may not be directly associated with COPD severity.

Table 3. Relation between RDW parameters and spirometry and arterial blood gas parameters

	RDW	
	r	P-value
FEV1	-0.229	0.003
FVC	-0.204	0.008
FEV1/FVC	-0.202	0.008
pH	-0.296	<0.001
PCO_2	0.171	0.026
$PHCO_3$	0.071	0.356

Table 4. Relation between RDW parameters and mMRC grades

	mMRC grade (Mean±SD)				P-value
	0	1	2	3	
RDW	14.48±1.78	14.46±2.32	14.24±2.36	15.30±2.99	**0.385**

Table 5. Relation between RDW parameters and CAT Score

	RDW	
	r	P-value
CAT Score	0.120	**0.119**

DISCUSSION

This study demonstrated that RDW levels are significantly higher in patients with COPD than in healthy individuals, indicating a potential role for RDW as a biomarker for differentiating COPD patients from non-COPD individuals. However, RDW levels did not show statistically significant correlations with COPD severity as assessed by CAT scores or mMRC grades. Similarly, no

significant correlations were observed between spirometry parameters of stable COPD and AECOPD patients.

Further analysis revealed a negative correlation between RDW levels and spirometry parameters, suggesting a potential link between elevated RDW and reduced lung function. RDW showed a positive and significant correlation with PCO_2 and a negative correlation with pH, though no significant relationship was observed with $PHCO_3$. Additionally, differences in CRP, pH, and PCO_2 between AECOPD and stable COPD groups underscore the impact of exacerbations, supporting the need for targeted interventions to manage inflammation and respiratory impairment in these patients.

Blood parameters, including RBC, Hb, HCT, PLT, WBC, and CRP levels, significantly differed between COPD patients and the healthy group, further supporting the systemic inflammatory profile associated with COPD. These findings underscore the multifaceted role of RDW and related parameters in the context of COPD and its associated systemic effects.

In multiple investigations, the RDW values of patients with stable COPD were significantly greater than those of controls (12-14). Nonetheless, some research endeavors failed to reveal any evidence of noteworthy correlations between RDW values and the existence of chronic COPD (15).

RDW in AECOPD patients is also reported to be substantially higher than in people with stable COPD (16, 17). Zhu et al.'s study found a positive association between RDW and duration of stay, suggesting that RDW may be a useful predictor of longer hospital stays in AECOPD patients (18). A retrospective study on COPD patients with exacerbations was conducted, which included a sample size of 804 patients. The results of the study showed that RDW has a significant correlation with the severity of acute exacerbation of COPD. This correlation was reflected through the level of $PaCO_2$ and the duration of hospitalization. The findings suggest that monitoring RDW could potentially aid in the identification of acute exacerbations and help in the management of COPD patients (19).

Elevated RDW has been found in COPD patients who are dependent on noninvasive mechanical ventilation (NIMV) compared to those who are not dependent on NIMV. Moreover, patients who require long-term oxygen therapy have significantly higher RDW levels than those who do not require such therapy, suggesting that COPD patients with elevated RDW levels have a poorer prognosis (20).

Research shows that COPD patients are at a higher risk of mortality when their RDW levels are increased. In critically ill COPD patients, an increase in RDW levels is associated with a higher risk of all-cause mortality within 28 days. Additionally, the combination of RDW levels and age in patients with stable COPD may predict the onset of conditions such as acute ischemic stroke, right ventricular dysfunction, and other cardiovascular diseases (13, 21-24).

Some research suggests that utilizing a combination of RDW and mean platelet volume parameters can serve as a useful biomarker for pulmonary heart disease (25). According to recent research, the red cell distribution width (RDW) to platelet ratio (RPR) has been identified as a useful tool in predicting the likelihood of in-hospital mortality for patients with AECOPD. This finding can be particularly helpful for clinicians, who can use this metric to quickly identify patients at high risk and take necessary measures to improve their outcomes (12).

It is commonly observed that patients with COPD exhibit local as well as systemic oxidative stress and an elevated level of inflammation. Studies have shown that inflammatory cytokines can obstruct the maturation of erythroid cells in the bone marrow, resulting in immature erythrocytes being released into the bloodstream. As a consequence, the size distribution of red blood cells in the circulation becomes more varied, and the RDW values are higher (26). The interplay between RDW and inflammatory biomarkers, such as C-reactive protein (CRP) and interleukins, underscores the systemic nature of COPD and its comorbidities, suggesting that RDW could be a valuable

tool for risk stratification and targeted therapeutic interventions (27, 28). Additionally, specific microRNAs, such as miR-23a-5p and miR-194-3p, have been identified as common regulators in COPD, indicating shared molecular mechanisms that may influence RDW levels and disease progression (29). Furthermore, metabolomic and transcriptomic analyses reveal that lipid metabolism pathways are significantly associated with COPD phenotypes, further elucidating the complex interplay of molecular factors affecting RDW in this context (30).

However, published research has yet to establish the potential pathophysiological mechanisms linking increased RDW levels to different diseases (31).

Another important point is that RDW is a routine inclusion in complete blood counts, which enhances its utility, as it is both inexpensive and easy to measure (32). Other studies also state RDW is cost-effective and a potentially accessible biomarker that can be used to evaluate the severity of exacerbation and predict hospitalization and further exacerbations in COPD patients (26, 33).

This study has two key limitations: its retrospective design and small sample size. Additionally, some of the correlations found were weak.

RDW is a biomarker with the potential for detecting systemic inflammation in diverse disorders. With its affordability, ease of use, and versatility, this parameter might be an ideal choice for clinicians looking to diagnose and monitor inflammatory conditions (34).

As mentioned before, although there are many studies suggesting that the RDW parameter can be a prognostic factor for COPD, some results have shown no significant relations or weak correlations.

Based on the available data, it appears that further investigation is necessary to gain a more comprehensive understanding of the precise relationship between the RDW parameter and COPD. To ensure the accuracy of the results, larger studies with a more diverse population should be conducted. Moreover, it is recommended that prospective studies be carried out to establish whether there exists a causal relationship between RDW parameters and COPD. This will help to shed more light on the potential mechanisms underlying the association between RDW and COPD, and could ultimately lead to more effective treatment and management strategies for patients with this condition. Also, the underlying mechanism behind the parameter increase in COPD and systemic inflammation remains largely unknown. In order to gain a better understanding of these mechanisms, further research is necessary.

CONCLUSION

While the current study did not establish a significant association between the severity of COPD and RDW, it did identify a significant correlation between RDW and blood parameters such as PCO_2 and pH. Additionally, we observed a negative correlation between increased RDW values and spirometry parameters. In conclusion, our findings suggest that RDW may serve as a potential predictor of COPD severity, particularly in relation to spirometric parameters.

Competing interests

The authors have no competing interests to declare.

Availability of data and material

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Funding

The present study is funded by Mashhad University of Medical Sciences, Mashhad, Iran.

Acknowledgments

The authors would like to thank the Vice-Chancellor of Mashhad University of Medical Sciences for their financial support of the present study.

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