Relationship of Red Cell Index with the Severity of COPD

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Research

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) has always attracted attention due to its high prevalence and high mortality. How to predict and diagnose COPD and assess the severity of the disease is our top priority. We aimed to evaluate the association between red cell index (RCI) and the severity of COPD, and compare predictive value among RCI, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) of indicating the severity of COPD.

Methods: A total of 207 participants were recruited (100 COPD patients and 107 healthy controls). COPD patients were divided into two groups according to receiver operating characteristics (ROC) curves cut-off value of RCI (RCI < 1.75, n = 54; RCI > 1.75, n = 46). Pearson's correlation test, logistic regression analysis and other tests were performed.

Results: Compared with low RCI group, the forced expiration volume in 1 second (FEV1) and FEV1 in percent of the predicted value (FEV1%) of high RCI group decreased (p = 0.016, p = 0.001). There is a negative correlation between RCI and FEV1% (r = -0.302, p = 0.004), while no correlation between FEV1% and NLR and PLR. RCI's ability to predict Global Initiative for Chronic Obstructive Lung Disease classification, is better than NLR and PLR, with a cut of 1.75, specificity of 85.2%, sensitivity of 57.6% and area under the curve (AUC) of 0.729 (p = 0.001). Multivariate logistic regression analysis proved RCI was an independent factor affecting lung function in COPD patients (odds ratio [OR] = 4.27, 95%CI: 1.57 - 11.63, p = 0.004).

Conclusion: RCI is a novel biomarker that can better assess respiratory function and severity of COPD than NLR and PLR. Higher RCI is independently related to deterioration of respiratory function.

Introduction

Chronic obstructive pulmonary disease (COPD) has always been a major public health problem, and it is still a severe challenge in the 21st century. At the same time, it has been attracting worldwide attention due to its high prevalence, morbidity, and mortality[1]. COPD is a common, preventable, and treatable disease characterized by progressive inflammation of the airways, alveoli, and capillaries caused by exposure to harmful particles or gases, as well as the resulting emphysema and lung parenchyma peripheral loss, persistent respiratory symptoms and airflow limitation and other pathophysiological changes[2, 3]. Inflammation is a series of complex interactions, and inflammatory cells including neutrophils, lymphocytes, etc.

In recent studies, neutrophil-lymphocyte ratio (NLR) has been proved to be a diagnostic and prognostic marker of COPD. Chronic inflammation leads to the accumulation of the main white blood cells, lymphocytes and neutrophils of COPD. After neutrophils are activated, neutrophil elastase, myeloperoxidase and other substances actively participate in the pathophysiological mechanism of emphysema and COPD, which is beneficial to the tissue destruction of COPD[4, 5]. Therefore, NLR is considered as a marker of disease severity and prognosis. NLR is a favorite marker of systemic inflammation.
inflammation, acute exacerbation of COPD (AECOPD) and mortality[6]. The results of other studies have shown that platelet-lymphocyte ratio (PLR) is also an effective marker of inflammation in evaluating the severity of COPD patients[7]. At the same time, PLR was significantly associated with an increase in 90-day mortality. In addition, there is no difference between NLR, PLR and COPD A-D groups[8]. Relevant studies have shown that the lung is related to the production of platelets[9]. Makhlof et al.[10] found that there is a significant positive correlation between platelet (PLT) and white blood cell (WBC), and there is a negative correlation between PLT and hemoglobin (Hb). In addition, red blood cell (RBC) has also been found to be related to the diagnosis of COPD, and there is a correlation between PLT and RBC[9].

Speaking of Hb, anemia (Hb < 13.0 g/dL for males, and < 12.0 g/dL for females[11]) has a negative impact on gas exchange and exercise tolerance during exercise in patients with severe COPD, which is Global Initiative for Chronic Obstructive Lung Disease (GOLD) [11]. The decrease in Hb level amplitude is related to oxygen intake. But anemia has little effect on pulmonary ventilation function and ventilation efficiency[12]. Rasmussen et al.[13] recently reported that low Hb was associated with an increased 90-day mortality of admission to the intensive care unit (ICU) in patients with COPD having acute respiratory failure. And higher levels of Hb were associated with a better long term survival[14]. Now, there is a new indicator related to PLT, RBC, Hb and lymphocyte (Lym), which is Red Cell Index (RCI). RCI is calculated by the following equation: (RBC × Hb) / (Lym × PLT)[15]. In theory, RCI is inversely proportional to respiratory function and is a simple and effective method to evaluate respiratory function, but there are no studies on the potential value of RCI as a COPD biomarker[15].

The purpose of our study was to evaluate the correlation between the new indicator RCI and the severity of COPD, and the comparison of RCI with NLR and PLR in predicting the severity of COPD.

Materials And Methods

Study Population and Data Collection

From February 2018 to February 2019, we conducted a cross-sectional study of COPD patients and recruited 100 subjects diagnosed with COPD from the Department of Respiratory Medicine, the Third Affiliated Hospital of Wenzhou Medical University, as well as 107 age and sex-matched cases served as healthy controls.

Inclusion criteria were as follows: 1) age more than 40 years; 2) diagnosis of COPD as defined in the GOLD guidelines. The exclusion criteria were: 1) obstructive sleep apnea hypopnea syndrome; 2) alimentary tract hemorrhage; 3) renal insufficiency; 4) arrhythmia; 5) coronary atherosclerotic heart disease; 6) cardiac insufficiency; 7) liver cirrhosis; 8) alcoholic hepatitis; 9) hypothyroidism; 10) hyperthyroidism; 11) hashimotos thyroiditis. (Fig. 1)

The study was approved by the Ethics Committee of the Third Affiliated Hospital of Wenzhou Medical University and conducted in accordance with the Declaration of Helsinki. All subjects signed a written informed consent form.
Following recruitment of subjects were taken during their hospitalizations for COPD, data like age, gender, body mass index (BMI), current smokers, duration of disease, and comorbidities such as hypertension and diabetes mellitus are collected. Blood cell related indicators such as red blood cells, lymphocytes, platelets, neutrophil and hemoglobin were collected on 24 hours admission to analyze blood routine parameters, and blood samples were also collected to analyze blood biochemistry and arterial blood gas for results of PaCO₂ and PaO₂. Parameters like RCI, NLR and PLR of COPD patients and healthy controls were calculated. RCI is calculated using the following equation: (RBC × Hb) / (Lym × PLT). FEV1 in percent of the predicted value (FEV1%), forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and FEV1/FVC of COPD patients were recorded as significant indicators of the severity of pulmonary function. Further more, we also collected scales of COPD patients within 7 days after hospital admission which including BODE (BMI, airway obstruction, dyspnea, severe exacerbations), ADO (age, dyspnea and airflow obstruction) and DOSE (MRC Dyspnea Scale, airflow obstruction, smoking status and exacerbations).

**Diagnostic Criteria Of Copd**

Patients with COPD were categorized in severity grades 1–4 using spirometry (GOLD I: FEV1 ≥ 80% predicted; GOLD II: 50% ≤ FEV1 < 80% predicted; GOLD III: 30% ≤ FEV1 < 50% predicted; GOLD IV: FEV1 < 30% predicted).

**Statistical analysis**

All statistical analysis was performed using SPSS 25.0 (IBM Analytics). Mean ± standard deviation was used to present continuous variables of normal distribution. The Chi-squared (χ²) test or Fisher test was used for the comparison of categorical variables. The independent sample t test was used to compare the differences of clinical characteristics between COPD patients and healthy controls, low RCI group and high RCI group. And multivariate logistic regression analysis was carried out to identify the contribution of the RCI as an independent predictor in GOLD. Relationships between RCI, NLR, PLR and FEV1% were evaluated by Pearson’s correlation test. In order to estimate the value of RCI for predicting pulmonary function compared with the existing indicator NLR and PLR, the receiver operating characteristics (ROC) curves were analyzed, besides, De Long method is used to calculate whether there is a significant difference in the area under the curve (AUC). In addition, through the GOLD classification, GOLD I and GOLD II are divided into one group, and GOLD III and GOLD IV are divided into one group, as the state variable of ROC test. Two-sided p values < 0.05 were considered significant in all analyses.

**Results**

**Baseline characteristics of the study subjects**
Within the 207 patients, 100 were COPD patients, namely the COPD group, and 107 were age and sex matched selected healthy persons as healthy control groups. The results indicate that, there is no significant difference in their age and gender between two groups. However, compared with the healthy control group, the NLR (4.02 ± 3.80 vs. 1.65 ± 0.74, \( p < 0.001 \)) and PLR (170.89 ± 101.61 vs. 99.74 ± 37.04, \( p < 0.001 \)) levels of the COPD group were significantly higher. In addition, a new marker RCI (2.10 ± 1.44 vs. 1.64 ± 0.64, \( p = 0.004 \)) is also higher than the healthy control group. The related results are shown in Table 1.

|                | Total (n = 207) | Group A (n = 100) | Group B (n = 107) | \( p \)   |
|----------------|-----------------|-------------------|-------------------|---------|
| Age (years)    | 70.14 ± 8.38    | 70.17 ± 8.41      | 70.12 ± 8.39      | 0.968   |
| Gender (male, n%) | 178 (83.18%)  | 87 (81.31%)       | 91 (85.05%)       | 0.467   |
| RBC (10^12/L)  | 4.50 ± 0.57     | 4.28 ± 0.44       | 4.70 ± 0.60       | < 0.001 |
| Hb (g/L)       | 137.85 ± 19.0   | 130.19 ± 13.82    | 145.08 ± 20.39    | < 0.001 |
| PLT (10^9/L)   | 219.84 ± 65.05  | 232.75 ± 75.34    | 207.66 ± 51.01    | 0.006   |
| Lym (10^9/L)   | 2.61 ± 9.30     | 1.62 ± 0.73       | 3.54 ± 12.91      | 0.138   |
| RCI            | 1.86 ± 1.12     | 2.10 ± 1.44       | 1.64 ± 0.64       | 0.004   |
| NLR            | 2.80 ± 2.95     | 4.02 ± 3.80       | 1.65 ± 0.74       | < 0.001 |
| PLR            | 134.29 ± 83.42  | 170.89 ± 101.61   | 99.74 ± 37.04     | < 0.001 |
| MPV            | 12.47 ± 21.73   | 10.78 ± 1.03      | 14.08 ± 30.40     | 0.280   |

Group A, Patients with COPD; Group B, Healthy people. COPD, chronic obstructive pulmonary disease; RCI, Red cell index; NLR, Neutrophil-Lymphocyte ratio; PLR, Platelet-Lymphocyte ratio; MPV, Mean platelet volume; RBC, Red blood cell; Hb, Hemoglobin; Lym, Lymphocyte; PLT, Platelet

NLR and PLR are known indicators that have been shown to be related to the severity of COPD. In order to gain a further understanding of the correlation between RCI and COPD severity, 100 COPD patients were divided into two groups based on ROC cutoff values of RCI (RCI < 1.75, \( n = 54 \); RCI > 1.75, \( n = 46 \)).

As can be seen from Table 2, in lung function, especially the four indicators of FEV1% (44.25 [29.37–59.13] vs. 34.10 [21.53–46.67], \( p = 0.001 \)), FEV1 (1.05 [0.56–1.54] vs. 0.84 [0.5–1.14], \( p = 0.016 \)), FVC (1.97 [1.24–2.7] vs. 1.67 [1.13–2.21], \( p = 0.027 \)), and PaCO\(_2\) (42.44 [36.97–47.91] vs. 46.73 [35.34–58.12], \( p = 0.025 \)), there are significant differences between the two groups. The values of FEV1%, FEV1, and FVC decrease with higher RCI. Conversely, the value of PaCO\(_2\) increases with the increase of RCI. But in the FEV1/FVC ratio and PaO\(_2\), there was no significant difference between the two groups. These
results indicate that RCI is related to respiratory function. The higher the RCI, the worse the patient's respiratory function, the higher the severity of COPD, RCI and COPD severity are positively correlated.
Table 2
T tests for groups divided according to RCI with severity of disease and other functions

| Baseline characteristic                  | RCI < 1.75 (n = 54) | RCI > 1.75 (n = 46) | p    |
|-----------------------------------------|----------------------|----------------------|------|
| Age                                     | 69.67 ± 9.46         | 71.28 ± 7.38         | 0.340|
| Sex (male, n%)                          | 40 (74.07)           | 42 (91.30)           | 0.021|
| Duration of Disease                     | 10.13 ± 8.69         | 15.69 ± 13.55        | 0.021|
| Smoking                                 | 36 (67.92)           | 38 (84.44)           | 0.054|
| Hypertension                            | 22 (40.74)           | 16 (34.78)           | 0.545|
| Diabetes mellitus                       | 9 (16.67)            | 6 (13.04)            | 0.617|
| Lung Function                           |                      |                      |      |
| FEV1 (L)                                | 1.05 ± 0.49          | 0.84 ± 0.34          | 0.016|
| FVC (L)                                 | 1.97 ± 0.73          | 1.67 ± 0.54          | 0.027|
| FEV1% (< 50%)                           | 44.25 ± 14.88 (53.7%)| 34.10 ± 12.57 (78.3%)| 0.001|
| FEV1/FVC ratio (%)                      | 52.16 ± 9.63         | 49.46 ± 7.69         | 0.150|
| PaO2                                    | 73.21 ± 12.33        | 72.57 ± 17.47        | 0.838|
| PaCO2                                   | 42.44 ± 5.47         | 46.73 ± 11.39        | 0.025|
| Severity of disease                     |                      |                      |      |
| GOLD                                    | 2.76 ± 0.84          | 3.31 ± 0.64          | 0.001|
| BODE                                    | 3.56 ± 2.22          | 4.25 ± 2.45          | 0.165|
| ADO                                     | 4.41 ± 1.41          | 5.05 ± 1.38          | 0.033|
| DOSE                                    | 2.24 ± 1.64          | 3.21 ± 1.74          | 0.051|
| mMRC                                    | 1.58 ± 0.97          | 1.77 ± 0.96          | 0.343|
| CAT (7d)                                | 17.45 ± 6.64         | 18.18 ± 6.91         | 0.601|

GOLD: Global Initiative for Chronic Obstructive Lung Disease; BODE, BMI, airflow obstruction, dyspnea and exercise capacity; CAT, COPD assessment test; SGRQ, St. George’s Respiratory Questionnaire; RCI, Red cell index; mMRC, modified Medical Research Council dyspnoea scale; DOSE, dyspnoea, obstruction, smoking and exacerbations; ADO, age, dyspnoea and obstruction; FEV1%, forced expiratory volume in 1 second in percent of the predicted value; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PaO2, partial pressure of oxygen in arterial blood; PaCO2, partial pressure of carbon dioxide in arterial blood.
|                | RCI < 1.75 (n = 54) | RCI > 1.75 (n = 46) | p     |
|----------------|----------------------|----------------------|-------|
| SGQR           | 36.30 ± 19.82        | 39.42 ± 2.55         | 0.415 |

GOLD: Global Initiative for Chronic Obstructive Lung Disease; BODE, BMI, airflow obstruction, dyspnea and exercise capacity; CAT, COPD assessment test; SGQR, St. George’s Respiratory Questionnaire; RCI, Red cell index; mMRC, modified Medical Research Council dyspnoea scale; DOSE, dyspnoea, obstruction, smoking and exacerbations; ADO, age, dyspnoea and obstruction; FEV₁%, forced expiratory volume in 1 second in percent of the predicted value; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; PaO₂, partial pressure of oxygen in arterial blood; PaCO₂, partial pressure of carbon dioxide in arterial blood.

In order to further explore the clinical significance of RCI, the two groups of low RCI and high RCI are compared in two aspects, the baseline characteristic and the severity of disease. From Table 2, we can see that there is no obvious difference in age, smoking, hypertension, diabetes mellitus in baseline characteristic, while there are significant differences in gender and duration of disease.

However, in the scale related to the severity of the disease, GOLD (2.76 [1.92–3.6] vs. 3.31 [2.67–3.95], p = 0.001), ADO (4.41 [3–5.82] vs. 5.05 [3.67–6.43], p = 0.031), DOSE (2.24 [0.6–3.88] vs. 3.21 [1.47–4.95], p = 0.051) has a significant correlation, but the BODE, SGQR, CAT, mMRC and other scales show no significant differences.

**Comparisons of the RCI, NLR and PLR in COPD**

The Pearson’s correlation indicates that there is a correlation between RCI and FEV₁% (r = -0.302, p = 0.004), while there is no correlation between NLR (r = -0.153, p = 0.148), PLR (r = -0.098, p = 0.354) and FEV₁% (Fig. 2B). Afterwards, the ROC curve analysis was performed to evaluate the utility of RCI, NLR and PLR for predicting COPD severity level here refers to GOLD. The analysis showed that the area under the curve (AUC) values of NLR and PLR were 0.654 (95%CI: 0.54–0.77, p = 0.020) and 0.611 (95%CI: 0.49–0.74, p = 0.095). On the contrary, at a cut-off value of 1.75, the specificity and sensitivity of RCI in predicting lung function were 57.6% and 85.2%, with an AUC of 0.729 (95%CI: 0.62–0.84, p = 0.001) (Fig. 3). It indicates that RCI’s AUC is significantly larger than the indicators related to the severity of COPD that have been proven, such as NLR, PLR, MPV, and PDW. And, RCI can be seen as a better and comprehensive marker of predicting GOLD as well as affect pulmonary function.

**RCI and respiratory function are closely related**

In low RCI group, 53.7% suffered from poor pulmonary function (FEV₁% < 50), while the proportion increases to 78.3% in high RCI group (Table 2), which indicates that the higher the RCI, the lower the FEV₁%, the worse the respiratory function, manifesting RCI and FEV₁% is inversely proportional.
In order to further explore the independent factors of pulmonary function, variables were subjected to univariate logistic regression analyses. Hence, duration of disease \( (p = 0.031) \), BMI \( (p = 0.020) \), FEV1/FVC \( (p < 0.001) \), PaCO\(_2\) \( (p < 0.001) \) and RCI \( (p = 0.003) \) were observed to have a significant correlation with GOLD severity (Mild: GOLD I, GOLD II; Severe: GOLD III, GOLD IV). (Table 3)

To control other potential confounding variables, multivariate logistic regression analyses were performed. In Model 1, nothing was adjusted (odds ratio [OR] = 2.53, 95% CI: 1.38–4.66, \( p = 0.003 \)). After adjusted for age, sex, BMI, and duration of disease in Model 2, the linkage between RCI and GOLD remained significant (odds ratio [OR] = 2.35, 95% CI: 1.24–4.45, \( p = 0.009 \)). On the basis of Model 2, we additionally made adjustments for, FEV1/FVC, and PaCO\(_2\) in Model 3, the linkage between RCI and GOLD still remained significant (odds ratio [OR] = 4.27, 95% CI: 1.57–11.63, \( p = 0.004 \)). After two adjustments, there is still a correlation between RCI and GOLD, which shows that RCI is probably an independent impact factor of GOLD. (Table 4)

Table 4

| OR (95% CI)  | \( p \)   |
|-------------|----------|
| Model1      | 2.533 (1.378–4.656) | 0.003 |
| Model2      | 2.348 (1.239–4.450) | 0.009 |
| Model3      | 4.272 (1.570–11.627) | 0.004 |

Model 1 is univariate analysis. Model 2 is adjusted by age, sex, duration of disease and Body mass index. Model 3 is adjusted by age, sex, duration of disease, BMI, FEV1/FVC and PaCO\(_2\)

**Discussion**

Our data shows that as the RCI value increases, the respiratory function decreases, which is manifested as a decrease in FEV1%, deterioration of lung function, and an increase in the severity of COPD, and finally an increase in the level of GOLD. Because RCI is obtained by calculating \((RBC \times Hb) / (Lym \times PLT)\) and is closely related to the four indicators of RBC, Hb, Lym, and PLT, the above results also indicate that it may be related to low lymphocyte count and PLT level.

In this study, we found that the lymphocyte count of COPD patients was significantly lower than that of healthy controls. Previously, studies have also shown that patients in the acute exacerbation of COPD have a decreased lymphocyte count compared with healthy controls or patients in the stable phase[20], and lymphopenia may have a higher risk of respiratory infections, one of the reasons for exacerbation of COPD is an increase in respiratory infections[3].

A low relative lymphocyte count is associated with a high mortality rate in elderly patients with severe COPD[21]. A characteristic cellular immune response with important diagnostic significance in the airway
and lung parenchyma. This immunopathology is driven by lymphocytes and responds to the targeted immune regulation of human lymphocytes. This is often seen in Autoimmune polyendocrinopathy-candidiasis-ectodermal-dystrophy (APECED). In APECED, the pathogenesis of lung autoimmune diseases with impaired central immune tolerance was found\[22\]. Hence, when the lymphocyte count is less than 1500, it often indicates malnutrition. Collins PF et al.\[23\] explained the relationship between the severity of COPD and malnutrition in a study. Malnutrition and nutritional deprivation are common among COPD patients.

COPD is related to systemic inflammation, and activated platelets can recruit inflammatory cells to make them aggregate. In patients with stable and acute COPD, platelet activation continues to increase, and platelet function may change due to COPD. The interaction between platelets and inflammatory cells can stimulate the release of chemokines and the further recruitment of immune substances\[24\]. In patients with stable COPD, the platelet count is associated with a U-shaped increase in the risk of all-cause death at 3 years. Despite this, it is still not clear that platelet levels above or below this level will increase mortality\[25\]. In addition, platelet reactivity will increase accordingly\[26\].

Karina et al.\[11\] believe that the abnormal inflammatory response associated with COPD may cause other diseases, such as anemia. Anemia is defined as Hb < 13.0 g/dL for males, and Hb < 12.0 g/dL for females which should be added to the overall management of respiratory diseases. The incidence of anemia in the general population increases with age. Inflammatory anemia or anemia of chronic disease occurs in many diseases.

In adults with COPD, anemia is associated with worse exercise capacity, greater breathing difficulties, and more serious diseases. The biomarkers found in the body weight of anemia suggest that inflammation, lung tissue, and oxidative stress may be the pathways for the poor prognosis of anemia and COPD. For example, increasing systemic inflammation and airway epithelial damage may cause anemia to adversely affect the outcome of COPD. Anemia may be one of several independent factors for poor outcomes in the subgroup of COPD patients with high levels of systemic inflammation and burden of comorbidities\[11\]. In addition, studies have shown that anemia is associated with an increase in the long-term mortality of COPD, and even mild anemia is also associated with a significant increase in risk\[27\]. In patients with acute exacerbations of COPD, anemia may be risk factors of hospital death for patients with severe COPD who need mechanical ventilation support\[28\]. As for red blood cell, red blood cell oxidative modification is a valuable biological indicator in the clinical treatment of COPD\[29\].

Increased levels of RBC and Hb can compensate for poor respiratory function\[30, 31\]. Therefore, these values can be used as appropriate criteria for evaluating respiratory function, under the premise of excluding the influence of other factors on the changes in red blood cell proliferation on RBC and Hb levels. Lym and PLT are rarely affected by other factors, so they are a benchmark used to measure the general level of blood cell proliferation. The red blood cell index obtained from this can accurately reflect the degree of compensation.
It is known that the increase in RBC and Hb levels reflects the sensitivity to hypoxia[32, 33]. When the body has respiratory failure, it is often in a poor state, so that the general blood cell proliferation level may be abnormal. Hence, it is necessary to determine that a variable accurately reflects the changes in blood cell proliferation levels. The COPD group is higher than the control group, which can further confirm that RCI is an effective and reliable indicator for the assessment of chronic pulmonary insufficiency. RCI is considered to reflect the compensatory increase in RBC count and Hb level secondary to poor lung function which can also reflect the true state of respiratory function[15]. Our research results indicate that RCI increases with the decrease of FEV1%, and there is a significant correlation between RCI and FEV1 (p = 0.016), FEV1% (p = 0.001) and FVC (p = 0.027), but there is no correlation between RCI and FEV1/FVC (p = 0.150). Compared with NLR and PLR, NLR, PLR and pulmonary function have no correlation, but there is a significant correlation between RCI and FVC (p = 0.004), indicating comparing with NLR and PLR, RCI can better predict the changes of COPD’s respiratory function.

Other research results show that the NLR of COPD patients in the stable phase is significantly higher than that of the healthy control group, and compared with the stable phase, it further increases in the acute exacerbation of the disease. Therefore, NLR is a fast, cheap, and easy-to-measure indicator that can be used for routine whole blood technical analysis[34]. The same conclusion was also drawn in the meta-analysis conducted by Paliogiannis et al.[35]

As for PLR, PLR is the same as NLR. The PLR of patients with stable COPD is significantly higher than that of healthy controls, while the PLR level of non-survivors with acute exacerbation of COPD is significantly higher, but compared with NLR, PLR is still more effective and simple prognostic indicators[36]. The cross-sectional multi-center study of Alexa et al.[8] showed that NLR and PLR are predictors of COPD, but there is no correlation between the two and FEV1, and there is no correlation between the two groups and the GOLD A-D group.

In addition, we also conducted a sub-group analysis of COPD patients, and conducted correlation studies according to gender, duration of disease, smoking, hypertension, diabetes, and hyperlipidemia. The results are presented in Fig. 2A. It can be observed that among the above-mentioned sub-groups, only the gender and hypertension sub-groups, there are differences between the RCI of COPD patients. The results in the figure cannot accurately illustrate that gender and hypertension must have an impact on RCI. Further research is needed.

Our article is the first to use RCI as a prognostic biomarker for the diagnosis of COPD. Previously, RCI was only used as an effective index for evaluating respiratory function, a replacement index for evaluating respiratory function with complete blood count parameters. Compared with the healthy control group, the COPD combined elderly group has high RCI, and the positive rate of abnormally elevated RCI in the COPD group and the elderly group is significantly higher than that of the control group[15].

However, our study also has certain limitations. Firstly, the sample size is relatively small. Secondly, we are a single-center cross-sectional survey that only focuses on the Chinese population. In addition, we only explored the clinical significance of the impact of RCI on COPD, lack of influence on cellular and
molecular mechanisms. In this regard, we need to conduct prospective cohort studies, conduct research on different ethnic groups, recruit more volunteers from multiple centers, and further study the mechanism of RCI in the progress of COPD to solve the above problems.

Conclusion

In summary, RCI is a novel biomarker that can better assess the respiratory function and severity of COPD than NLR and PLR. Increased RCI is independently related to deterioration of lung respiratory function.

Abbreviations

COPD, chronic obstructive pulmonary disease; RCI, red cell index; NLR, neutrophil-lymphocyte ratio; PLR, platelet-lymphocyte ratio; Hb, Hemoglobin; Lym, Lymphocyte; PLT, Platelet; FEV1\%, forced expiratory volume in 1 second in percent of the predicted value; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; BODE, body mass index, airway obstruction, dyspnoea, severe exacerbations; SGRQ, St. George's Respiratory Questionnaire; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ADO, age, dyspnea and airflow obstruction; DOSE, MRC Dyspnea Scale, airflow obstruction, smoking status and exacerbations; BMI, body mass index; PaCO$_2$, partial pressure of carbon dioxide in arterial blood; PaO$_2$, partial pressure of oxygen in arterial blood; ROC, receiver operating characteristics; AUC, the area under the curve.

Declarations

Ethics approval and consent to participate

All participants provided written informed consent for participation in this study. The study was conducted in accordance with the ethical standards of the Ethics Committees of the Third Affiliated Hospital of Wenzhou Medical University (YJ20170015).

Consent for publication

Not applicable.

Availability of data and material

The data used or analyzed underlying this article are not publicly available due to individual privacy. The data will be available from the corresponding author on reasonable request.

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**Competing interests**

The authors report no declarations of competing interest.

**Authors’ Contributions**

XZ2, YH, JW participated in the conception and design; JS, KD, HH, CY, FF, BH, WP, JJ, WT, XZ1 are responsible for data acquisition; JS, KD, CY, FF, BH participated in data analysis and interpretation; YH, JW are responsible for drafting the article; XZ2, YH, JW, HH are responsible for critically revising the article for important intellectual content. All the authors read and approved the final manuscript.

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**Table**

Due to technical limitations, table 3 is only available as a download in the Supplemental Files section.

**Figures**
Consecutive include previously diagnosed COPD patients admitted to the hospital in February 2018—February 2019
N=138

31 Exclude
1 obstructive sleep apnea hypopnea syndrome
4 alimentary nauseum
4 renal insufficiency
15 heart failure
2 chronic liver damage
5 thyroid disease

107 eligible patients

Excluded 7 miss data

Included 107 healthy control

Total 207 patients were enrolled

Figure 1

Flow Chart Showing the Literature Search and Selection. Specific reasons for exclusion of studies are also shown. Abbreviations: Chronic obstructive pulmonary disease.
Figure 2

(A) Sub-group analysis of COPD patients, and conducted correlation studies according to gender, duration of disease, smoking, hypertension, diabetes, and hyperlipidemia. (B) Correlations of the RCI, NLR and PLR with FEV1%. Notes: Correlations between RCI, NLR and PLR levels in COPD patients and FEV1% were assessed by Pearson's correlation test, RCI, \( r = -0.302, p = 0.004 \); NLR, \( r = -0.153, p = 0.148 \); and PLR, \( r = -0.098, p = 0.354 \).
Figure 3

ROC curves of the RCI, NLR, PLR, MPV and PDW of COPD patients. The area under ROC curve: 0.729; 95% CI: 0.619 - 0.839; \( p = 0.001 \).

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- Table3.pdf