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Association of Red Cell Distribution Width and 1-year Hospital Readmission in Chronic Obstructive Pulmonary Disease Patients: A Retrospective Cohort Study

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Abstract

Objectives: This retrospective cohort study aimed to investigate the relationship between admission RDW-SD and 1-year COPD-related readmission in patients with AECOPD. Methods: A total of 875 patients with AECOPD admitted to the Second People's Hospital of Banan District in Chongqing, China, between January 2023 and December 2023 were enrolled. Patients were divided into quartiles according to admission RDW-SD levels. Cox regression models, Kaplan–Meier analysis, and RCS regression were used to evaluate the association. Results: The 1-year COPD-related readmission rate was 34.5% (n = 304). After adjustment for comprehensive confounders, patients in the highest RDW-SD quartile had a 59% higher risk of 1-year readmission compared with those in the lowest quartile (HR = 1.59, 95% CI: 1.11–2.26, P = 0.011). Kaplan–Meier curves revealed that higher RDW-SD was associated with increased readmission risk over follow-up (Log-rank P < 0.001). RCS regression confirmed a linear association between RDW-SD and readmission risk. Subgroup analyses demonstrated that this association remained stable across most subgroups, with only sex showing a significant interaction effect. Conclusion: Our findings indicate that admission RDW-SD is an independent predictor of 1-year COPD-related readmission in patients with AECOPD, with a linear dose-response relationship. This easily accessible biomarker could help clinicians identify high risk patients for targeted post-discharge interventions.

Keywords: chronic obstructive pulmonary disease, red blood cell distribution width,

readmission, prognosis

1.Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by persistent expiratory airflow limitation, chronic airway inflammation and/or emphysema[1,2]. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2026 report, the number of COPD cases globally is substantial and increasing, and it is projected to approach nearly 600 million by 2050. COPD is the third leading cause of death worldwide with a significant economic and social burden, and acute exacerbations of COPD (AECOPD) account for the greatest proportion of the total COPD burden on the healthcare system [3,4]. Therefore, it is desirable to find easily accessible biomarkers that are associated with hospital readmission in patients with COPD.

Red blood cell distribution width (RDW), a numerical measure of the size variability of circulating erythrocytes, reflects the degree of heterogeneity in red blood cell volume[5,6]. Previous studies have demonstrated that RDW has been linked to systemic inflammation and has strong prognostic value for many systemic diseases such as cardiovascular diseases, connective tissue diseases, diabetes and respiratory diseases [7-11]. In various studies, RDW is related to mortality in patients with COPD [12,13], and can predict COPD severity [14,15]. Mengpei Zhu [16] confirmed that the dynamic increase of RDW is an independent prognostic factor of 30-day all-cause readmission of patients with AECOPD. However, there is limited studies about the relationship between RDW and long-term readmission in AECOPD patients. We aimed to explore the role of RDW in predicting readmission risk in COPD patients.

2. Materials and methods

2.1 Study design and population

We retrospectively collected patients with COPD admitted to the hospital due to acute exacerbation from January 2023 to December 2023 in the Second People's Hospital of Banan District in Chongqing. The inclusion criteria were as follows: (1) patient age ≥40 years; (2) the diagnosis of COPD was confirmed by the pulmonary function test of airflow obstruction, with post-bronchodilator forced expiratory volume in one second/forced vital capacity (FEV1/FVC) < 70%. Acute exacerbation was defined as increased dyspnea and/or cough and sputum that may be accompanied by tachypnea and/or tachycardia over a few days (up to 14 days) [3,16]. The exclusion criteria were as follows: (1) patients diagnosed with uncured malignancy, active

tuberculosis, pleural effusions, immune diseases and acute coronary syndrome (ACS); (2) patients with missing data on RDW and other covariates. Our study did not include patients who died during the index hospitalization.

This retrospective cohort study was conducted in accordance with the tents of the Declaration of Helsinki. The research protocol was received approval from the Ethics Committee of the Second People's Hospital of Banan District in Chongqing. Due to the retrospective design of this study, obtaining informed consent from the participants was not necessary.

2.2 Data collection

All demographic were collected for all patients at admission, including age, sex, height, weight, smoking status, comorbidities. Laboratory parameters, such as blood routine, arterial blood gas analysis, chest computed tomography (CT), were obtained within 24 hours after admission. Information pertaining to hospitalizations on file up to one year following the index hospitalization was also extracted through the electronic medical system.

The main independent variable was RDW-standard deviation (RDW-SD) on the first inpatient blood routine available during the index hospitalization. In accordance with RDW-SD, all patients were divided into quartiles. The outcome was 12-month COPD-related readmission.

2.3 Statistical analyses

Categorical variables were expressed as proportions (%) and tested with Chi-square test. Normally distributed continuous variables were reported as mean ± standard deviation (SD) and tested with one-way ANOVA, non-normally distributed were reported as median and interquartile range (IQR) and tested with Kruskal-Wallis H-test.

Cox regression models were used to evaluate the association between RDW and the risk of readmission, with hazard ratios and their 95% confidence intervals calculated. Four models were constructed: Model 1, unadjusted; Model 2, adjusted for age, sex, height, weight; Model 3, adjusted for age, sex, height, weight, smoking status, pack-years of smoking and comorbidities (hypertension, diabetes); Model 4, based on Model 3, but further adjusted for white blood cell count, eosinophil count, hemoglobin, Potential of Hydrogen (PH), Partial Pressure of Oxygen (PaO_2), Partial Pressure of Carbon Dioxide ($PaCO_2$) and chest CT parameters (emphysema, chronic bronchitis). The risk of readmission was assessed using Kaplan-Meier survival curves according to RDW-SD quartiles and evaluated using the Log-rank test. In addition, restricted cubic spline (RCS) regression was performed with 4 knots at the 5th, 35th, 65th, and 95th percentiles of RDW to assess linearity between RDW and

readmission after adjusting variables in Model 4.

To further explore the stability of the results, we conducted interaction and subgroup analyses based on sex, age (<65 years and ≥65 years), emphysema and chronic bronchitis. Interaction across subgroups was tested using the likelihood ratio test.

To investigate the potential mediating role of pH in the relationship between RDW and readmission for acute exacerbation of COPD, a causal mediation analysis framework based on structural equation modeling was employed. The indirect effect, direct effect, and proportion mediated were estimated using the bias-corrected percentile bootstrap method (with 5000 resamples).

For the percentage of covariates with missing data is small (<5%), missing values of covariates were imputed via multiple imputation [17]. Specifically, we imputed five sets of missing values and then selected one set for analyses. All statistical analyses were performed using R 4.2.2 and a P-value <0.05 (two-tailed) was considered statistically significant.

3.Results

3.1 Participants characteristics

Based on the above inclusion and exclusion criteria, 875 patients were included in our study (Table 1). Among all these patients, the average age of the participants was 72.7±9.4 years and 70.2% were male. Compared with the lowest quartile of RDW-SD, patients in the highest group were older and exhibited lower body weight, more smokers, diabetes and hypertension. They also had lower partial pressure of oxygen (PaO2), lower hemoglobin (Hb) levels, higher partial pressure of carbon dioxide (PaCO2), and more emphysema on CT scans.

Table 1 Baseline characteristics of the study population

Characteristics	**Participants**					
	Total	**Q1**	**Q2**	**Q3**	**Q4**	***p***
		(2.43-42.4)	**（42.5-44.4）**	**(44.5-46.9)**	**(47-84.2)**	
No.	875	209	225	222	219	
Sex, n (%)						0.182
Male	614 (70.2)	134 (64.1)	161 (71.6)	161 (72.5)	158 (72.1)	
Female	261 (29.8)	75 (35.9)	64 (28.4)	61 (27.5)	61 (27.9)	
Age, years (Mean ± SD)	72.7 ± 9.4	69.5 ± 10.0	72.5 ± 8.6	74.0 ± 9.1	74.6 ± 9.0	< 0.001
Height, cm (Mean ± SD)	159.9 ± 8.2	159.7 ± 8.2	159.7 ± 7.8	160.1 ± 8.4	160.0 ± 8.4	0.941
Weight, kg (Mean ± SD)	56.9 ± 11.7	57.3 ± 11.5	58.8 ± 10.8	56.7 ± 11.6	54.6 ± 12.5	0.002

Smoking status, n (%)						0.022
Never	355 (40.6)	102 (48.8)	86 (38.2)	94 (42.3)	73 (33.3)	
Ex-smoker	212 (24.2)	43 (20.6)	54 (24)	47 (21.2)	68 (31.1)	
Current smoker	308 (35.2)	64 (30.6)	85 (37.8)	81 (36.5)	78 (35.6)	
Smoking index, pack year (IQR)	15.0 (0.0, 40.0)	4.0 (0.0, 30.0)	15.0 (0.0, 40.0)	20.0 (0.0, 40.0)	20.0 (0.0, 40.0)	0.067
Hypertension, n (%)						0.298
No	573 (65.5)	144 (68.9)	146 (64.9)	135 (60.8)	148 (67.6)	
Yes	302 (34.5)	65 (31.1)	79 (35.1)	87 (39.2)	71 (32.4)	
Type 2 diabetes, n (%)						0.091
No	785 (89.7)	182 (87.1)	196 (87.1)	204 (91.9)	203 (92.7)	
Yes	90 (10.3)	27 (12.9)	29 (12.9)	18 (8.1)	16 (7.3)	
WBC, 10^9/L (Mean ± SD)	8.2 ± 4.5	8.0 ± 3.5	8.4 ± 4.5	8.1 ± 3.3	8.2 ± 6.1	0.753
Eosinophil, 10^9/L (Mean ± SD)	0.2 ± 0.3	0.1 ± 0.3	0.2 ± 0.3	0.2 ± 0.3	0.2 ± 0.3	0.34
HB, g/L (Mean ± SD)	130.4 ± 19.0	130.5 ± 15.8	132.3 ± 17.6	132.2 ± 19.1	126.7 ± 22.6	0.006
PH, (Mean ± SD)	7.4 ± 0.0	7.4 ± 0.0	7.4 ± 0.0	7.4 ± 0.0	7.4 ± 0.1	< 0.001
pO2, mmHg (Mean ± SD)	83.8 ± 22.2	82.3 ± 20.2	84.0 ± 19.9	86.6 ± 25.2	82.0 ± 22.8	0.113
pCO2, mmHg (Mean ± SD)	31.8 ± 8.6	29.6 ± 6.4	31.1 ± 7.0	31.7 ± 8.5	34.8 ± 11.1	< 0.001
emphysema, n (%)						0.075
No	200 (22.9)	50 (23.9)	61 (27.1)	52 (23.4)	37 (16.9)	
Yes	675 (77.1)	159 (76.1)	164 (72.9)	170 (76.6)	182 (83.1)	
chronic bronchitis, n (%)						0.308
No	657 (75.1)	165 (78.9)	172 (76.4)	159 (71.6)	161 (73.5)	
Yes	218 (24.9)	44 (21.1)	53 (23.6)	63 (28.4)	58 (26.5)	
COPD-related readmission, n (%)						0.046
No	573 (65.5)	149 (71.3)	149 (66.2)	147 (66.2)	128 (58.4)	
Yes	302 (34.5)	60 (28.7)	76 (33.8)	75 (33.8)	91 (41.6)	

Abbreviations: WBC: white blood cell; HB: hemoglobin; PH: potential of hydrogen; pO2: partial pressure of oxygen; pCO2: partial pressure of carbon dioxide.

3.2 Associations of RDW and readmission

The 12-month COPD-related readmission rate was 34.5% (n=304). In the multivariable Cox proportional hazard model, patients in the highest RDW-SD quartile had a two times higher risk for returning to the hospital within 12 months after discharge compared to those in the lowest RDW-SD quartile (HR 2.00, 95% CI 1.44~2.79, P<0.001, Table 2). After adjusting for potential confounders, this correlation remained independent (HR 1.59, 95% CI 1.11~2.26, P=0.011, Table 2, Model 4). We used Cox regression model to generate a survival curve for each RDW group, which showed that, with increasing follow-up time, the COPD-related readmission rate increased with higher RDW-SD levels (log-rank test P<0.001, Figure 1). Restricted cubic spline curves indicated a linear relationship between RDW-SD and readmission rate after adjusting for confounders (P for non-linearity=0.742, Figure 2).

Table 2Multivariate Cox regression analysis on associations between RDW-SD and 1-year COPD-related readmission

RDW	No.	Event (%)	Model 1		Model 2		Model 3		Model 4	
			HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Quartiles										
Q1	209	60 (28.7)	1(Reference)		1(Reference)		1(Reference)		1(Reference)	
Q2	225	76 (33.8)	1.46 (1.04~2.07)	0.03	1.41 (1~2.01)	0.053	1.43 (1.01~2.04)	0.045	1.35 (0.94~1.93)	0.099
Q3	222	75 (33.8)	1.44 (1.02~2.04)	0.036	1.35 (0.95~1.92)	0.09	1.42 (1~2.03)	0.051	1.34 (0.94~1.92)	0.105
Q4	219	91 (41.6)	2 (1.44~2.79)	<0.001	1.85 (1.32~2.6)	<0.001	1.85 (1.31~2.61)	<0.001	1.59 (1.11~2.26)	0.011
Trend test	875	302 (34.5)		<0.001		0.001		0.001		0.017

Model 1: unadjusted model.
Model 2: adjusted for age, sex, height, weight.
Model 3: adjusted for age, sex, height, weight, smoking status, smoking index, hypertension, Type 2 diabetes.
Model 4: adjusted for age, sex, height, weight, smoking status, smoking index, hypertension, Type 2 diabetes, WBC, neutrophil, HB, PH, pO2, pCO2, emphysema, chronic bronchitis.

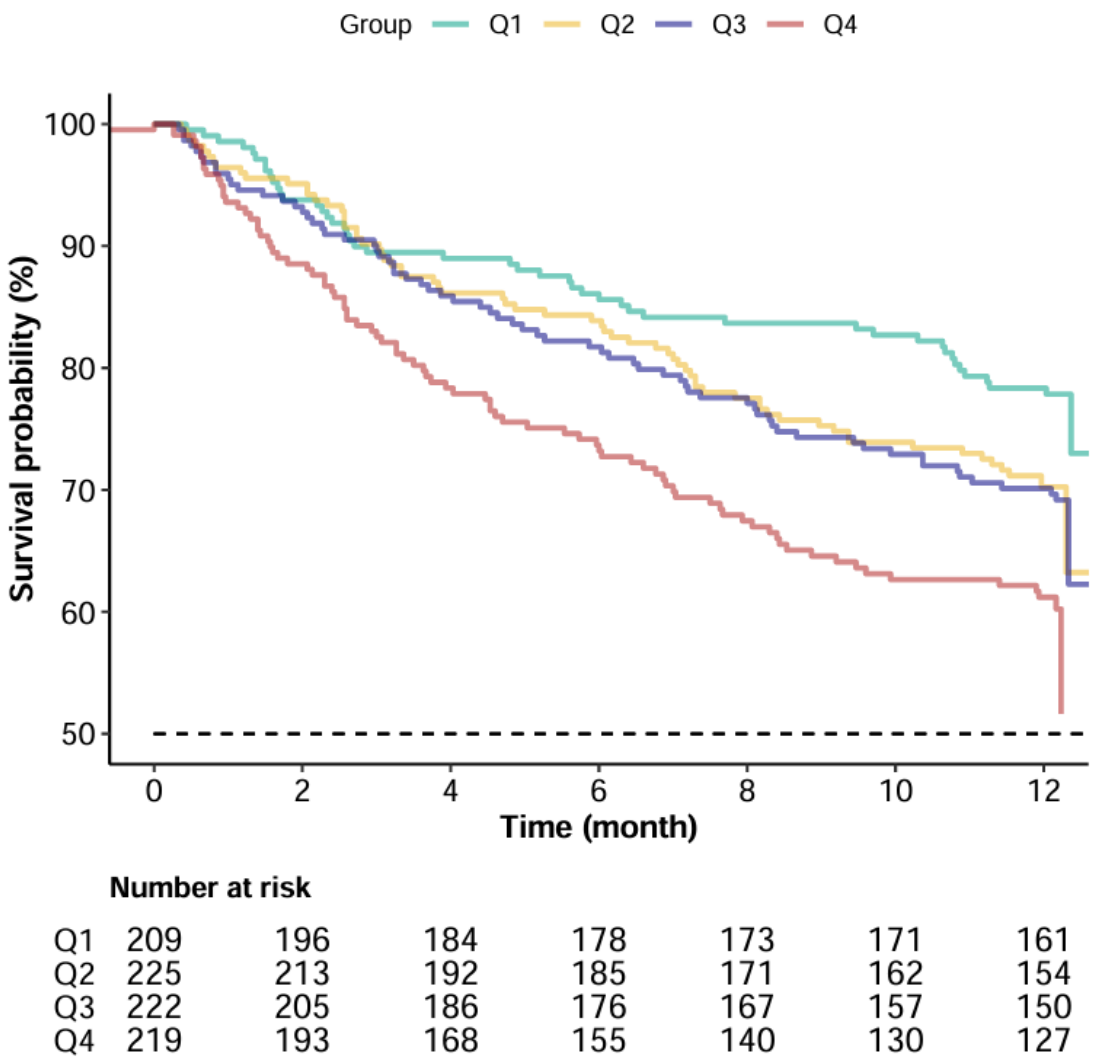


Figure 1 A Kaplan-Meier survival curve of RDW-SD with COPD-related readmission

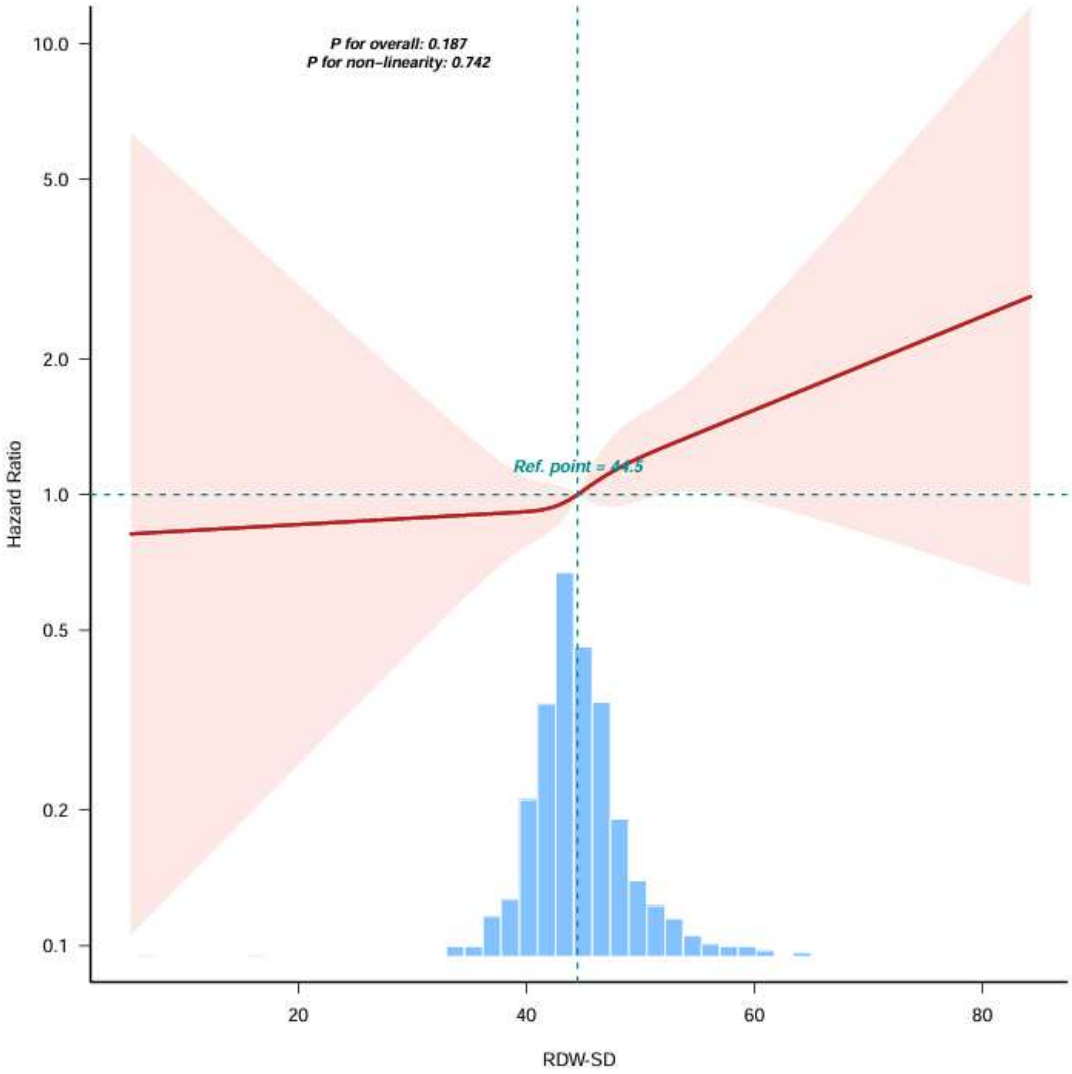


Figure 2 The RCS curve showed a dose response between RDW-SD and COPD-related readmission. Adjusted for age, sex, height, weight, smoking status, smoking index, hypertension, Type 2 diabetes, WBC, neutrophil, HB, PH, pO2, pCO2, emphysema, chronic bronchitis

3.3 Subgroup analyses

Stratified analyses were conducted based on sex (male, female), age (<65 years, ≥65 years), emphysema (yes, no), chronic bronchitis (yes, no). The results revealed that the association between RDW-SD and readmission in patients with AECOPD generally remained stable across different subgroups (Figure 3). However, only sex showed an interaction between RDW-SD and readmission (P for interaction=0.01).

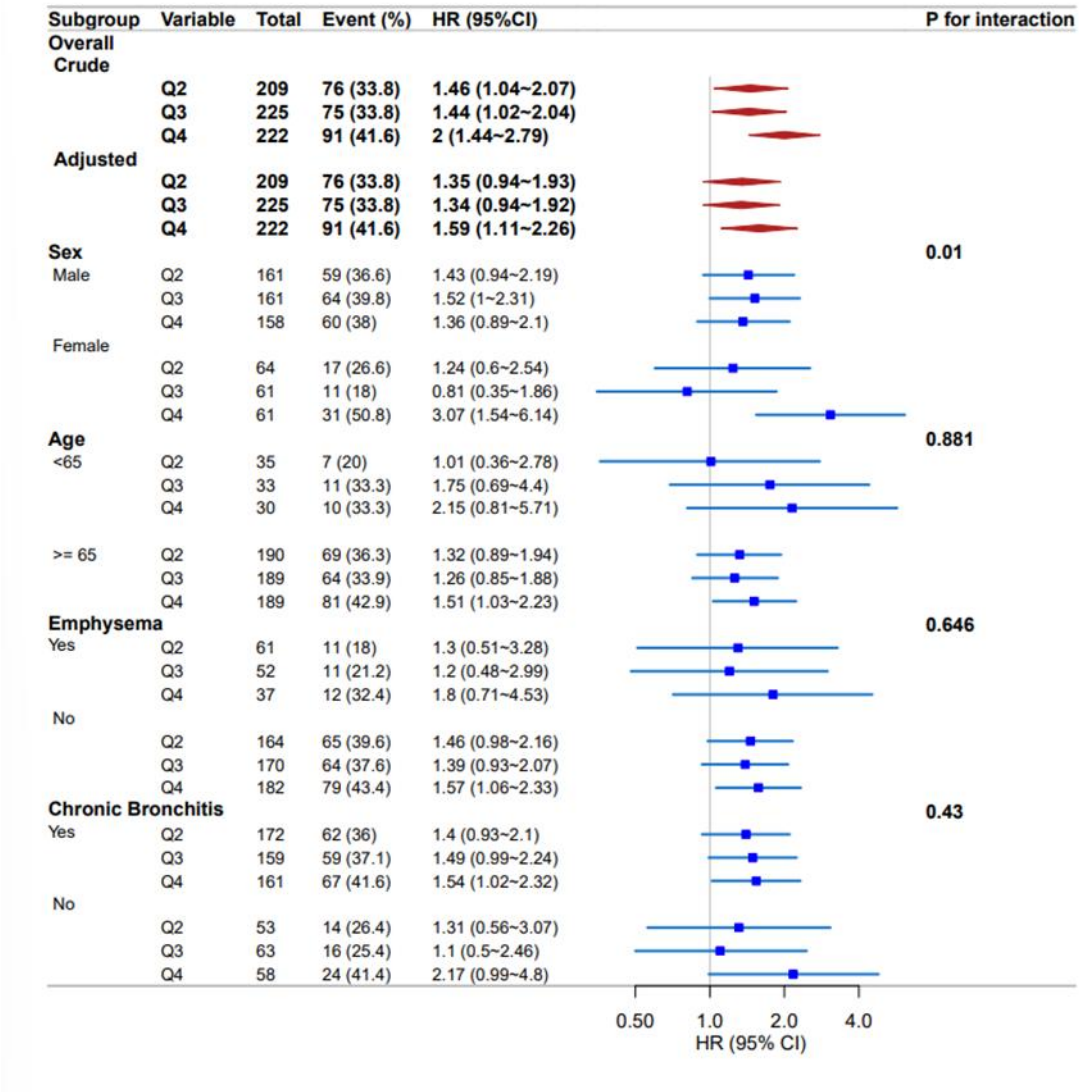


Figure 3 Associations between RDW-SD and COPD-related readmission among subgroups

3.4 Mediating Effect of Arterial Blood pH

The results of the mediation analysis of arterial blood pH in the relationship between RDW and readmission risk are presented in Figure 4. The total effect of RDW on readmission risk was significant (HR 1.033 per 1-fL increase, 95% CI 1.007–1.061, P = 0.012). This effect was decomposed into direct and indirect effects: after controlling for pH, the direct effect of RDW remained significant (HR=1.026, 95% CI: 1.000–1.052, P=0.048); The indirect effect through arterial pH was β = 0.0068 (95% CI 0.0030–0.0129), corresponding to an HR ratio of 1.007 (95% CI 1.003–1.013), and the proportion mediated was 20.7% (95% CI, add bootstrap value). These results indicated that arterial blood pH played a significant partial mediating role in the

relationship between RDW and 1-year readmission risk.

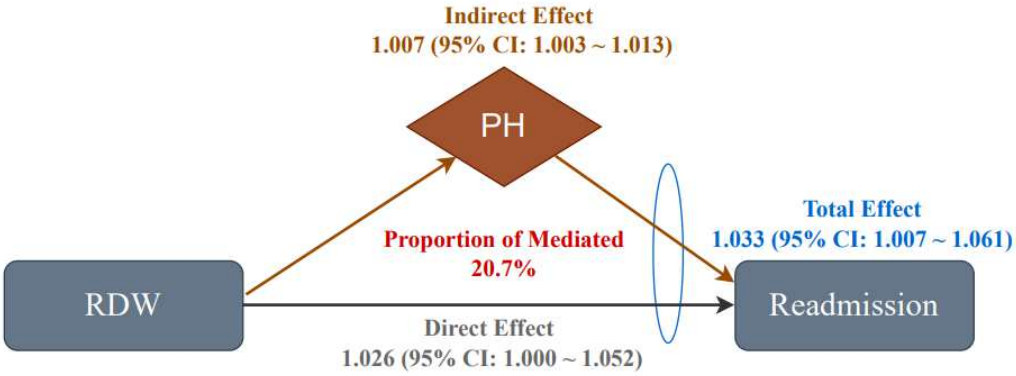


Figure 4 The mediating effect of PH on the relationship between RDW-SD and hospital readmission among chronic obstructive pulmonary disease patients. Adjusted for age, sex, height, weight, smoking status, smoking index, hypertension, Type 2 diabetes, WBC, neutrophil, HB, PH, pO2, pCO2, emphysema, chronic bronchitis

4.Discussion

This retrospective cohort study demonstrated the relationship between RDW-SD levels and the risk of 1-year COPD-related readmission in patients with AECOPD. This association remained significant after adjustment for multiple potential confounders, exhibited a linear dose–response relationship, and showed no evidence of a threshold effect; higher RDW-SD levels were associated with an increased risk of readmission. Furthermore, subgroup analyses confirmed that this predictive effect was consistent across subgroups stratified by age, and the presence of emphysema or chronic bronchitis, indicating the robustness of our findings. This finding provided novel mechanistic insights into the prognostic role of RDW in AECOPD patients: elevated RDW may be linked to acid-base imbalance in this population, which in turn contributed to the increased risk of subsequent readmission. This was consistent with previous evidence that abnormal pH at discharge was associated with adverse post-discharge outcomes in AECOPD patients[18], which further validated our findings.

Previous studies have demonstrated the prognostic value of RDW in patients with COPD, but most have focused on short-term outcomes or mortality. For example, Zhu et al. and Ephrem G et al. found that dynamic increase in RDW was an independent predictor of 30-day all cause readmission in patients with AECOPD [16,19]. Another study by Epstein et al. reported that increased RDW was associated with 60-day adverse outcomes, including readmission after

AECOPD hospitalization [18]. However, evidence regarding long-term readmission risk, particularly 1-year outcomes, has been limited. Our study extends these findings by confirming that RDW is associated with 1-year readmission risk, providing new evidence for the long-term prognostic role of RDW in patients with AECOPD.

Consistent with our results, several previous studies have also indicated an association between RDW and long-term prognosis in COPD. Hu et al. found that RDW was an independent risk factor for 1-year mortality in patients with AECOPD [12], supporting the prognostic value of RDW for long-term outcomes. Marvisi et al. reported that RDW was correlated with the risk of exacerbations in patients with COPD, which aligns with our finding that higher RDW predicted higher readmission risk, as readmission is mostly triggered by acute exacerbations [20]. Collectively, these findings suggest that RDW could serve as a reliable biomarker for both short-term and long-term adverse outcomes in COPD.

The underlying mechanism linking elevated RDW to increased readmission risk is likely multifactorial. First, RDW is closely related to systemic inflammation, a key feature of COPD. Previous studies have found that RDW is positively correlated with inflammatory markers such as C-reactive protein (CRP), ESR [21-23], indicating that elevated RDW may reflect the severity of systemic inflammation in patients with AECOPD. Severe systemic inflammation could lead to more frequent exacerbations and worse clinical outcomes, thereby increasing readmission risk. Second, malnutrition and oxidative stress, which are common in patients with COPD, could also contribute to elevated RDW [24,25]. Malnutrition can impair erythropoiesis, leading to anisocytosis, whereas oxidative stress can damage red blood cells, resulting in increased variability of red cell size. These factors may both reflect the poor nutritional and functional status of patients, which is associated with a higher risk of readmission.

Notably, our study found a linear relationship between RDW-SD and readmission risk, meaning that even a mild increase in RDW within the normal range could be associated with higher readmission risk. This finding is important because it suggests that RDW can be used as a continuous predictor rather than merely a binary marker with a fixed cutoff value. This could help clinicians better stratify patient risk, even for those with RDW values within the traditional normal range.

The strengths of our study include the relatively large sample size, comprehensive adjustment for confounders, and the use of restricted cubic spline analysis to explore the dose–response relationship. In addition, we conducted a mediation analysis to explore the underlying

mechanism, which provided new insights into the relationship between RDW and readmission risk. Furthermore, subgroup analyses confirmed the stability of our findings across different populations, enhancing the generalizability of our results. However, several limitations should be noted. First, this was a single center retrospective study, which may limit the generalizability of our findings to other populations. Second, we measured only admission RDW and did not evaluate dynamic changes in RDW during hospitalization, which might provide additional prognostic information as suggested by a previous study [16]. Third, we did not include some other potential biomarkers (such as CRP) in the adjustment, which could represent residual confounding. Future multicenter prospective studies are needed to confirm our findings.

5.Conclusion

In conclusion, our study demonstrates that admission RDWSD is an independent predictor of 1-year COPD-related readmission in patients with AECOPD, with a linear dose–response relationship. This association was stable across most subgroups, and arterial blood pH partially mediated this association. These findings indicated that RDW could be a useful, low-cost, and easily accessible biomarker for risk stratification of patients with AECOPD after discharge. Incorporating RDW into clinical risk assessment could help clinicians identify high-risk patients early and implement targeted post-discharge interventions to reduce readmission rates and improve long-term outcomes in patients with COPD.

Abbreviations

COPD Chronic Obstructive Pulmonary Disease

AECOPD acute exacerbations of COPD

RDW Red Blood cell Distribution Width

RDW-SD RDW-standard deviation

FEV1 Post-bronchodilator Forced Expiratory Volume in one second

FVC Forced Vital Capacity

PH Potential of Hydrogen

RCS Restricted Cubic Spline

Clinical trial number

Not applicable.

Human Ethics and Consent to Participate declarations

This is an observational study, and the Ethics Committee of the Second People's Hospital of Banan District approved the exemption of ethical review for this study (approval No.2025-KL-014). Due to the retrospective design of this study, obtaining informed consent from the participants was not necessary.

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Declaration of interest statement

The authors declare no financial or commercial conflict of interest in this work.

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