The role of elevated red blood cell distribution width in the prognosis of AECOPD patients
A retrospective study

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Abstract
Chronic obstructive pulmonary disease (COPD) is still a constant threat to people’s health. We aimed to identify the relationship between increased red blood cell distribution width (RDW) on admission and length of hospitalization in acute exacerbation of chronic obstructive pulmonary disease patients (AECOPD).

Patients with AECOPD were recruited and divided into 3 groups based on RDW tertiles. Two hundred eighty six patients with AECOPD admitted to our department during January 1, 2017 and June 30, 2019 were enrolled in the study. According to the RDW tertiles (<12.8%, 12.9% to 13.6%, >13.6%), the patients were divided into 3 groups. Length of stay was significantly related to RDW (P < .001) in AECOPD patients. Correlation analysis indicated that RDW was negatively associated with FEV1% predicted (r = −0.142, P = .016). However, RDW was positively associated with prolonged of stay (r = 0.298, P < .001) in AECOPD patients. Multivariate regression analysis discovered that RDW was independently associated with the length of hospitalization (P = .001). Receiver operating characteristic (ROC) curve showed that RDW was a good predictor of prolonged hospital stay in AECOPD patients, and the area under the curve (AUC) was 0.818 (95% CI: 0.769–0.868). The highest sensitivity to predict prolonged hospital stay was 83.8% and the specificity was 71.6% with the cut-off 13.35%.

In conclusion, prolonged hospital stay in AECOPD patients was closely associated with increased RDW. Elevated RDW may be an independent predictor for prolonged hospitalization in AECOPD patients.

Abbreviations: AECOPD = acute exacerbation of chronic obstructive pulmonary disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, FEV1 = forced expiratory volume in one second, HB = hemoglobin, PaCO2 = partial pressure of carbon dioxide, PaO2 = partial pressure of oxygen, PLT = platelet, RDW = red blood cell distribution width, WBC = white blood cells.

Keywords: biomarkers, chronic obstructive pulmonary diseases, length of stay, prognosis, red cell distribution width

1. Introduction
Chronic obstructive pulmonary disease (COPD), which is the third leading cause of death worldwide,[1] affects more than 174 million people globally.[2–3] COPD killed 3.2 million people in 2017, a toll expected to reach 4.4 million yearly by 2040.[1,4] COPD is a worldwide public health challenge due to its high prevalence and related disability and mortality.[6–9] Acute exacerbation of COPD (AECOPD), particularly leading to hospitalization, play the key role in mortality and worsening disease severity, and contribute to the economic burden of COPD.[10–24]

As part of regular complete blood cell count report, red cell distribution width (RDW) is a parameter reflecting the heterogeneity of red blood cell volume. The increase of RDW is used to diagnosis of anemia, hematopoietic abnormality or congenital erythrocyte abnormality. In previous studies, increased RDW is reported in a variety of diseases, including COPD, pulmonary hypertension,[11–13] cerebrovascular disease,[14] congestive heart failure (CHF)[16] and some other diseases.[17–19]

As for COPD, previous studies have revealed that increased RDW is a useful marker to estimate clinical outcomes including: predicting COPD severity,[20–21] independent predictor of mortality,[22–24] readmission rate,[25] right heart failure,[26,27] pulmonary hypertension,[26,28] increased BODE index,[20] and other negative prognostic markers. However, as one of the prognostic factors, studies of increased RDW and length of hospitalization in AECOPD patients have not been reported.

2. Material and methods

2.1. Study design
We conducted a retrospective study on AECOPD patients hospitalized in the department of respiratory medicine of the
Liyuan hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology, during January 1, 2017 and June 30, 2019. The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the Medical Institutional Review Board Approval of Liyuan hospital. Written informed consent was obtained from each patient.

2.2. Participants

We collected 286 patients admitted for AECOPD. The inclusion criteria were as follows: All participants were adults who had been diagnosed with COPD by a physician in accordance with 2020 GOLD guidelines, which is a postbronchodilator forced expiratory volume in one second (FEV1)forced vital capacity (FVC) ratio <0.7. Acute exacerbation was defined as shortness of breath, expectoration of sputum, color change of sputum, cough, wheezing, chest tightness etc., with at least 2 symptoms aggravating or reappearing. Exclusion criteria included participants with severe left heart failure, pulmonary embolism, immune diseases, renal failure, mental disorders, patients with any other infections whether acute or chronic and hospitalization days >30 days or <2 days.

As is known to all, there is no published definition of prolonged length of hospital stay, we defined a length of hospitalization longer than the 75th percentile as prolonged length of hospital stay, we defined a length of hospitalization days as prolonged length of hospital stay, which is consistent with other studies.[29,30]

2.3. Data Collection

We collected each patient’s age, gender, smoking history, blood gas analysis, the length of hospitalization, as well as lung function (FEV1% predicted). And the laboratory results including C-reactive protein (CRP), creatinine, hemoglobin (HB), white blood cells (WBC), PLT, neutrophils, lymphocytes, eosinophils, and RDW were recorded. At the same time, we recorded a detailed history of hypertension, diabetes, CHF, atrial fibrillation and malignancy.

Complete blood count was measured by automated hematology analyzer Sysmex XN-1000. Lung function was measured by Ledoumit automatic blood gas analyzer (Danish, ABL 800). The Ray blood gas analyzer was used to blood gas analysis (made in Danish).

2.4. Statistical analysis

The software SPSS 26.0 was used for statistical analysis. Kolmogorov–Smirnov test was used to determine whether the variables are normally distributed. Participant characteristics were compared across the RDW categories using ANOVA and Chi-Squared test, independent samples Kruskal–Wallis test was used when variances are not uniform. Pearson correlation analysis was used for correlation between RDW and other continuity parameters. Univariate and multivariate logistic regression model were used to identify the variables correlated with length of hospital stay in AECOPD patients. The predictive value of RDW for length of stay in AECOPD patients was assessed by ROC curve. P values <.05 were considered statistically significant.

3. Results

286 patients were grouped according to the RDW tertiles (≤12.8%, 12.9%–13.6%, >13.6%), as follows:

1. 102 (35.6%) in the lowest tertile, 2. 92 (32.2%) in the intermediate tertile, 3. 92 (32.2%) in the highest tertile.

| Table 1 | Baseline characteristics of patients according to tertiles of baseline RDW level. |
|---------|-----------------------------------------------------------------------------|
| Parameters | Lowest (n=102) | Intermediate (n=92) | Highest (n=92) | P |
| Age, years | 72.42 ± 10.506 | 72.36 ± 10.15 | 77.11 ± 10.22 | .002 |
| Males | 80 (78.4%) | 74 (80.4%) | 73 (79.3%) | .942 |
| Smoking (no/ ever/yes) | 57/27/18 | 43/30/19 | 52/25/19 | .681 |
| WBC × 10^9/L | 7.67 ± 3.50 | 8.05 ± 4.02 | 8.39 ± 4.19 | .435 |
| HB g/L | 131.75 ± 17.55 | 127.13 ± 17.77 | 113.54 ± 21.53 | <.001 |
| PLT × 10^9/L | 213.37 ± 68.28 | 217.21 ± 74.14 | 204.15 ± 81.45 | .475 |
| Neutrophils × 10^9/L | 5.64 ± 3.47 | 5.90 ± 3.94 | 6.40 ± 4.03 | .369 |
| Lymphocytes × 10^9/L | 1.37 ± 0.67 | 1.40 ± 0.70 | 1.16 ± 0.63 | .029 |
| Eosinophils × 10^9/L | 0.1349 ± 0.1337 | 0.1784 ± 0.2223 | 0.1524 ± 0.1785 | .247 |
| CRP mg/l | 10.7 (2.65, 50.7) | 9.2 (2.93, 34.20) | 34.7 (5.13, 77.93) | .149 |
| Creatinine ummol/l | 82.99 ± 40.54 | 74.26 ± 22.14 | 81.17 ± 42.24 | .219 |
| Diabetes | 15 (14.7%) | 19 (20.7%) | 22 (23.9%) | .259 |
| Hypertension | 45 (44.1%) | 50 (54.3%) | 44 (47.8%) | .357 |
| CHF | 5 (4.9%) | 14 (15.2%) | 30 (32.6%) | <.001 |
| Atrial fibrillation | 11 (10.3%) | 6 (6.5%) | 10 (10.9%) | .509 |
| Malignant tumor | 2 (2.0%) | 6 (6.5%) | 6 (6.5%) | .231 |
| FEV1% predicted | 64.40 ± 14.09 | 64.76 ± 10.68 | 59.34 ± 12.62 | .004 |
| PaCO2 mm Hg | 39.52 ± 10.63 | 40.57 ± 9.94 | 43.55 ± 12.52 | .147 |
| PaO2 mm Hg | 84.86 ± 17.27 | 87.16 ± 20.72 | 89.21 ± 20.08 | .413 |
| pH | 7.42 ± 0.06 | 7.42 ± 0.05 | 7.41 ± 0.06 | .878 |
| length of stay | 7.41 ± 2.03 | 8.89 ± 3.56 | 10.59 ± 3.47 | <.001 |

CHF = congestive heart failure, CRP = C-reactive protein, FEV1 = forced expiratory volume in one second, HB = hemoglobin, PaCO2 = partial pressure of carbon dioxide, PaO2 = partial pressure of oxygen, PLT = platelet, RDW = red blood cell distribution width, WBC = white blood cells.
Table 2
The associations between RDW and other clinical parameters were analyzed by Pearson correlation.

| Variable   | r       | P value |
|------------|---------|---------|
| age        | 0.079   | .198    |
| HB         | –0.470  | <.001   |
| FEV1%predicted | –0.142  | .016    |
| Length of stay (>11days) | 0.250†  | <.001   |

*Correlation is significant at the 0.01 level (2-tailed).
FEV1 = forced expiratory volume in one second, HB = hemoglobin, PLT = platelet, r = Pearson correlation coefficient, RDW = red cell distribution width.

The basic characteristics of AECOPD patients were presented in Table 1.

The age of patients in the lowest, intermediate, and highest tertile group was 72.42 ± 10.506, 72.36 ± 10.15 and 77.11 ± 10.22, respectively. Mean FEV1% predicted ± SD were 64.40 ± 14.09, 64.76 ± 10.68 and 59.34 ± 12.62, respectively. As tertiles increased, patients’ lung function deteriorated (P = .004). Mean white blood cell counts ± SD were 7.67 ± 3.50, 8.05 ± 4.02 and 8.39 ± 4.19, respectively. While the eosinophils were 0.134 ± 0.1337, 0.1784 ± 0.2223 and 0.1524 ± 0.1785, respectively, HB and the increase of RDW significant correlation (P < .001). Median CRP of the 3 study group were 10.7 (2.65, 50.7), 9.20 (2.93, 34.20), and 34.7 (5.13, 77.93), respectively. In 3 groups, the length of hospital stay was 7.41 ± 2.03, 8.89 ± 3.36 and 10.59 ± 3.47, with the increase of RDW the length of hospital stay was significant extended (P < .001).

In Pearson correlation analysis, we found that there was an obvious negative correlation between RDW and HB (r = –0.470, P < .001). Similarly, RDW was positively correlated with FEV1% predicted (r = –0.142, P = .016). Nevertheless, there was a positive correlation between RDW level and length of stay (r = 0.250**, P < .001) (Table 2).

The 75th percentile of length of stay was 11 days in 286 patients, which divided the prolonged group from the normal group. In the univariate logistic regression analysis, several factors were associated with longer hospital stay, including: age, FEV1% predicted, WBC, RDW, neutrophils, HB, acidosis (pH < 7.35), hypercapnia (PaCO2 > 45 mm Hg), diabetes, and CHF (Table 3). Then, we reintegrated these factors into multivariate logistic regression analysis to determine the independent variables. Increased RDW (P = .001) and CHF (P = .030) were independent predictor for prolonged hospital stay in patients with AECOPD (Table 4).

ROC curve (Fig. 1) indicated that RDW was a good predictor of prolonged hospital stay in AECOPD patients, and the area under the curve (AUC) was 0.818 (95% CI: 0.769–0.868). The highest sensitivity to predict prolonged hospital stay was 83.8% and the specificity was 71.6% with the cut-off 13.35%.

4. Discussion

To our knowledge, this is the first study to report the association of increased RDW with the length of hospitalization in AECOPD. Length of hospitalization is also an important part about prognostic models for outcome prediction in COPD patients. Based on recent researches, elevated RDW is connected with a variety of diseases, including cardiovascular diseases, cerebrovascular diseases, pulmonary embolism, cancer, diabetes mellitus, acute kidney failure, and other diseases. In addition, RDW is considered to be a powerful and independent dangerous factor in predicting mortality. However, the possible pathophysiological mechanisms between elevated RDW and various diseases is of heart failure.
still unclear according to the published research. Most researchers believe that an elevated RDW reflects a serious imbalance of homeostasis in the red blood cell caused by impaired erythropoiesis and abnormal erythrocyte survival, due to all kinds of metabolic disturbance including shortening of telomere length, oxidative stress, inflammation, hypoproteinemia, dyslipidemia, hypertension, erythrocyte fragmentation, and changes in the function of erythropoietin.

In the current study, RDW increased with age in patients with AECOPD. This was consistent with the results of a cohort study of 8089 individuals that RDW increases with age. Length of hospitalization increased in the higher RDW group compared to the other groups. Our study demonstrated that elevated RDW may be an independent predictor for prolonged hospital stay. Moreover, the association between RDW and FEV1% predicted suggested that increased RDW may serve as a reference for determining the severity of disease in AECOPD patients. The result was consistent with the Tertemiz KC team’s findings that the increased RDW could be used to determine the severity of the disease in patients with chronic obstructive pulmonary disease. In univariate regression analysis, FEV1 was associated with LOH (P=.013), but this correlation disappeared in multivariate regression analysis (P=.281). Previous studies show that FEV1 is associated with length of hospitalization and mortality in AECOPD patients. However, like our results, there are some other studies indicate that FEV1 is not related to length of hospitalization in AECOPD patients. The discrepancy of results may be due to the limited sample capacity, and FEV1 was analyzed as a categorical variable in previous studies, whereas FEV1 was analyzed as a continuous variable in our study. Therefore, further studies are needed to confirm the relationship between FEV1 and length of hospitalization in AECOPD.

Though elevated RDW is related to prognosis in a variety of diseases, the pathophysiological mechanism of which has not been fully understood. About the association between elevated RDW and length of hospitalization, we try to provide some possible explanations.

Based on previous studies, the length of AECOPD patient’s hospital stay is determined by a number of factors including age, disease severity, comorbidities, hypercapnia (PaCO₂ >43 mm Hg), mechanical ventilation, hypoproteinemia, the dyspnea perception and the respiratory rate. Previous studies have indicated that increased RDW is correlated with COPD severity, mortality, 60-day readmission rate combined with right heart failure predicting pulmonary hypertension and the need of mechanical ventilation in COPD patients. Complications, readmitted rates, hypercapnia, severity of disease or mechanical ventilation, all lead to prolonged hospital stays in patients with COPD. The elaboration of the relationships between RDW and inflammation, oxidative stress, tissue hypoxia, disease severity, and heart failure may help
understand why this marker was related to length of stay in patients with AECOPD.

This study includes some limitations. First, RDW was affected by a number of factors that we did not assess, including iron, folic acid, and vitamin B12. Second, interventions for all AECOPD were not identical, which may lead to intervention bias. Finally, this was a single-center retrospective study with limited sample capacity.

Collectively, we indicated that elevated RDW may be an important predictor correlated with increased length of stay in AECOPD patients. As an item in the regular report of the CBC counts, although this laboratory parameter is widely available and low-cost, it has provided valuable information on the prognosis of AECOPD patients. RDW can predict the risk of adverse events and hospitalization expenses and provide high-quality discharge decisions. These findings may guide further wholesale prospective studies aimed at assessing the associated between RDW and the length of stay in AECOPD patients. And this will further enrich the prognostic indicators of clinical AECOPD patients.

5. Conclusions

Prolonged hospital stay was closely associated with increased RDW on admission in AECOPD patients. Elevated RDW may be an independent predictor for prolonged hospital stay in AECOPD patients.

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