

Investigating the Utility of Red Blood Cell Distribution Width as a Prognostic Indicator for Deterioration of Patients with Chronic Obstructive Pulmonary Disease Within One Year

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Background: Considerable studies have demonstrated a significant association between red blood cell distribution width (RDW) and clinical adverse events in cardiovascular or respiratory diseases, infections, and pulmonary embolism. However, there are limited data on prognostic predictions for patients suffering from chronic obstructive pulmonary disease (COPD).

Methods: This study conducted a retrospective cohort analysis using data gathered from patients who diagnosed with COPD in the respiratory department of The Central hospital of Enshi Tujia and Miao Autonomous Prefecture between 2018 and 2021. Specifically, the RDW was recorded on their first admission. Multivariate logistic regression analysis were employed to examine the correlation between RDW and deterioration of COPD within one-year period.

Results: The cohort of 1799 patients in the study comprised 74.7% male and had an average age of 68.9 ± 9.9 years. The fully adjusted model revealed that, the RDW-middle group ($\leq 13.7, > 12.8$; OR 1.5, 95% CI 1.0–2.3, $p=0.055$) and the RDW-high group (> 13.7 ; OR 1.7, 95% CI 1.1–2.6, $p=0.013$) had a 50% and 70% increased risk of deterioration within 1 year, respectively, in comparison with the RDW-low group (≤ 12.8). Subgroup analysis indicated that this trend was more significant in patients with hypertension (p for interaction = 0.016), and the probability of deterioration within 1 year in the RDW-high group was 3.3 times higher compared to the RDW-low group (OR 3.3, 95% CI 1.4–7.9, $p=0.008$).

Conclusion: A significant association was observed between the increase in RDW and the heightened risk of deterioration within a year in patients diagnosed with COPD. Most importantly, our findings suggested the importance of RDW in enhancing the risk stratification and prevention of deterioration of COPD.

Keywords: red blood cell distribution width, COPD, prognosis, deterioration, risk stratification

Introduction

Chronic obstructive pulmonary disease (COPD) is a medical disease marked by chronic respiratory symptoms and persistent airflow obstruction caused by abnormalities in the airway or alveoli. The Global Burden of Disease study forecasts that the number of individuals worldwide suffering from COPD will exceeds 170 million.¹ Globally, COPD ranks as the third greatest prevalent cause of mortality, claiming the lives of over 3 million people annually.² Investigating the mechanisms underlying acute exacerbation and deterioration of COPD, as well as early detection and risk reduction to mitigate future disease progression, are critical goals in COPD management. Additionally, they serve as significant strategies to alleviate disease burden, avert irreversible lung damage, and prevent premature mortality.³

More and more studies have found that mMRC or CAT score,⁴ BODE index,⁵ and frailty⁶ are clinical indicators of worse prognosis in patients with COPD. Unfortunately, the current state of clinical practice, particularly in patients experiencing severe exacerbations, does not align with the process of testing and assessment. In recent years, there has been extensive use of blood sample collection owing to its inherent benefits, including little danger, high patient adherence, and improved repeatability. Eosinophils,⁷ hypercapnia,⁸ plasma fibrinogen,⁹ and interleukin family, C-reactive protein¹⁰ have been identified as biomarkers that indicate a poor prognosis in COPD patients.

Red Cell Distribution Width (RDW) is a hematological parameter reflecting the variability in red blood cell size. Elevated RDW has been closely associated with increased mortality in various diseases.¹¹ Further research has demonstrated its close correlation with pathophysiological processes such as inflammation, cardiovascular diseases, and infections.¹² Patients with Chronic Obstructive Pulmonary Disease (COPD) experience chronic hypoxemia and inflammatory states, which can impact red blood cell production and function, potentially leading to an increase in RDW.¹³ However, the prognostic significance of RDW in predicting exacerbations of COPD remains unclear. This study aims to investigate the role of RDW in predicting disease deterioration in COPD patients.

Materials and Methods

Study Population

Between January 2018 and December 2021, patients diagnosed with COPD who were admitted to the Department of Respiratory and Critical Care Medicine at The Central hospital of Enshi Tujia and Miao Autonomous Prefecture participated in this retrospective study. Patients were chosen on the basis of the International Classification of Diseases, Tenth Revision (ICD-10) codes (J44, J440, J449). This research only considered the first admission for patients. Exclusion criteria: Patients with hospital stays less than 24 hours and missing key data, such as RDW values, will be excluded. This study employed outcome measures more aligned with real-world clinical practice, focusing on deterioration within 1 year post-diagnosis, defined as re-hospitalization due to COPD exacerbation during this period. The follow-up deadline was December 2022. The ethics committee of The Central hospital of Enshi Tujia and Miao Autonomous Prefecture granted clearance of the study protocol (Granted number: 2024-004-01). It strictly complied with the principles defined in the Declaration of Helsinki. Due to the anonymity of the analysis and the protection of the data, informed consent waivers were obtained.

Data Collection

Laboratory data and general information such as Gender, Age, Hypertension, Type 2 diabetes, Heart failure, Coronary atherosclerotic heart disease, and Respiratory failure were obtained by reviewing the hospital's electronic medical record system.

Laboratory data included Red blood cell (RBC) distribution width CV, Lymphocyte to monocyte ratio (LMR), Platelet to lymphocyte ratio (PLR), Neutrophil to lymphocyte ratio (NLR), Platelet to white blood cell ratio (PWR), and Platelet to hemoglobin ratio (PHR). These were the initial examination results obtained upon admission.

Statistical Analysis

Categorical variables were expressed as frequencies (percentages), and group differences were evaluated using either the Chi-square test or Fisher's exact test. Continuous variables were reported as mean $\pm$ standard deviation (SD) or median (quartile), and intra-group comparisons were performed using either the *T*-test or Mann-Whitney test. An independent correlation between RDW and an unfavorable prognosis in COPD was investigated in this study via Multivariate Logistic regression. The Odds ratio (OR) and 95% confidence interval (95% CI) were used to determine the second to third quantiles of the RDW, with the first quantile serving as the reference point. In addition to the original model, Model 1 included adjustments for Gender, Age, Hypertension, Type 2 diabetes, Heart failure, Coronary atherosclerotic heart disease, and Respiratory failure, and Model 2 was additionally modified to incorporate laboratory indicators. In order to enhance the stratification of the evaluation regarding the reliability of our results, we conducted subgroup analyses and

cross-validation tests. Statistical significance was defined as a $P < 0.05$, and all statistical analyses were performed utilizing the R Foundation's statistical software package (<http://www.R-project.org>, The R Foundation).

Results

Clinical Characteristics of Enrolled Patients

In accordance with the predetermined criteria for inclusion and exclusion, the study enrolled a total of 1799 patients who were initially diagnosed with COPD in Figure 1. With the average age of 68.9 ± 9.9 years, male comprised 74.7% of the sample. In this study, there were a total of 190 patients who experienced disease deterioration, while the number of patients who did not exacerbate was 1609, as shown in Table 1. The results indicate that compared to the non-deterioration group, patients in the deterioration group had a significantly higher average age, suggesting that age may be a risk factor for COPD deterioration ($p=0.001$). Respiratory failure ($p=0.007$) and elevated red cell distribution width coefficient of variation (RDW-CV) ($p=0.009$) were more prevalent in the deterioration group, indicating a significant correlation with disease deterioration. Gender distribution also showed significant differences, with a higher proportion of male patients in the deterioration group ($p=0.051$). Although some blood indicators such as absolute neutrophil count and absolute lymphocyte count showed numerical differences between the two groups, these differences did not reach statistical significance.

Univariate Analysis of the Correlation Between RDW and COPD Deterioration

The univariate analysis results were illustrated in Table 2. In COPD patients, the univariate Logistic proportional hazards model identified a number of prognostic indicators for deterioration. These factors include Age (High group, OR 1.7, 95% CI 1.1–2.4), Respiratory failure (Type II respiratory failure, OR 1.8, 95% CI 1.2–2.6), RBC (Middle group, OR 1.6, 95% CI 1.0–2.3; High group, OR 1.8, 95% CI 1.2–2.7), and NLR (High group, OR 1.5, 95% CI 1.0–2.2).

Model Adjustment

Confounders with the potential to affect the results were taken into account in order to show independent prognostic value of RDW in Table 3. In Model 1, after accounting for age, sex, and race, the OR for the RDW-middle group was 1.5 (95% CI=1.0–2.2, $p=0.061$), while the OR for the RDW-high group was 1.7 (95% CI=1.1–2.5, $p=0.017$). After fully adjusting for Sex, Age, Hypertension, Type 2 diabetes, Heart failure, Coronary atherosclerotic heart disease, Respiratory failure, LMR, PLR, NLR, PWR, and PHR (Model 2), it was found that compared to the RDW-low group, the RDW-

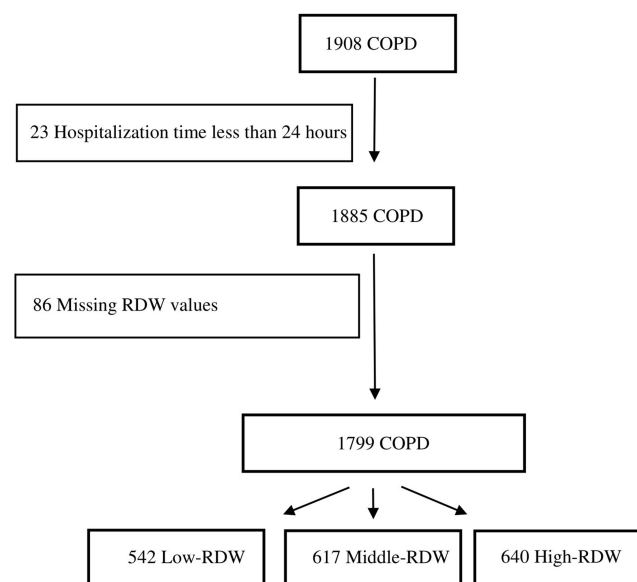


Figure 1 Study profile.

Table 1 Baseline Characteristics of the Study Population

Clinical features, laboratory indicators	No-Deterioration (N=1609)	Deterioration (N=190)	P-value
Age	68.66 (9.84)	71.07 (10.13)	0.001
Neutrophil Absolute Count	4.31 (3.16–6.16)	4.51 (3.29–6.58)	0.198
Monocyte Absolute Count	0.43 (0.32–0.58)	0.42 (0.33–0.60)	0.699
Lymphocyte Absolute Count	1.11 (0.77–1.50)	1.01 (0.75–1.38)	0.069
White Blood Cell	6.24 (4.91–8.17)	6.38 (4.94–8.29)	0.569
Red Blood Cell Distribution Width CV	13.30 (12.70–14.10)	13.55 (13.00–14.20)	0.008
Platelet	186.40 (74.32)	184.32 (71.58)	0.714
Hemoglobin	126.00 (114.00–139.00)	126.50 (115.00–138.00)	0.725
LMR	2.64 (1.72–3.95)	2.49 (1.62–3.73)	0.195
PLR	157.52 (110.67–242.51)	170.20 (111.08–262.14)	0.232
NLR	3.89 (2.40–6.84)	4.28 (2.74–8.33)	0.064
PWR	27.63 (20.81–35.96)	26.84 (20.31–35.92)	0.486
PHR	1.37 (1.04–1.83)	1.30 (1.05–1.82)	0.603
Sex			0.051
Female	418 (25.98%)	37 (19.47%)	
Male	1191 (74.02%)	153 (80.53%)	
Hypertension			0.608
Nothing	1246 (77.44%)	144 (75.79%)	
Have	363 (22.56%)	46 (24.21%)	
Type 2 diabetes			0.149
Nothing	1540 (95.71%)	186 (97.89%)	
Have	69 (4.29%)	4 (2.11%)	
Heart failure			0.133
Nothing	1317 (81.85%)	147 (77.37%)	
Have	292 (18.15%)	43 (22.63%)	
Coronary atherosclerotic heart disease			0.125
Nothing	1483 (92.17%)	169 (88.95%)	
Have	126 (7.83%)	21 (11.05%)	
Respiratory failure			0.007
Nothing	1136 (70.60%)	116 (61.05%)	
Type I respiratory failure	215 (13.36%)	27 (14.21%)	
Type II respiratory failure	258 (16.03%)	47 (24.74%)	
Red Blood Cell Distribution Width CV			0.009
Low(≤ 12.8)	502 (31.20%)	40 (21.05%)	
Middle($\leq 13.7, > 12.8$)	549 (34.12%)	68 (35.79%)	
High(> 13.7)	558 (34.68%)	82 (43.16%)	

Abbreviations: LMR, Lymphocyte to monocyte ratio; PLR, Platelet to lymphocyte ratio; NLR, Neutrophil to lymphocyte ratio; PWR, Platelet to white blood cell ratio; PHR, Platelet to hemoglobin ratio.

middle group (OR 1.5, 95% CI 1.0–2.3, $p=0.055$) and the RDW-high group (OR 1.7, 95% CI 1.1–2.6, $p=0.013$) had a 50% and 70% increased risk of poor prognosis in COPD patients, respectively, showing a significant level-dependent correlation between RDW levels and prognosis.

Analysis of RDW in Different Subgroups of COPD

A stratified analysis was performed in order to further investigate the predictive effect of RDW in various subgroups of COPD patients in Table 4. The results consistently shown a correlation between RDW and worse outcome in most subgroups of COPD. Particularly, there was a substantial correlation between hypertension and RDW levels. In patients with hypertension, the risk of deterioration within one year was significantly greater in the RDW-high group compared to the RDW-low group. Specifically, the risk was 3.3 times higher in the RDW-high group (OR 3.3, 95% CI 1.4–7.9, $p=0.008$, p for interaction = 0.016) than that of the RDW-low group.

Table 2 Univariate Logistic Analysis of Prognostic Factors for Chronic Obstructive Pulmonary Disease

Characteristics	Statistics	OR (95% CI)	P value
Sex			
Female	455 (25.3%)	1	
Male	1344 (74.7%)	1.5 (1.0, 2.1)	0.052
Age	68.9 ± 9.9	1.0 (1.0, 1.0)	0.002
Age tertile			
Low	563 (31.3%)	1	
Middle	632 (35.1%)	1.0 (0.7, 1.5)	0.990
High	604 (33.6%)	1.7 (1.1, 2.4)	0.008
Hypertension			
Nothing	1390 (77.3%)	1	
Have	409 (22.7%)	1.1 (0.8, 1.6)	0.608
Type 2 diabetes			
Nothing	1726 (95.9%)	1	
Have	73 (4.1%)	0.5 (0.2, 1.3)	0.158
Heart failure			
Nothing	1464 (81.4%)	1	
Have	335 (18.6%)	1.3 (0.9, 1.9)	0.134
Coronary atherosclerotic heart disease			
Nothing	1652 (91.8%)	1	
Have	147 (8.2%)	1.5 (0.9, 2.4)	0.127
Respiratory failure			
Nothing	1252 (69.6%)	1	
Type I respiratory failure	242 (13.5%)	1.2 (0.8, 1.9)	0.361
Type II respiratory failure	305 (17.0%)	1.8 (1.2, 2.6)	0.002
RBC distribution width CV			
Low	542 (30.1%)	1	
Middle	617 (34.3%)	1.6 (1.0, 2.3)	0.034
High	640 (35.6%)	1.8 (1.2, 2.7)	0.002
LMR			
Low	600 (33.4%)	1	
Middle	599 (33.3%)	0.8 (0.5, 1.1)	0.175
High	600 (33.4%)	0.7 (0.5, 1.0)	0.064
PLR			
Low	600 (33.4%)	1	
Middle	599 (33.3%)	1.0 (0.7, 1.4)	0.931
High	600 (33.4%)	1.2 (0.8, 1.7)	0.309
NLR			
Low	600 (33.4%)	1	
Middle	599 (33.3%)	1.2 (0.8, 1.7)	0.426
High	600 (33.4%)	1.5 (1.0, 2.2)	0.033
PWR			
Low	600 (33.4%)	1	
Middle	599 (33.3%)	0.9 (0.6, 1.2)	0.411
High	600 (33.4%)	0.8 (0.6, 1.2)	0.306
PHR			
Low	600 (33.4%)	1	
Middle	599 (33.3%)	1.0 (0.7, 1.4)	0.992
High	600 (33.4%)	0.9 (0.6, 1.3)	0.637

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval; RBC, Red blood cell; LMR, Lymphocyte to monocyte ratio; PLR, Platelet to lymphocyte ratio; NLR, Neutrophil to lymphocyte ratio; PWR, Platelet to white blood cell ratio; PHR, Platelet to hemoglobin ratio.

Table 3 Association Between RDW Levels and Worse Outcome in Different Models

RDW	Model 1		Model 2	
	OR (95% CI)	P value	OR (95% CI)	P value
RBC distribution width CV				
Low	1		1	
Middle	1.5 (1.0, 2.2)	0.061	1.5 (1.0, 2.3)	0.055
High	1.7 (1.1, 2.5)	0.017	1.7 (1.1, 2.6)	0.013

Notes: Adjust I model adjust for: Sex, Age, Hypertension, Type 2 diabetes, Heart failure, Coronary atherosclerotic heart disease, Respiratory failure Adjust II model adjust for: Sex, Age, Hypertension, Type 2 diabetes, Heart failure, Coronary atherosclerotic heart disease, Respiratory failure, LMR, PLR, NLR, PWR, PHR.

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval; RDW, red blood cell distribution width; RBC, Red blood cell; LMR, Lymphocyte to monocyte ratio; PLR, Platelet to lymphocyte ratio; NLR, Neutrophil to lymphocyte ratio; PWR, Platelet to white blood cell ratio; PHR, Platelet to hemoglobin ratio

Table 4 Subgroup Analysis of the Relationship Between RDW Levels and Outcomes

RDW	N	Low	Middle		High		P value for interaction
			OR (95% CI)	P value	OR (95% CI)	P value	
Sex							0.841
Female	455	1	2.3 (0.8, 6.6)	0.127	2.9 (1.1, 8.0)	0.040	0.016
Male	1344	1	1.5 (0.9, 2.3)	0.098	1.7 (1.1, 2.7)	0.015	
Hypertension							0.573
Nothing	1390	1	1.6 (1.0, 2.5)	0.046	1.5 (1.0, 2.4)	0.057	0.561
Have	409	1	1.5 (0.6, 3.9)	0.396	3.3 (1.4, 7.9)	0.008	
Type 2 diabetes							0.555
Nothing	1726	1	1.5 (1.0, 2.3)	0.037	1.8 (1.2, 2.6)	0.005	0.118
Have	73	1	inf. (0.0, Inf)	0.995	inf. (0.0, Inf)	0.994	
Heart failure							0.527
Nothing	1464	1	1.8 (1.1, 2.7)	0.013	1.9 (1.2, 3.0)	0.005	0.527
Have	335	1	0.6 (0.2, 1.9)	0.397	1.0 (0.4, 2.6)	0.990	
Coronary atherosclerotic heart disease							0.527
Nothing	1652	1	1.6 (1.0, 2.4)	0.036	1.9 (1.2, 2.9)	0.003	0.527
Have	147	1	1.1 (0.3, 3.9)	0.907	1.2 (0.3, 4.4)	0.740	
Respiratory failure							0.527
Nothing	1252	1	1.9 (1.1, 3.1)	0.019	2.6 (1.5, 4.3)	<0.001	0.527
Type I respiratory failure	242	1	0.7 (0.3, 2.0)	0.550	0.5 (0.2, 1.4)	0.216	
Type II respiratory failure	305	1	1.5 (0.6, 3.8)	0.399	1.2 (0.5, 2.8)	0.681	
Age tertile							0.527
Low	563	1	1.9 (0.8, 4.2) 0.135		2.6 (1.2, 5.6)	0.015	0.527
Middle	632	1	1.2 (0.6, 2.6) 0.564		1.6 (0.8, 3.1)	0.200	
High	604	1	1.5 (0.8, 2.8) 0.239		1.5 (0.8, 2.8)	0.197	

Abbreviations: OR, Odds ratio; 95% CI, 95% confidence interval; RDW, red blood cell distribution width.

Discussion

The primary discovery of this study revealed a significantly association between RDW and COPD deterioration within one year in COPD patients. This suggested that the initial RDW levels upon admission might use as a robust and independent predictor of unfavorable outcomes in COPD patients one year after being discharged.

Heterogeneity in the volume of red blood cell is reflected by RDW. Patients with COPD often have hypoxemia and may potentially develop respiratory failure during episodes of acute exacerbation. The body's compensatory response to tissue hypoxia is first seen as an elevation in the secretion of erythropoietin by the renal cortex. This results in the

imbalance of red blood cell homeostasis and the increase of red blood cell size distribution.¹³ At the same time, acute inflammation is also a significant factor contributing to a worse prognosis in COPD. During the stage of systemic inflammatory response, there is an intensification of the pro-inflammatory response, leading to a surge of cytokines and a disruption in the balance of the body's inflammatory and immune system reactions. Red blood cell maturation is inhibited by the release of pro-inflammatory cytokines, leading to the generation of ineffectual red blood cells and an increase in the heterogeneity of red blood cells.¹⁴ Additionally, several studies have shown a significant relationship between nutritional indicators, such as albumin, and RDW.¹⁵ Furthermore, studies has shown a strong correlation between elevated RDW and renal insufficiency.¹⁶ Overall, the increase in RDW may be implicated in several pathogenic mechanisms, such as heightened oxidative stress, infection, malnutrition, and renal impairment, which might coexist in patients with unfavorable prognosis of COPD.

Multiple studies have consistently shown a correlation between RDW and unfavorable prognosis and even mortality in critically sick patients. A retrospective study conducted by Meynaar et al¹⁷ analyzed 2915 patients who were hospitalized to the intensive care unit (ICU) and discovered that higher levels of RDW at admission were linked to patient mortality. RDW was demonstrated to remain an independent risk factor for mortality even after the adjustment for APACHE II score, age, type of admission, and mechanical ventilation. In a retrospective study on a wide range of ICU patients by Fernandez et al,¹⁸ it was discovered that elevated levels of RDW was identified as an indicator of in-hospital mortality following ICU discharge. Furthermore, it was seen that the inclusion of RDW measurements enhanced the predictive accuracy of the Sabadell score in determining mortality in the general ward. Researchers have recently focused extensively on the severity and mortality of RDW and COPD. An association between RDW and the categorization of COPD patients based on GOLD was found to be statistically significant by Tertemiz et al.¹⁹ Additionally, they observed that the RDW group exhibited a greater mortality rate than the RDW-low group (69% vs 25%). In a cohort of 539 patients with acute exacerbations of COPD, Epstein et al²⁰ discovered a noteworthy correlation between elevated RDW levels at admission and unfavorable outcomes, including readmission or mortality within 60 days following discharge (OR 1.83; 95% CI 1.22–2.74). According to a comprehensive study,²¹ including 3244 severely sick COPD patients in the MIMIC database, it was shown that a rise in RDW was linked to a higher likelihood of 28-day all-cause mortality, which was established using multivariate Logistic regression analysis. As far as we know, this study was a comprehensive study conducted in China, utilizing a substantial sample size, and its findings align with the results mentioned above.

Moreover, we discovered that the proportion of COPD patients with heart failure and coronary heart disease in the RDW-high group was significantly higher compared to that in the RDW-low group. At the same time, among patients with hypertension, the RDW-high group had a notably elevated risk of unfavorable prognosis compared to the RDW-low group. One potential reason is that higher RDW values reflect the complexity of multiple pathological mechanisms to some degree. A clear association exists between the number of comorbidities and the effect on RDW levels, which suggests an increased likelihood of a negative prognosis. Acute respiratory failure in patients induces the activation of reactive oxygen species, resulting in the release of a substantial amount of immature red blood cells into the circulation, which subsequently causes an elevation in RDW. Previous studies have shown²² that even after adjusting for multiple confounding factors, a high level of RDW remained an independent risk factor for mechanical ventilation (OR 2.6; 95% CI 1.4–4.9; $p=0.004$). This is similar to our findings that respiratory failure was associated with high levels of RDW. Finally, our study results highlight that RDW can serve as an early marker in blood tests to predict disease exacerbation in COPD patients in the following year. Future research should explore integrating RDW with other biomarkers into predictive models to improve prognostic accuracy. Moreover, long-term studies are needed to elucidate RDW's role in predicting mortality and its broader impact on COPD management.

Research Limitation

RDW is a laboratory parameter that is practical, repeatable, and inexpensive, and it has a high level of operability. In clinical practice, it is feasible to promptly acquire clinical data for patients with COPD upon admission, promptly assess the patients' risk, and choose the most suitable treatment for each patient individually. However, COPD is an unstable disease, and the RDW in the same patient may vary over time. In addition, considering the complexity of COPD, a combination of multiple markers will be more accurate in predicting prognosis, which is the avenue our team intends to

investigate further. Generally speaking, this study is a retrospective study that exclusively utilizes clinical data, and is conducted at a single clinical center. The findings of this investigation, therefore, need validation by larger-scale and multicenter prospective clinical trials.

Conclusion

Our study identified a notable correlation between elevated RDW levels and an increased risk of deterioration within a year among COPD patients. These findings underscore the potential of RDW as a crucial marker for enhancing risk assessment and preventive strategies aimed at managing COPD exacerbations.

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Disclosure

The authors declare that there are no competing interests in this work.

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