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CORRELATION OF THE RED BLOOD CELL DISTRIBUTION WIDTH WITH SEVERITY AND OUTCOMES OF ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Background: Red cell distribution width (RDW) has emerged as a potential marker of systemic disease severity. This study evaluated its association with severity and clinical outcomes in acute exacerbation of chronic obstructive pulmonary disease (AECOPD).
Methods: This hospital-based observational study included 101 AECOPD presentations. RDW was compared across exacerbation-severity groups and according to ventilatory support, mortality, discharge oxygen requirement, and length of stay.
Results: Mean RDW increased progressively from mild to moderate and severe exacerbations (12.91±1.26%, 14.06±1.30%, and 15.34±1.54%, respectively; p<0.001). RDW was significantly higher in patients requiring non-invasive ventilation, mechanical ventilation, and in those who died (all p<0.001). RDW correlated positively with hospital stay (r=0.433, p=0.008) and ICU stay (r=0.412, p=0.011). Its association with oxygen requirement at discharge was not significant.
Conclusion: Elevated RDW was associated with greater AECOPD severity and poorer short-term outcomes.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease of the lungs that is characterized by chronic respiratory symptoms and persistent airflow obstruction, and acute exacerbations are important events in the clinical course of COPD. Acute exacerbations of COPD (AECOPD) are an important cause of emergency department attendance, hospitalisation, worsening of health status, disease progression and death. Airway and systemic inflammation are often increased during exacerbations, and severe exacerbations can lead to respiratory failure that requires non-invasive or invasive ventilatory support [1].

Clinically relevant markers that are easily accessible and cheap to obtain and that reflect the severity and prognosis of AECOPD should therefore be identified. Red blood cell distribution width (RDW) is a parameter that is routinely reported in the complete blood count and measures the variation in the size of circulating red blood cells. RDW has traditionally been used in the differential assessment of anaemia, but increased RDW has been linked to systemic inflammation, oxidative stress, impaired erythropoiesis, nutritional deficiencies and some chronic inflammatory and cardiovascular diseases [2]. These processes are also seen in advanced COPD and during acute exacerbations, providing a biological basis for further study of RDW as a marker of COPD burden. In stable COPD patients, evidence indicated that RDW might be associated with disease severity and prognosis. Seyhan et al. showed that higher RDW was associated with inflammatory markers, right ventricular dysfunction, pulmonary hypertension, and mortality in patients with COPD [3]. The relationship of RDW with various functional measures of COPD and survival was then shown by Tertemiz et al., who further suggested that anisocytosis may be a marker of systemic effects of advanced pulmonary disease [4].

RDW has also been investigated specifically in the context of acute exacerbations. Epstein et al. reported that higher RDW was independently associated with poor short-term outcomes in patients admitted to hospital with AECOPD [5]. Hu et al. found that RDW was associated with in-hospital and 1-year mortality in a cohort of 442 patients with AECOPD; an RDW level of 13.75% identified patients at increased risk of in-hospital mortality [6]. Increased RDW has also been linked to longer hospital stays. Zhu et al. showed a positive association between RDW and hospital length of stay and found a cut-off of around 13.35% to be useful for discriminating prolonged hospital admission [7].

In addition to immediate outcomes, RDW can also be a sign of the overall exacerbation phenotype. Marvisi et al. found a relationship between higher RDW and C-reactive protein, COPD Assessment Test scores, exacerbation frequency and GOLD disease severity, indicating that RDW could combine inflammatory and clinical aspects of COPD burden [8]. However, variations in the patient population, the definition of the severity of exacerbation, underlying comorbidities, and outcome measures have led to differences in published studies.

The low cost, wide availability and the fact that no additional blood samples are required make RDW a potentially useful tool in the early identification of risk for clinically relevant AECOPD outcomes. The present study thus assessed the association of RDW with the severity of exacerbation and investigated its relationship with the need for non-invasive and mechanical ventilation, in-hospital mortality, supplemental oxygen at discharge, and hospital and intensive care unit (ICU) length of stay.

MATERIALS AND METHODS

Study design and participants

This was a hospital-based observational analytical study carried out for 18 months at a tertiary care centre in Mangalore, Mangalore, India. Adults aged >18 years presenting with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) to inpatient or outpatient services were eligible. All patients with previously diagnosed COPD and newly diagnosed cases who met the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were included; spirometry was performed at discharge in newly diagnosed cases.

Patients with renal failure, haemoglobin <10 g/dL, hospitalization for an acute infection within the preceding 7–30 days, or blood transfusion within the preceding 120 days were excluded. Written informed consent was obtained prior to enrolment. There were 101 AECOPD presentations included in the final analysis.

Sample size

The sample size was determined using Fisher's z transformation for an expected correlation coefficient of 0.407. The minimum sample size required was approximately 101 with a two-sided α of 0.05 and 99% power.

Clinical and laboratory evaluation

A structured proforma was used to record demographic characteristics, smoking history, previous hospitalisation for AECOPD, inhaler use and relevant clinical findings. Laboratory parameters evaluated were haemoglobin, red cell distribution width (RDW), mean corpuscular volume, peripheral blood smear and renal function tests. RDW was obtained from the initial haematological assessment, expressed as a percentage, and analysed as a continuous variable.

Exacerbation severity and outcomes

AECOPD severity was determined using treatment-based GOLD criteria. Short-acting bronchodilators were used for mild exacerbations, while moderate exacerbations were treated with short-acting bronchodilators and oral corticosteroids, either with or without antibiotics, and severe exacerbations required hospitalization or an emergency department visit.

Clinical outcomes were requirement for non-invasive ventilation (NIV), mechanical ventilation, in-hospital mortality, supplemental oxygen at discharge, hospital length of stay, and intensive care unit (ICU) length of stay. Mechanical ventilation and NIV were considered as separate, non-mutually exclusive outcomes. Oxygen requirement at discharge was analysed among survivors. Available positive duration records were analysed separately for hospital and ICU stay.

Statistical analysis

Data for continuous variables were presented as mean ± SD and, where appropriate, median (IQR) and range, and categorical variables as n (%). Welch's one-way analysis of variance was used to compare RDW among the mild, moderate, and severe exacerbation groups, and Welch independent-samples t-tests with Holm adjustment were used for the three pairwise comparisons.

Welch independent-samples t-tests were also performed to compare RDW based on the requirement for NIV, mechanical ventilation, mortality, and discharge oxygen requirement. Mean differences with 95% confidence intervals were reported using the Welch–Satterthwaite method.

The association of RDW with length of stay in the hospital and in the intensive care unit (ICU) was evaluated by Pearson correlation, and 95% confidence intervals were calculated using Fisher's z transformation. Sensitivity analysis was carried out using Spearman rank correlations. Available paired observations with positive documented durations were used in length-of-stay analyses and no imputations were made for missing values.

The tests were all two-sided and $p<0.05$ was deemed statistically significant. Severity pairwise comparisons were performed with Holm-adjusted p-values, while other outcome comparisons were exploratory and unadjusted. SPSS was used for analyses.

Ethical considerations

The study was approved by the Institutional Ethics Committee ofertiary care centre in Mangalore. All participants gave written informed consent, and confidentiality was ensured throughout the study.

RESULTS

Cohort characteristics

A total of 101 presentations with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) were included in the analysis. Mean age was 70.82 ± 10.33 years, and 72 (71.3%) were male. Previous hospitalization for AECOPD was reported in 61 (60.4%). Baseline demographic characteristics, treatment history and haematological measurements are summarized in Table 01.

Mean red cell distribution width (RDW) was 14.19 ± 1.72%, with a median of 14.20% (interquartile range [IQR], 13.00–15.20%) and a range of 10.00–18.10%. Severe exacerbations accounted for 40 (39.6%) presentations, while the remaining presentations were classified as mild or moderate.

RDW and exacerbation severity

RDW increased across exacerbation categories, with an overall difference between groups on Welch analysis of variance (Table 2). Mean RDW was 12.91 ± 1.26% in mild exacerbations, 14.06 ± 1.30% in moderate exacerbations and 15.34 ± 1.54% in severe exacerbations. The distribution of individual values showed overlap between categories despite the higher central values in the severe group (Figure 01).

All three pairwise comparisons remained statistically significant after Holm adjustment. The largest contrast was between severe and mild exacerbations, with a mean difference of 2.43 percentage points (95% confidence interval [CI], 1.78–3.09). Moderate exacerbations also had higher RDW than mild exacerbations, and severe exacerbations had higher RDW than moderate exacerbations. Detailed effect estimates and test statistics are presented in Table 02.

Ventilatory support and mortality

Non-invasive ventilation was required in 36 (35.6%) presentations and mechanical ventilation in 31 (30.7%); 30 (29.7%) received both forms of support. Death occurred in 13 (12.9%). RDW was higher in those requiring either form of ventilation and in those who died (Table 3).

The mean RDW differences were 1.88 percentage points for non-invasive ventilation and 1.67 percentage points for mechanical ventilation. The mortality contrast was 2.25 percentage points (95% CI, 1.40–3.09). All three comparisons had p<0.001, and their confidence intervals excluded zero.

Oxygen requirement at discharge

Among 88 surviving presentations, 21 (23.9%) required oxygen at discharge. RDW was numerically higher in the oxygen group, but the difference was not statistically significant (mean difference, 0.50 percentage points; 95% CI, −0.38 to 1.38; p=0.254). Group summaries and the corresponding Welch test are provided in Table 3.

Duration of hospital and intensive care unit stay

Hospital length of stay was available for 36 presentations, with a median of 10 days (IQR, 9–14). Among 37 presentations with a positive intensive care unit (ICU) stay duration, the median was 6 days (IQR, 4–8). RDW was positively correlated with hospital stay (r=0.433, p=0.008) and ICU stay (r=0.412, p=0.011), as shown in Figure 2. Both relationships were also present in rank-based analyses. Length-of-stay summaries, correlation confidence intervals and test statistics are reported in Table 04.

Table 01. Baseline characteristics of the study cohort (N=101).

Characteristic	Value
Age, years	70.82 ± 10.33
Age range, years	44–98
Sex	
Male	72 (71.3%)
Female	29 (28.7%)
Clinical history	
Previous hospitalization for AECOPD	61 (60.4%)
Previous inhaler use	81 (80.2%)
History of smoking	49 (48.5%)
Haematological measurements	
Haemoglobin, g/dL	12.50 ± 2.21
RDW, %	14.19 ± 1.72
RDW, median (IQR), %	14.20 (13.00–15.20)
RDW range, %	10.00–18.10

Values are n (%) or mean ± standard deviation unless otherwise stated. Percentages use N=101. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; IQR, interquartile range; RDW, red cell distribution width. This table is descriptive; no hypothesis tests were applied.

Table 02.1: RDW according to exacerbation severity and pairwise comparisons.

Exacerbation severity	n (%)	RDW, mean ± SD, %
Mild	33 (32.7%)	12.91 ± 1.26
Moderate	28 (27.7%)	14.06 ± 1.30
Severe	40 (39.6%)	15.34 ± 1.54
Overall comparison	F(2, 63.62) = 27.24	p<0.001

Table 02.2: Pairwise group comparisons using Welch's t-test with 95% CIs and Holm-adjusted p-values.

Pairwise comparison	Mean difference (95% CI)	Welch t (df)	Holm-adjusted p
Moderate versus mild	1.15 (0.49 to 1.81)	3.50 (56.80)	<0.001
Severe versus mild	2.43 (1.78 to 3.09)	7.42 (71.00)	<0.001
Severe versus moderate	1.28 (0.59 to 1.97)	3.69 (63.58)	<0.001

The overall comparison used Welch one-way analysis of variance. Pairwise comparisons used two-sided Welch t-tests with Holm adjustment across the three comparisons. Mean differences are the first group minus the second group, expressed in RDW percentage points. Confidence intervals are individual, unadjusted 95% intervals. CI, confidence interval; df, degrees of freedom; RDW, red cell distribution width; SD, standard deviation.

Table 03: RDW according to ventilatory support, mortality and discharge oxygen requirement.

Outcome	Present RDW, %	Absent RDW, %	Mean difference (95% CI)	Welch t (df)	p
Non-invasive ventilation	n=36 15.40 ± 1.63	n=65 13.52 ± 1.38	1.88 (1.24 to 2.52)	5.84 (62.81)	<0.001
Mechanical ventilation	n=31 15.35 ± 1.75	n=70 13.68 ± 1.45	1.67 (0.95 to 2.39)	4.65 (48.96)	<0.001
Mortality	n=13 16.15 ± 1.32	n=88 13.90 ± 1.59	2.25 (1.40 to 3.09)	5.58 (17.58)	<0.001
Oxygen at discharge	n=21 14.28 ± 1.78	n=67 13.78 ± 1.51	0.50 (-0.38 to 1.38)	1.16 (29.63)	0.254

RDW is expressed as mean ± SD. Mean differences are outcome-present minus outcome-absent, in percentage points. Tests are two-sided Welch independent-samples t-tests; outcome comparisons are unadjusted. Discharge oxygen analyses include surviving inpatient and outpatient presentations (n=88); deaths are excluded. Non-invasive and mechanical ventilation categories were not mutually exclusive. CI, confidence interval; df, degrees of freedom.

Table 04.1. Length of stay and its association with RDW.

Measure	n	Mean ± SD, days	Median (IQR), days	Range, days
Hospital	36	11.17 ±	10 (9–14)	4–25

stay		4.25		
ICU stay	37	6.62 ± 4.23	6 (4–8)	2–25

Table 04.2: Correlations between RDW and hospital and ICU stay using Pearson's and Spearman's correlation coefficients with 95% CIs and p-values.

Association with RDW	Pearson r (95% CI)	t (df)	p	Spearman ρ	p
Hospital stay	0.433 (0.122 to 0.667)	2.80 (34)	0.008	0.507	0.002
ICU stay	0.412 (0.102 to 0.650)	2.68 (35)	0.011	0.611	<0.001

Length-of-stay analyses include positive durations only and use the available pairs for each outcome; zero days do not represent an ICU stay. Pearson confidence intervals use Fisher's z transformation. Pearson t-statistics have n−2 degrees of freedom. Spearman correlations are rank-based sensitivity analyses with two-sided asymptotic p-values. All correlation p-values are unadjusted. CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; RDW, red cell distribution width; SD, standard deviation.

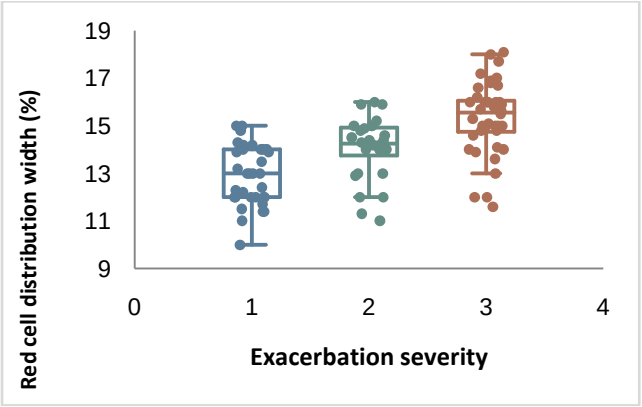


Figure 01: Distribution of red cell distribution width across exacerbation-severity categories.

Each point represents one presentation; horizontal jitter separates overlapping observations without altering RDW values. Boxes show the interquartile range, horizontal lines indicate medians, and whiskers extend to the most extreme values within 1.5 interquartile ranges of the box. All observations, including values outside the whiskers, are displayed. Group sizes were 33 for mild, 28 for moderate and 40 for severe exacerbations. RDW, red cell distribution width.

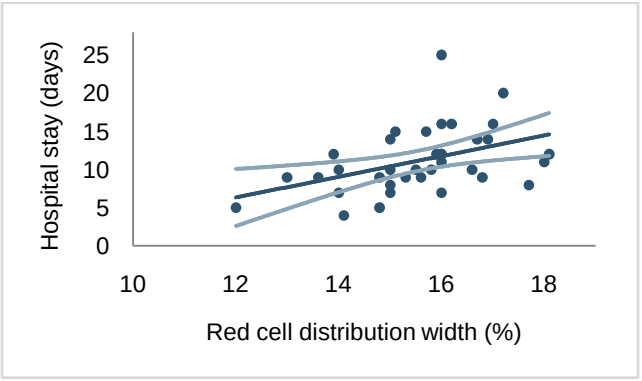
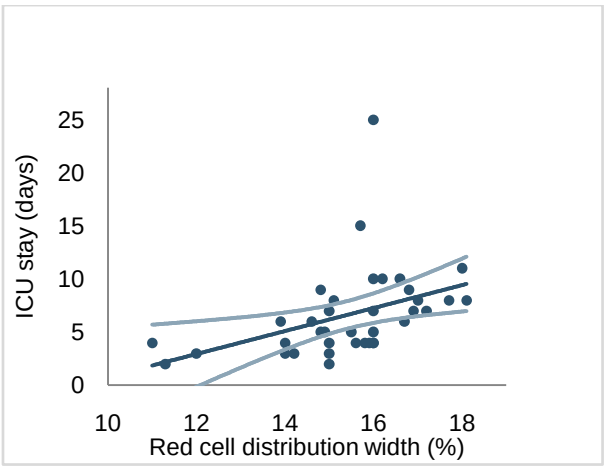


Figure 02 Panel A:



Panel B

Figure 02: Association of red cell distribution width with hospital and intensive care unit length of stay.

(A) Hospital stay (n=36). (B) ICU stay (n=37). Points represent individual presentations with positive stay durations. Solid lines show ordinary least-squares fits, and shaded bands indicate pointwise 95% confidence intervals for the mean fitted relationship. Correlations and p-values are from two-sided Pearson tests. The analyses use separate available-pair samples for the two outcomes. ICU, intensive care unit; RDW, red cell distribution width.

DISCUSSION

The present study showed a significant rise in RDW with increasing severity of AECOPD. The mean RDW increased from 12.91% in mild exacerbations to 14.06% in moderate and 15.34% in severe exacerbations, and all pairwise comparisons were significant after correction for multiple testing. Patients who needed non-invasive ventilation (NIV), mechanical ventilation and those who died also had higher RDW. Moreover, moderate positive correlations between RDW and hospital and ICU length of stay were found. The association with supplemental oxygen requirement at discharge was not statistically significant, however. These data collectively indicate that RDW could be an indicator of acute disease burden and short-term adverse outcomes, but the current analyses were not adjusted for other factors and should be interpreted as associative rather than independently prognostic.

This link with respiratory support is well supported by the work of Karampitsakos et al. [9], who investigated 160 patients admitted to hospital with AECOPD. Patients who needed NIV had a higher median RDW than those who did not (14.8% vs 13.5%, p<0.001), and those who went on to require long-term oxygen therapy had a higher median RDW than those who did not (14.2% vs 13.2%, p=0.001). They additionally found higher RDW among patients with a hospitalization during the preceding year. The current findings of differences of 1.88 percentage points and 1.67 percentage points for NIV and mechanical ventilation, respectively, corroborate these observations and suggest an association between increased anisocytosis and worsening respiratory compromise.

Our mortality results also align with other studies that assessed more general adverse outcomes. He et al. [10] conducted a 12-month follow-up of 132 patients with AECOPD, and determined that 40 patients had a poor prognosis based on death or early readmission. The poor-prognosis group had higher mean RDW (13.56% vs 12.75%)

and RDW was independently associated with poor prognosis on multivariable analysis (OR 2.01, 95% CI 1.34–3.02). The AUC obtained for RDW alone was 0.691, with a cut-off of >12.75% indicating higher risk. In the present cohort, patients who died showed an RDW 2.25 percentage points higher than those who survived, which is concordant with the observation that higher RDW is associated with clinically relevant adverse outcomes during AECOPD.

Not all published studies have demonstrated the same directional relationship. Alparslan Bekir et al. [11] analysed 2,771 AECOPD presentations across outpatient, ward and ICU settings. Interestingly, the percentage of patients with low RDW increased from 31% in outpatients to 66% in the ward and 83% in the ICU, while the percentage of patients with high RDW decreased from 54% to 24% and 10%, respectively. The authors therefore reported lower RDW with greater exacerbation severity. This is very different from the progressive rise in RDW that we saw. This discrepancy may be due to differences in laboratory categorization, reporting of RDW, patient selection, comorbidity profile, and retrospective data extraction, and highlights the importance of population-specific interpretation.

The positive correlation between RDW and hospital stay in our study is corroborated by studies on composite erythrocyte-derived indices. Eraslan et al. [12] studied the RDW/albumin ratio in 58 patients admitted to hospital for COPD exacerbation. A ratio ≥5.22 was associated with hospitalization of ≥10 days with 68.4% sensitivity and 74.4% specificity. The same measure was not significantly associated with 30-day mortality (p=0.14). In our study, RDW correlated with hospital stay (r=0.433) and ICU stay (r=0.412), indicating that erythrocyte size heterogeneity may be associated with factors that lead to longer acute-care stays even when its relationship with every downstream outcome is not uniform.

More recent critical-care data also corroborate the prognostic value of markers derived from erythrocytes. Long et al. [13] analyzed 624 patients in the ICU with AECOPD and studied the RDW/hematocrit ratio. A ratio ≥0.473 was associated with significantly increased 28-day all-cause mortality, and this relationship remained after propensity-score matching of 145 matched patient pairs. Combining the RDW/hematocrit ratio with the SOFA score significantly improved predictive discrimination compared with SOFA alone. The results are consistent with our observation that higher RDW was linked to both ICU-related outcomes and mortality, and indicate that RDW may prove more useful when combined with other physiological parameters than when used alone.

Similarly, Zhou and Pan [14] studied 594 patients with AECOPD complicated by respiratory failure. The participants were split into tertiles of the RDW-to-albumin ratio, and each increment of one unit in the RDW-to-albumin ratio was linked to a 74% rise in the adjusted odds of in-hospital mortality (OR 1.74, 95% CI 1.19–2.55). They also showed that the ratio was linearly related to the risk of mortality. Despite their population being restricted to patients with respiratory failure and their marker incorporating albumin, the direction of association is consistent with the markedly elevated RDW seen in the nonsurvivors and ventilated patients in this cohort.

This gradient of severity is also supported by Huang et al. [15], who used a clinical cohort and a meta-analysis. RDW >14.0% was associated with worse airflow limitation in their retrospective sample: lower FEV1% and FEV1/FVC, higher $PaCO_2$ and higher GOLD and BODE severity scores. RDW was still significantly related to a higher BODE index after adjustment for age, sex, disease duration, smoking, hypertension and diabetes (adjusted OR 1.85, 95% CI 1.05–3.26). Their meta-analysis of 25 studies with 10,960 participants revealed that higher RDW was seen in severe COPD than in mild COPD and in AECOPD than stable COPD, and was associated with mortality and poor prognosis. The results support the trend of progressive elevation of RDW in mild, moderate, and severe exacerbations observed in the present study.

The prognostic value of RDW could also be improved by using it together with other blood parameters that are routinely available. Chen et al. [16] analyzed 1,922 critically ill patients with AECOPD from MIMIC databases and externally evaluated their model in 1,738 eICU patients. During follow-up, 262 patients in the derivation cohort died. After adjustment, the RDW-to-platelet ratio continued to be associated with in-hospital mortality (OR 1.36, 95% CI 1.01–1.84), and a multivariable prediction model that included the RDW-to-platelet ratio and clinical variables yielded AUCs of 0.785, 0.721, and 0.795 in the training, test, and external validation sets, respectively. In summary, these findings indicate that RDW could be a valuable component of a more comprehensive risk-stratification strategy rather than a stand-alone diagnostic tool. The biological basis for these associations is likely multifactorial. Acute COPD exacerbations are accompanied by systemic inflammation, oxidative stress, hypoxemia, nutritional disturbances, and altered erythropoiesis, all of which may increase heterogeneity in circulating erythrocyte size. Greater RDW may therefore integrate several physiological disturbances rather than represent a disease-specific pathway. This interpretation also explains why RDW was strongly related to severe clinical outcomes in the present cohort but did not significantly distinguish survivors who did and did not require oxygen at discharge. Long-term oxygen requirement depends on persistent hypoxemia, underlying lung-function impairment, and recovery from the acute episode, factors that may not be captured adequately by a single admission RDW measurement.

The present study has several strengths, including evaluation of RDW across defined exacerbation-severity categories and examination of clinically relevant outcomes including NIV, invasive ventilation, mortality, discharge oxygen requirement, and both hospital and ICU stay. The observed graded rise in RDW across severity groups and its consistent association with several adverse outcomes strengthens the internal coherence of the findings. Nevertheless, important limitations should be acknowledged. The study was conducted at a single centre with a relatively modest sample size, and outcome comparisons were unadjusted for potential confounders such as age, COPD severity before exacerbation, cardiovascular comorbidity, systemic inflammation, nutritional status, and treatment received. RDW may also be affected by iron, vitamin B12, or folate deficiency despite exclusion of marked anaemia. Length-of-stay analyses were based on smaller available subsets, limiting precision. Finally,

the observational design does not establish that increased RDW directly contributes to adverse outcomes.

CONCLUSION

Higher red cell distribution width was associated with greater AECOPD severity, increased need for ventilatory support, higher mortality, and longer hospital and ICU stay. RDW may therefore serve as a simple, readily available adjunctive marker for early risk stratification in AECOPD.

CONFLICT OF INTEREST

The authors declare no conflicts of interest related to this study.

FINDING

Nil

AUTHOR CONTRIBUTION

Both are contributed equally.

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Not Declared

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