ORIGINAL RESEARCH

Association of Red Cell Index and Adverse Hospitalization Outcomes in Chronic Obstructive Pulmonary Disease Patients with Acute Exacerbation: A Retrospective Cohort Study

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Purpose: Previous studies have shown that the red cell index (RCI) can be considered as a simple and useful method to evaluate respiratory function. However, at present its association with adverse hospitalization outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is not fully understood. Our study aimed to examine the relationship between adverse hospitalization outcomes and RCI among AECOPD patients.

Patients and Methods: We performed a retrospective analysis of consecutive patients from January 2015 to October 2021. In this study, RCI was the independent variable, measured at baseline, and adverse hospitalization outcome was the dependent variable. According to the RCI median (RCI=2.221), we divided 377 patients into two roughly equal groups (188 and 189, respectively). Next, the association between RCI and adverse hospitalization outcomes was explored using multivariable logistic regression models. To identify any non-linear relationship, a generalized additive model (GAM) was employed.

Results: With a total of 377 patients with AECOPD, we divided them into two roughly equal groups to compare the clinical factors and RCI levels. The patients in the higher RCI group showed poorer outcome incidence (18 [9.57%] vs 31 [16.40%]; $p = 0.049$). After accounting for potential confounders, the results showed that RCI was positively associated with adverse hospitalization outcomes (odds ratio [OR] = 1.15, 95% CI: 1.01–1.32). In addition, a non-linear relationship was detected between RCI and adverse hospitalization outcomes, which had an inflection point of 3.2. There were odds ratios and confidence intervals of 0.8 (0.7–1.0) and 1.3 (1.2–1.4) on the left and right sides of the inflection point, respectively.

Conclusion: The RCI and adverse hospitalization outcomes exhibited a non-linear relationship in the AECOPD patients. RCI is strongly positively correlated with adverse hospitalization outcomes when it was greater than 3.2.

Keywords: AECOPD, RCI, worse hospitalization outcomes, non-linearity

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable chronic lung disease that causes progressive breathing difficulties. According to the World Health Organization, in 2019, 3.23 million people died from COPD globally, accounting for 6% of all global deaths in that year, and over 90% of these deaths occurred in low- and middle-income countries, including China.[1] Over the next 40 years, the prevalence of COPD is expected to rise, with more than 5.4 million people likely to die from COPD and related conditions each year by 2060.[2–4] AECOPD is defined as ≥2 respiratory symptoms (increased frequency or severity of cough, increased sputum volume or purulent sputum, and wheezing) that cause the patient's attending physician to change the original treatment.[5] It is the most common cause of hospitalization and a significant contributor to mortality among COPD patients.[6]

The diagnosis of COPD is currently based on a forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio of less than 0.70 as determined by spirometry after bronchodilator use.[5] For many years, physical methods have been used to evaluate pulmonary ventilation and respiratory function, such as the vital capacity test.[7,8] However, these methods are often susceptible to patient subjective factors, and they are particularly inappropriate for children and bedridden individuals. A blood gas analysis can be used for evaluating the respiratory function of bedridden patients. When using this method, it is crucial to collect arterial blood samples under vacuum conditions and then to perform rapid analysis under vacuum. The results may be affected if the preliminary treatment is not appropriate.[9]

It is known that increased levels of red blood cells (RBC) and hemoglobin (Hb) can compensate for poor pulmonary function and reflects hypoxia sensitivity.[10] These values may therefore be considered an appropriate criterion for evaluating respiratory function.[11] In COPD patients, lymphocytes (Lym) are the main inflammatory cells in the central airways and lung parenchyma, which is correlated with the number of alveolar injuries and the extent of airway obstruction.[12] Platelets (PLT) and their functional consequences in COPD are of interest. There has been previous evidence that platelets and platelet activation influence bronchoconstriction, bronchial reactivity, inflammation, and remodeling in the airways in animals.[13] Guang et al have been demonstrated that lymphocytes and platelets can be used to measure blood cell proliferation as a baseline.[11] Now, the red blood cell index (RCI) is being used, and it's based upon platelet count, lymphocyte count, hemoglobin and red blood cells count. The formula for calculating RCI is as follows: (RBC × Hb)/(Lym × PLT).[11] RCI is inversely proportional to pulmonary function in theory, and it can be used to measure pulmonary function.[11,14] However, its association with poorer outcomes among AECOPD patients is not fully understood.

This study aimed to investigate the association between adverse hospitalization outcomes and RCI in patients with AECOPD.

Patients and Methods
Study Population
Patients with AECOPD who were admitted in the First Affiliated Hospital of Sun Yat-sen University from January 2015 to October 2021 were retrospectively and consecutively enrolled in this study.

The patients were included this study if they met the following criteria: 1) the diagnosis of COPD was made by a pulmonary specialist based on past smoking history, clinical evaluation, and pulmonary function testing which showed air flow obstruction even when taken with bronchodilators (forced expiratory volume in 1 second to forced vital capacity of less than 0.70);[5,15] 2) AECOPD is defined as an acute worsening of respiratory symptoms such as dyspnea, cough, and sputum volume or purulence;[5] and 3) age ≥40 years. In cases where a patient had been admitted to the hospital multiple times, only the first admission was recorded. The following patients were excluded: 1) other respiratory diseases, such as bronchiectasis, lung cancer, asthma, tuberculosis, interstitial lung disease; 2) severe cardiovascular disease, including acute left heart failure; 3) septic shock; 4) diseases of the blood system, including chronic lymphocytic leukemia, multiple myeloma, myelofibrosis etc. Finally, a total of 377 patients were included in the study (Figure 1).

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was reviewed and approved by the institutional review board of the First Affiliated Hospital of Sun Yat-sen University.

Data Collection
We collected demographic and clinical data from electronic medical records, including sex, age, BMI, drinking history, smoking history, comorbidities, length of hospital stay, and vital capacity parameters from the last stable period in the last two years (FEV_1/FVC, FEV_1% Pred, FEV_1 and FVC). We collected the blood count and other inflammatory parameters at the time of admission before administering antibiotics and steroids. Additionally, blood samples were collected for analysis of arterial blood gas (PaO_2, $PaCO_2$ and pH value). In this study, smoking was categorized into three classes: never-smoker (never smoked in their lifetime), current smoker (smoked in the past year) and ever-smoker (smoked sometime in their lifetime, but not currently). The RCI of each subject was calculated and analyzed. The formula for calculating RCI was as follows: (RBC × Hb)/(Lym × PLT).[11] Each participant's clinical outcomes were recorded.
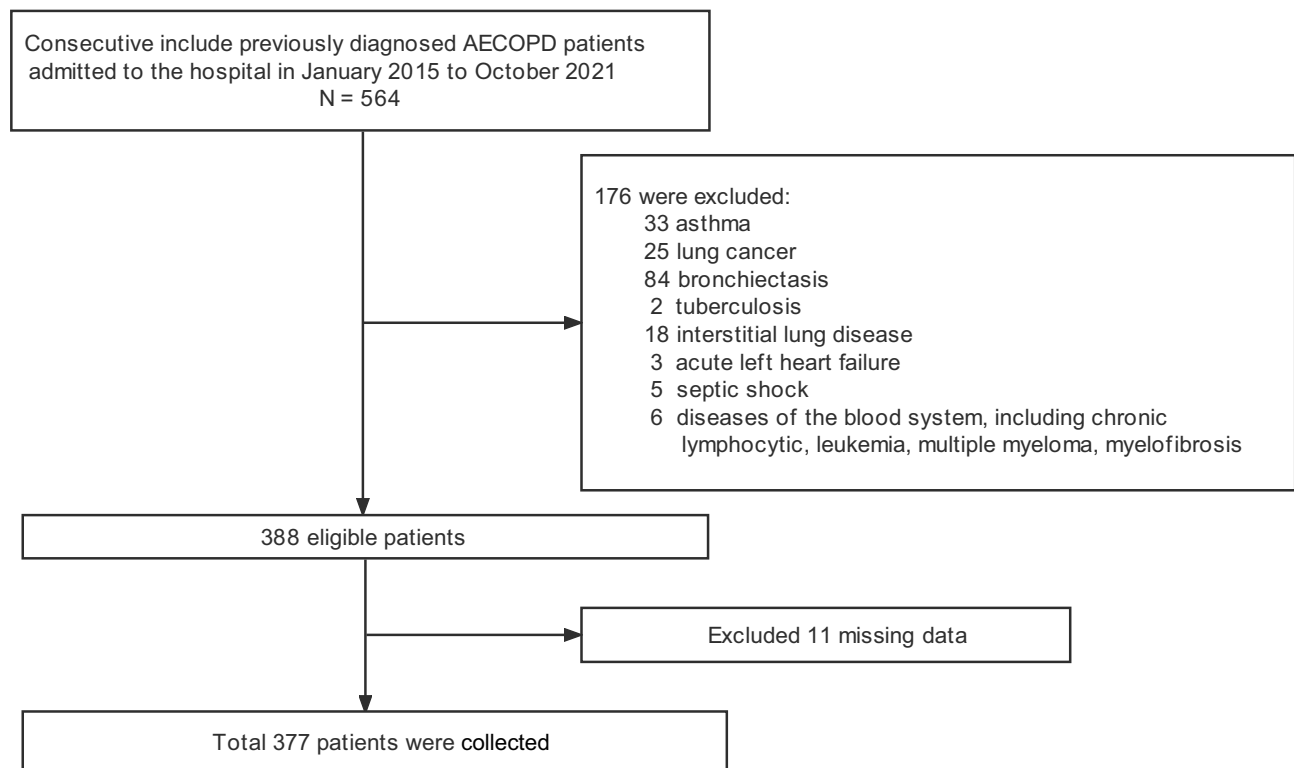
Figure 1 Flowchart of the study participants.
Abbreviation: AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Patients who met any of these three criteria were considered to have a poor hospitalization outcome: requiring invasive ventilator, intensive care unit (ICU) admission, or death in hospital.

Statistical Analysis

Continuous variables are presented as mean ± SDs (normal distribution) or medians and IQRs (skewed distribution), while categorical variables are presented as number (%). One-Way Anova tests (normal distribution), Kruskal–Wallis H (skewed distribution) test and chi-square tests (categorical variables) were used to determine any statistical differences between the means and proportions of the groups.

Firstly, a univariate model was used to evaluate whether the RCI and other biochemical variables were associated with adverse hospitalization outcomes. Secondly, to determine the relationship between adverse hospitalization outcomes and the RCI, a smooth curve was fitted. Once non-linearity was detected, the inflection point was calculated using the recursive algorithm, then a two-piecewise linear regression on either side of the inflection point was constructed. We then compared the two-piecewise linear regression model and one-line model. The optimal fitting model was determined according to the *p*-value of logarithmic likelihood ratio test. If the *P* value of less than 0.001 for the log-likelihood ratio test indicates that the two-side linear regression was more appropriate for fitting the association between RCI and adverse outcomes, because it can accurately reflect the relationship between them. Thirdly, multivariate logistic regression models were used to examine whether RCI had an independent effect on adverse hospitalization outcomes. We used the following principles to determine whether the potential confounders were adjusted: reported as relevant or used in previous studies[14,16] (especially in the study about predictor of AECOPD) and the potential confounders effect estimates individually changed by at least 10%.[17] A total of three models were established: the crude model did not adjust other covariates; model 1 adjusted for age, sex, BMI and smoking status; model 2 further adjusted for comorbidities (including hypertension, diabetes, congestive heart failure, coronary artery disease, chronic kidney disease and arrhythmia), therapy in stable stage, inflammatory parameters (including PCT, CRP, LDH), FEV_1/FVC, and $PaCO_2$. Finally, we performed subgroup analysis using the stratified linear regression model. Interactions were evaluated using likelihood ratio tests.

Since 18.8% of patients were missing BMI and 34% were missing CRP, we used multiple imputations (MIs), based on five replications and a chained equation approach method in the R MI procedure.[18,19] Then, the regression coefficients and standard error of five regression models were combined.[20]

All analyses were performed using Empower (R) (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA) and R (http://www.R-project.org, The R Foundation). A *p*-value of <0.05 was considered statistically significant.

Results

Baseline Characteristics of the Study Subjects and Univariate Analyses

According to the RCI median (RCI=2.221), we divided the 377 patients into two equal groups: RCI<2.221 was defined as the lower RCI group (n=188), while RCI≥2.221 was defined as the higher RCI group (n=189). The clinical characteristics of participants are listed in Table 1. We found no significant differences between the two groups in terms of age, sex, and BMI. Compared with the lower RCI group, the RCI (4.7 ± 2.4 vs 1.4 ± 0.5, $p < 0.001$), red blood cell (4.7 ± 0.7 vs 4.4 ± 0.8, $p < 0.001$), hemoglobin (136.1 ± 16.8 vs 127.7 ± 22.8, $p < 0.001$), CRP (16.8 [4.6,56.4] vs 6.0 [2.0,39.0], $p = 0.001$), LDH (231.7 ± 116.9 vs 215.2 ± 83.0, $p = 0.017$), length of stay (10.2 ± 5.7 vs 9.5 ± 11.1, $p < 0.001$), poorer outcome (31 [16.4%] vs 18 [9.6%], $p = 0.049$) levels in the higher RCI group were higher. Inversely, compared with the lower RCI

Table 1 Baseline Characteristics of Participants

RCI	Lower RCI Group (RCI <2.221)	Higher RCI Group (RCI ≥2.221)	*P* value
Number	188	189	
Age, years	73.55 ± 8.89	75.08 ± 8.21	0.083
Male, n (%)	160 (85.11)	169 (89.42)	0.209
BMI, kg/m^2	20.86 ± 3.97	20.58 ± 3.90	0.535
Smoking history, n (%)			0.017
Current-smoker	49 (26.06)	27 (14.36)	
Ever-smoker	111 (59.04)	126 (67.02)	
Never-smoker	28 (14.89)	35 (18.62)	
Drinking, n (%)	17 (9.04)	13 (6.91)	0.446
SBP, mmHg	134.80 ± 19.99	134.84 ± 20.56	0.985
DBP, mmHg	77.89 ± 12.48	77.94 ± 12.52	0.967
Comorbidities, n (%)			
Coronary artery disease	35 (18.62)	30 (15.87)	0.481
Congestive heart failure	7 (3.72)	8 (4.23)	0.800
Arrhythmia	6 (3.19)	12 (6.35)	0.151
Chronic kidney disease	7 (3.72)	3 (1.59)	0.197
Diabetes	23 (12.23)	21 (11.11)	0.734
Hypertension	86 (45.74)	87 (46.03)	0.955
Pulmonary Function Test[a]			
FEV$_1$, L	0.80 ± 0.28	0.73 ± 0.32	0.028
FEV$_1$/FVC, %	43.86 ± 10.84	43.02 ± 11.54	0.600
FEV$_1$%Pred, %	34.71 ± 13.61	32.94 ± 14.81	0.386
GOLD grade, I/II/III/IV[b]	1/14/46/45	0/12/32/45	0.532
Therapy in stable stage, n (%)			0.683
LABA monotherapy	0 (0.00)	1 (0.53)	
LAMA monotherapy	10 (5.32)	13 (6.95)	
LABA+ICS	21 (11.17)	17 (9.09)	
LAMA+LABA	1 (0.53)	1 (0.53)	
LABA+LAMA+ICS	29 (15.43)	37 (19.79)	

(Continued)

Table 1 (Continued).

RCI	Lower RCI Group (RCI <2.221)	Higher RCI Group (RCI ≥2.221)	P value
Blood cell count			
Leukocytes, ×10^9/L	9.59 ± 3.39	8.67 ± 4.58	0.027
Lymphocytes, ×10^9/L	1.72 ± 0.60	0.91 ± 0.37	<0.001
Neutrophils, ×10^9/L	5.98 (4.55–8.21)	5.88 (3.75–8.25)	0.623
Monocytes, ×10^9/L	0.66 (0.52–0.91)	0.58 (0.41–0.82)	0.012
Eosinophils, ×10^9/L	0.17 (0.07–0.26)	0.05 (0.01–0.15)	<0.001
Hemoglobin, g/L	127.74 ± 22.77	136.07 ± 16.78	<0.001
Platelet, ×10^9/L	276.65 ± 101.58	188.87 ± 60.49	<0.001
Red blood cell, ×10^12/L	4.36 ± 0.76	4.68 ± 0.71	<0.001
RCI	1.40 ± 0.51	4.72 ± 2.44	<0.001
Inflammatory parameters			
CRP, mg/L[c]	6.00 (2.00–39.00)	16.79 (4.60–56.40)	0.001
PCT, ng/mL[d]	0.07 (0.05–0.11)	0.08 (0.05–0.14)	0.988
LDH, IU/L[e]	215.23 ± 82.95	231.67 ± 116.89	0.017
NT-proBNP	168.15 (61.28–741.00)	360.50 (95.75–1473.00)	0.014
D-dimer, mg/L	0.60 (0.34–1.35)	0.68 (0.38–1.56)	0.505
Fibrinogen, g/L	4.09 ± 1.47	4.06 ± 1.39	0.856
Creatinine, umol/L	88.99 ± 41.64	82.73 ± 35.15	0.116
BUN, mmol/L	7.03 ± 3.26	6.95 ± 3.40	0.818
Total protein, g/L	66.86 ± 7.34	67.17 ± 7.56	0.689
Albumin, g/L	37.13 ± 4.23	37.00 ± 4.53	0.773
Length of stay, days	7.00 (5.00–10.00)	9.00 (7.00–12.00)	<0.001
Require NIMV, n (%)	19 (10.11)	52 (27.51)	<0.001
Worse outcome, n (%)	18 (9.57)	31 (16.40)	0.049
Invasive ventilation	11 (5.85)	15 (7.91)	
ICU admission	14 (7.45)	27 (14.29)	
Mortality	6 (3.19)	7 (3.37)	
PH	7.39 ± 0.06	7.37 ± 0.07	0.03
PaO_2, mmHg	84.65 ± 27.90	81.23 ± 34.87	0.376
PaCO_2, mmHg[f]	49.29 ± 16.69	59.74 ± 20.28	<0.001

Notes: [a]Pulmonary function test was performed on 195 subjects, 106 in the lower RCI group and 89 in the higher RCI group; [b]GOLD grade was determined by pulmonary function test; [c]CRP was available in 250 subjects, 120 with lower RCI and 130 with higher RCI; [d]PCT was available in 350 subjects, 170 with lower RCI and 180 with higher RCI; [e]LDH was available in 323 subjects, 160 with lower RCI and 163 with higher RCI; and [f]PaCO_2 was available in 276 subjects, 131 with lower RCI and 145 with higher RCI.
Abbreviations: SBP, systolic blood pressure; DBP, Diastolic blood pressure; BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; FEV_{1%}Pred, forced expiratory volume in 1 second in percent of the predicted value; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LAMA, long-acting antimuscarinic antagonists; LABA, long-acting beta-agonists; RCI, red cell index; PCT, procalcitonin; CRP, C-reactive protein; LDH, lactic dehydrogenase; NIMV, noninvasive mechanical ventilation; ICU, intensive care unit; PaO_2, partial pressure of oxygen in arterial blood; PaCO_2, partial pressure of carbon dioxide in arterial blood.

group, the lymphocytes (0.9 ± 0.4 vs 1.7 ± 0.6, $p < 0.001$) and platelet (188.9 ± 60.5 vs 276.6 ± 101.6, $p < 0.001$) levels in the higher RCI group were lower. In addition, higher PaCO_2 (59.7 ± 20.3 vs 49.3 ± 16.7, $p < 0.001$) and lower FEV_1 (0.7 ± 0.3 vs 0.8 ± 0.3, $p = 0.028$), FEV_{1%}Pred (32.9 ± 14.8 vs 34.7 ± 13.6) were observed among the AECOPD patients with higher RCI. However, there was no significant difference between the two groups in terms of FEV_1/FVC ratio and PaO_2. The results show that RCI may have an association with pulmonary function. RCI has a positive correlation with COPD severity. In the univariate analyses (Table 2), the outcome variable was associated with diastolic blood pressure (DBP), lymphocytes, red blood cell, hemoglobin, RCI, length of stay, Require NIMV, pH, and PaCO_2.

Table 2 The Results of Univariate Analysis

	Statistics	**Effect size (OR)**	**P value**
Age, years	74.32 ± 8.58	1.02 (0.99, 1.06)	0.2496
Sex			
Female	48 (12.73)	Ref	
Male	329 (87.27)	0.60 (0.27, 1.33)	0.2085
BMI, kg/m^2	20.72 ± 3.93	0.98 (0.87, 1.10)	0.7121
Smoking history, n (%)			
Current-smoker	76 (20.21)	Ref	
Ever-smoker	237 (63.03)	2.02 (0.82, 5.01)	0.1286
Never-smoker	63 (16.76)	1.70 (0.56, 5.18)	0.3529
Drinking, n (%)			
No	346 (92.02)	Ref	
Yes	30 (7.98)	1.76 (0.68, 4.55)	0.2427
SBP, mmHg	134.82 ± 20.25	1.00 (0/98, 1.01)	0.8474
DBP, mmHg	77.91 ± 12.48	0.97 (0.95, 0.99)	0.0161
Hypertension, n (%)			
No	204 (54.11)	Ref	
Yes	173 (45.89)	1.05 (0.58, 1.92)	0.8743
Diabetes, n (%)			
No	333 (88.33)	Ref	
Yes	44 (11.67)	1.88 (0.84, 4.21)	0.1225
Coronary artery disease, n (%)			
No	312 (82.76)	Ref	
Yes	65 (17.24)	0.39 (0.13, 1.12)	0.0808
Arrhythmia, n (%)			
No	359 (95.23)	Ref	
Yes	18 (4.77)	0.83 (0.18, 3.72)	0.8076
Congestive heart failure, n (%)			
No	362 (96.02)	Ref	
Yes	15 (3.98)	1.72 (0.47, 6.32)	0.4157
Chronic kidney disease, n (%)			
No	367 (97.35)	Ref	
Yes	10 (2.65)	1.70 (0.35, 8.26)	0.5092
White blood cell, ×10^9/L	9.13 ± 4.05	1.02 (0.95, 1.10)	0.5645
Lymphocytes, ×10^9/L	1.31 ± 0.64	0.55 (0.32, 0.94)	0.0291
Neutrophils, ×10^9/L	6.91 ± 3.95	1.04 (0.97, 1.12)	0.2536
Eosinophils, ×10^9/L	0.11 (0.02–0.22)	0.21 (0.03, 1.53)	0.1241
Platelet, ×10^9/L	232.64 ± 94.30	1.00 (0.99, 1.00)	0.2241
Red blood cell, ×10^{12}/L	4.52 ± 0.75	0.54 (0.36, 0.81)	0.0028
Haemoglobin, g/L	131.92 ± 20.40	0.98 (0.96, 0.99)	0.0009
Monocytes, ×10^9/L	0.72 ± 0.69	0.80 (0.35, 1.81)	0.5880
RCI	3.06 ± 2.42	1.18 (1.06, 1.31)	0.0024
CRP, mg/L	10.84 (2.83–51.00)	1.00 (1.00, 1.01)	0.2733
PCT, ng/mL	0.23 ± 0.77	1.01 (0.68, 1.49)	0.9627
LDH, IU/L	223.53 ±101.68	1.00 (1.00, 1.00)	0.8422
NT-proBNP	223.20 (86.80–1029.00)	1.00 (1.00, 1.00)	0.3319
D-dimer, mg/L	0.62 (0.36–1.42)	1.09 (1.00, 1.19)	0.0517
Fibrinogen, g/L	4.08 ± 1.43	0.91 (0.72, 1.14)	0.4116

(*Continued*)

Table 2 (Continued).

	Statistics	Effect size (OR)	P value
Albumin, g/L	37.07 ± 4.38	0.94 (0.87, 1.01)	0.0687
Length of stay, days	8.00 (6.00–12.00)	1.15 (1.10, 1.21)	<0.0001
Require NIMV, n (%)			
No	306 (81.17)	Ref	
Yes	71 (18.83)	6.39 (3.36, 12.12)	<0.0001
FEV_1, L	0.77 ± 0.30	0.24 (0.01, 4.29)	0.3321
FEV_1/FVC, %	43.48 ± 11.15	0.97 (0.91, 1.04)	0.4215
FEV_1 pred, %	33.91 ± 14.16	0.98 (0.92, 1.04)	0.4398
pH	7.38 ± 0.07	0.00 (0.00, 0.00)	<0.0001
PaO_2, mmHg	82.86 ± 31.73	1.00 (0.98, 1.01)	0.4452
$PaCO_2$, mmHg	54.78 ± 19.35	1.05 (1.03, 1.07)	<0.0001

Abbreviations: SBP, systolic blood pressure; DBP, Diastolic blood pressure; BMI, body mass index; RCI, red cell index; PCT, procalcitonin; CRP, C-reactive protein; LDH, lactic dehydrogenase; NIMV, noninvasive mechanical ventilation; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood.

Relationship Between RCI and Adverse Hospitalization Outcomes

We developed three models to control other potential confounding variables and assess the independent effects of RCI on adverse hospitalization outcomes (Table 3). We first treated RCI as a continuous variable. After adjusted sex, age, BMI, smoking status, comorbidities, therapy in stable stage, CRP, PCT, LDH, FEV_1/FVC and $PaCO_2$, each 1-unit increase in RCI was associated with a 15% (OR=1.15; 95% CI: 1.01–1.32) increased risk of adverse clinical outcomes. We also treated RCI as a categorical variable (lower and higher groups) for sensitivity analysis. In the crude model, compared to the lower RCI group reference, the OR for the higher RCI group (OR=1.85; 95% CI: 1.00–3.44) was significantly higher. After accounting for sex, age, BMI and smoking status in model 1, the RCI remained independently related to the poor hospitalization outcome, the higher RCI group (OR=1.90; 95% CI: 1.00–3.59). After further adjustment for comorbidities, therapy in stable stage, inflammatory parameters, FEV_1/FVC and $PaCO_2$, compared with the lower RCI group, the risk of poorer clinical outcome in the higher RCI group was increased by 77% (OR=1.77, 95% CI: 0.82–3.84), although this was not statistically significant.

Since 69 (377) patients were missing BMI and 127 (377) patients were missing CRP, we used multiple imputation for missing data. Five datasets were created and analyzed together (Tables S1–S5).

Non-Linearity of RCI and Adverse Hospitalization Outcomes

As RCI was a continuous variable, it was necessary to explore whether there was a non-linear relationship between RCI and adverse hospitalization outcomes (Table 4, Figure 2). The smooth curve showed a nonlinear relationship (adjusted for

Table 3 Association Between RCI and Adverse Hospitalization Outcomes in AECOPD Patients

Exposure	Crude model (OR, 95% CI)	Model 1 (OR, 95% CI)	Model 2 (OR, 95% CI)
RCI (per unit)	1.18 (1.06, 1.31)	1.19 (1.06, 1.32)	1.15 (1.01, 1.32)
RCI			
Lower RCI group (RCI <2.221)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Higher RCI group (RCI ≥2.221)	1.85 (1.00, 3.44)	1.90 (1.00, 3.59)	1.77 (0.82, 3.84)

Notes: Model 1 adjusted for sex, age, BMI and smoking status; Model 2 further adjusted for comorbidities (including diabetes, hypertension, arrhythmia, congestive heart failure, chronic kidney disease and coronary artery disease), therapy in stable stage, inflammatory indicators (including PCT, CRP, LDH), FEV_1/FVC, $PaCO_2$. Among them, 69 patients were missing BMI, accounting for about 18% of the total patients; 127 patients were missing CRP, accounting for about 34% of the total patients. We used multiple imputation for missing data and presented the results after multiple imputation.
Abbreviations: RCI, red cell index; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; PCT, procalcitonin; CRP, C-reactive protein; LDH, lactic dehydrogenase; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; OR, Odd ratios; CI, confidence intervals.

Table 4 The Results of Two-Piecewise Linear Regression Model

	OR	95% CI	P value
Fitting model by standard linear regression	1.2	1.1 to 1.2	<0.001
Fitting model by two-piecewise linear regression			
The inflection point of RCI			
<3.2	0.8	0.7 to 1.0	0.058
≥3.2	1.3	1.2 to 1.4	<0.001
P for the log-likelihood ratio test		<0.001	

Notes: Effect: worse outcome cause: red cell index adjusted: sex; age; BMI; smoking history; comorbidities (including diabetes, hypertension, arrhythmia, congestive heart failure, chronic kidney disease and coronary artery disease), therapy in stable stage, PCT, CRP, LDH, FEV_1/FVC, $PaCO_2$.
Abbreviations: RCI, red cell index; BMI, body mass index; PCT, procalcitonin; CRP, C-reactive protein; LDH, lactic dehydrogenase; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; OR, Odd ratios; CI, confidence intervals.

age, sex, BMI, smoking status, comorbidities CRP, PCT, LDH, FEV_1/FVC and $PaCO_2$) between the RCI and adverse hospitalization outcomes. We calculated the inflection point as 3.2 by using two-piecewise linear regression model. The effect size, 95% CI and *P* value for the right side of the inflection point (RCI ≥3.2) were of 1.3, 1.2 to 1.4 and *P* value of <0.001, respectively. However, the relationship could not be observed on the left side of the inflection point (RCI < 3.2) (OR = 0.8, 95% CI: 0.7–1.0, *P* = 0.058). This result suggested a threshold effect on the independent association between the RCI and adverse hospitalization outcomes.
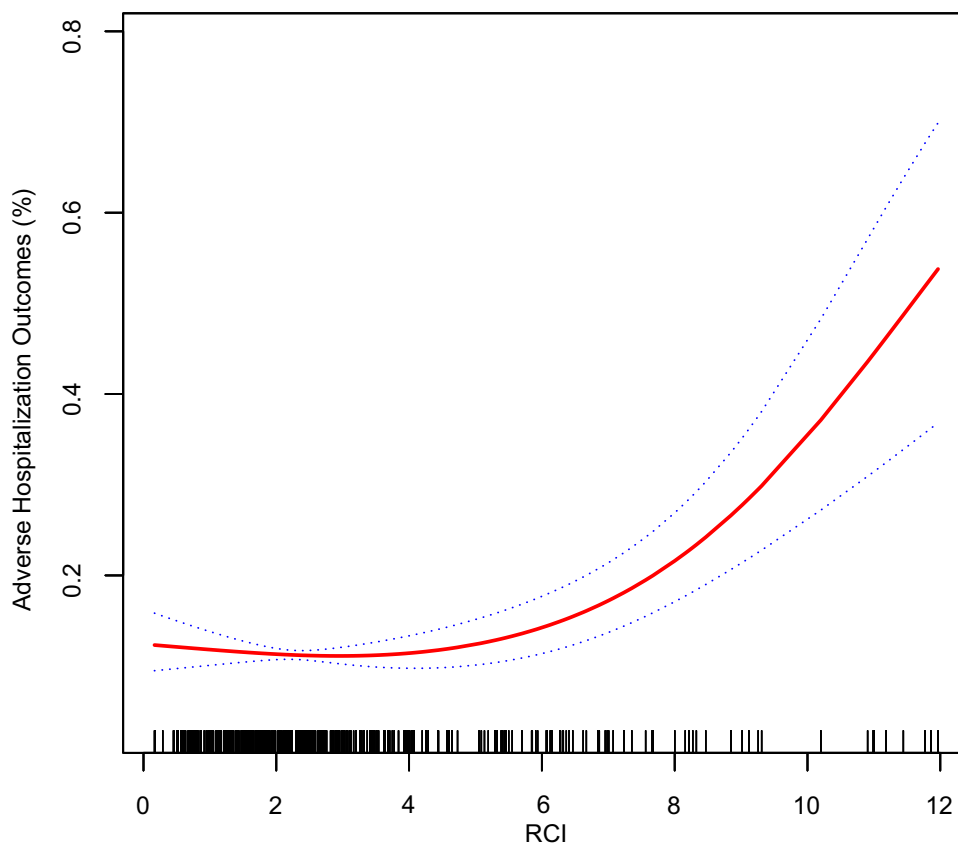
Figure 2 General additive model demonstrate the relationship between RCI and the risk of adverse hospitalization outcomes. A nonlinear relationship between the two was detected after adjusting for sex; age; BMI; smoking history; comorbidities (including diabetes, hypertension, arrhythmia, congestive heart failure, chronic kidney disease and coronary artery disease), therapy in stable stage, PCT, LDH, CRP, FEV_1/FVC and $PaCO_2$. The red line represents the best-fit line, and the blue lines are 95% confidence intervals.
Abbreviations: RCI, red cell index; BMI, body mass index; PCT, procalcitonin; CRP, C-reactive protein; LDH, lactic dehydrogenase; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; $PaCO_2$, partial pressure of carbon dioxide in arterial blood.

Subgroup Analysis

We used stratification variables in the subgroup analysis, including sex, age, BMI, smoking history, diabetes, hypertension, arrhythmia, congestive heart failure, chronic kidney disease, coronary artery disease and $PaCO_2$ (Table 5). In the stratified analysis, the association between the RCI and adverse hospitalization outcomes was similar for most strata ($P > 0.05$). A significant interaction was observed only for age ($P = 0.0003$). The RCI had a positive correlation with adverse hospitalization outcomes among patients younger than 75 (OR=1.60, 95% CI: 1.23–2.07).

Table 5 Subgroup Analyses of the Association Between RCI and Adverse Hospitalization Outcomes in AECOPD Patients

Subgroup	Participants (n)	OR (95% CI)	P value	P for Interaction
Age, years				0.0003
<75	184	1.60 (1.23, 2.07)	0.0004	
≥75	193	0.89 (0.72, 1.11)	0.3018	
Sex				0.3305
Female	48	0.94 (0.62, 1.43)	0.7724	
Male	329	1.17 (0.99, 1.37)	0.064	
BMI, kg/m²				0.166
≤20.43	154	1.41 (1.08, 1.84)	0.0121	
>20.43	154	1.05 (0.74, 1.50)	0.7686	
Smoking history				0.3908
Current-smoker	76	1.20 (0.85, 1.70)	0.31	
Ever-smoker	237	1.17 (0.98, 1.40)	0.0851	
Never-smoker	63	0.86 (0.54, 1.37)	0.5323	
Hypertension				0.1285
No	204	1.26 (1.03, 1.54)	0.0268	
Yes	173	0.99 (0.77, 1.27)	0.9248	
Diabetes				0.3626
No	333	1.16 (0.99, 1.36)	0.0689	
Yes	44	0.91 (0.55, 1.49)	0.7086	
Coronary artery disease				0.6792
No	312	1.15 (0.98, 1.36)	0.0964	
Yes	65	1.04 (0.66, 1.65)	0.863	
Arrhythmia				0.0785
No	359	1.10 (0.94, 1.30)	0.2465	
Yes	18	1.81 (0.93, 3.53)	0.0804	
Congestive heart failure				0.9753
No	362	1.14 (0.97, 1.33)	0.1112	
Yes	15	1.13 (0.67, 1.90)	0.6502	
Chronic kidney disease				0.1771
No	367	1.14 (0.98, 1.34)	0.0956	
Yes	10	0.08 (0.00, 5.82)	0.2475	
$PaCO_2$, mmHg				0.0871
≤45	102	1.63 (1.12, 2.37)	0.0104	
>45	174	1.15 (0.98, 1.35)	0.0841	

Notes: Model adjusted for sex; age; BMI; smoking history; comorbidities (including diabetes, hypertension, arrhythmia, congestive heart failure, chronic kidney disease and coronary artery disease), therapy in stable stage, CRP, PCT, LDH, FEV_1/FVC, $PaCO_2$. All covariates except the stratification variable were adjusted for.
Abbreviations: RCI, red cell index; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; PCT, procalcitonin; CRP, C-reactive protein; LDH, lactic dehydrogenase; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1s; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; OR, Odd ratios; CI, confidence intervals.

Discussion

Based on our population-based retrospective cohort study, we drew the following conclusions: (1) After adjusting for potential confounding variables, we found a positive correlation between RCI and adverse hospitalization outcomes among the AECOPD patients. (2) Our analysis results revealed non-linearity between RCI and adverse hospitalization outcomes. We found that the trend of the effect sizes on the left and right sides of the inflection point was inconsistent [right (OR=1.3, 95% CI: 1.2–1.4, P < 0.001); left (OR=0.8, 95% CI: 0.7–1.0, *P*=0.058)]. This result suggested a threshold effect on the independent association between RCI and incident of adverse hospitalization outcomes. Interestingly, we found that RCI had a positive correlation with adverse hospitalization outcomes among patients younger than 75.

Hemoglobin is a special protein in red blood cells that transports oxygen. In people with COPD, hemoglobin abnormalities, such as anemia and polycythemia, are common.[21,22] Due to hypoxia's promotion of erythropoiesis, COPD has long been associated with secondary polycythemia.[10] There is evidence that polycythemia can lead to cor-pulmonale and pulmonary hypertension, which are associated with a poor prognosis.[23] In the present study, we also observed higher erythrocyte and hemoglobin levels in the higher RCI group in patients with AECOPD. However, the anemia prevalence rate reported in recent study was shown to be more frequent in COPD patients occurring in 7.5–17% of patients.[24] RBC count and hemoglobin level are known to reflect hypoxia susceptibility. A reduction in respiratory function suggested chronic hypoxic conditions, which in turn result in an increase in RBC count and hemoglobin concentration. It is unclear how lymphocytopenia affects chronic inflammatory diseases, but it is associated with a poor prognosis for acute inflammatory diseases.[25] Additionally, lymphocytopenia has been linked to all-cause mortality among COPD patients.[26,27] Similarly, Acanfora's study also found an association between a low relatively lymphocyte count and high mortality among elderly patients with COPD.[28] An immune response characteristic of lymphocytes is likely to explain lymphocyte influence on COPD. In our study, we also identified a lower lymphocyte count in the high RCI group than in the low RCI group in patients with AECOPD. Lymphocytes are responsible for this immunopathology, which is regulated by targeted immune responses in human lymphocytes. In addition, lymphocyte counts below 1500 is often a sign of malnutrition, Collins et al explained the correlation between malnutrition and COPD severity.[29] Platelets modulate inflammatory response.[25] While platelet counts in COPD patients have not been studied extensively, thrombocytopenia has been reported in AECOPD patients, and has been associated with poor outcomes and increased mortality.[30] Consistent with these findings, we also found lower platelet counts in the higher RCI group than in the lower RCI group in patients with AECOPD. Since lymphocytes and platelets tend to be little affected by other factors, thus they are used as benchmarks for measuring the total permeability of a blood cell.

RCI is a new and composite index. An advantage of this index is that in the context of acute exacerbation of COPD, it acts as a comprehensive indicator, combining association of single hemoglobin, platelet, lymphocyte, and RBC. Recent studies have reported that RCI reflects respiratory function. Patients with higher RCI level are prone to have lower FEV_1/FVC and higher $PaCO_2$ values. In the present study, lower FEV_1 (0.7±0.3 vs 0.8±0.3, *p*=0.028) were observed among AECOPD patients with higher RCI. This suggested that RCI was related to lung function to some extent. However, perhaps due to the limited sample size of this study, there was no significant difference between the two groups in terms of FEV_1/FVC ratio and FEV_1% predicted. Blood gas analysis can also be used to assess a patient's respiratory function. However, arterial blood gas analysis is a technically complex process, and puncturing the arterial vessel may cause hematoma and other complications, which results in low patient compliance. Moreover, the analysis may require several attempts before success, making it a less than ideal method for clinical practice. Recently, a cohort study of 415 patients with AECOPD in Asia, Australia, and New Zealand found low compliance with blood gas testing, especially in Southeast Asia.[31] In contrast, RCI, which is based on complete blood count parameters, is easier to obtain and use to evaluate respiratory function in patients with AECOPD.

In this study, we are the first to investigate the relationship between RCI and adverse hospitalization outcomes in patients with AECOPD. Previously, RCI was considered an efficient index for evaluating lung function based on the results of complete blood counts. As compared with the healthy control group, both the COPD and elderly groups showed significantly higher positive rates of abnormally elevated RCI.[11] As shown in Table 1, the RCI was higher in people who had never smoked. However, as one possible explanation for this, we found that the non-smokers were older

and more of them had hypertension, suggesting that these people may be in poor health and were thus not capable of smoking, thus their lung function was also poor and RCI was higher.

Subgroup analysis is a crucial aspect of a scientific study. We used sex, age, BMI, smoking history, hypertension, diabetes, arrhythmia, congestive heart failure, chronic kidney disease, coronary artery disease and $PaCO_2$ as the stratification variables, of which only age had an interaction. Due to the lack of similar findings in previous studies, we were unable to explain why the linearly increasing correlation between RCI and adverse hospitalization outcomes occurred only among patients younger than 75. Future studies in other settings are needed to confirm this finding.

Our study has some strengths. (1) We used the generalized additive model (GAM) to clarify the nonlinear relationship between RCI and adverse hospitalization outcomes. There are obvious advantages to GAM in handling non-linear relationships, in handling smoothing factors, as well as fitting a regression curve. Therefore, we can use GAM to better understand the actual relationship between exposures and outcomes. (2) As an observational study, our results may be susceptible to potential confounders. In order to reduce residual confounding, we used strict statistical adjustment methods. (3) By handling the target independent variable as both a continuous and categorical variable, we were able to reduce the contingency and enhance the robustness of the results. (4) Using effect modifier factor analysis improves the use of data. In the subgroup analysis, a positive association was observed between RCI and adverse hospitalization outcomes in patients younger than 75. (5) We had the positive finding that when RCI was greater than 3.2, for every unit increase in RCI, the incidence of adverse hospital outcomes increased by 30%. The clinical significance of this observation is that the association between RCI and adverse hospital outcomes was only apparent when RCI reaches a certain threshold.

However, our study also has some limitations. First, our research had a small sample size. The data in Table 1 indicate that the majority of our study population is male, which may influence the observation of the relationship between RCI and adverse hospitalization outcomes in female AECOPD patients. Researchers have previously found that male and female patients have significant differences regarding disease severity, prognosis, and comorbidities.[32,33] COPD has traditionally been seen as a disease of older men, but in recent years its prevalence among female patients has steadily increased. Future studies are needed to focus more on women with COPD. Second, we excluded patients with other respiratory diseases such as asthma, patients with sepsis shock, and patients with diseases of the blood system from analysis; therefore, these findings cannot be extrapolated to these people. Third, the BMI and CRP covariate data were respectively missing for 18.8% and 34% of the participants. However, we used MIs to address the problem of missing data, and the results were robust. Fourth, RCI is currently used only in Chinese patients with COPD. In order to investigate the mechanisms of RCI in the progression of COPD, we must conduct prospective cohort studies in different ethnic populations. Finally, this is a retrospective study with all the inherent limitations of retrospective studies. Further exploration and confirmation of our conclusions is necessary.

Conclusion

In conclusion, the present study showed a non-linear relationship between RCI and adverse hospitalization outcomes. The RCI was strongly positively related to adverse hospitalization outcomes when the RCI is greater than 3.2. Considering that this is a retrospective study, in the future we must conduct well-designed and large-scale longitudinal studies to confirm our results, and explore the predictive role of RCI in patients susceptible to unfavorable evolution.

Abbreviations

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; RCI, red cell index; Hb, hemoglobin; RBC, red blood cells; PLT, platelet; Lym, lymphocyte; BMI, body mass index; PCT, procalcitonin; CRP, C-reactive protein; LDH, lactic dehydrogenase; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; $FEV_{1\%}$Pred, forced expiratory volume in 1 second in percent of the predicted value; PaO_2, partial pressure of oxygen in arterial blood; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; NIMV, noninvasive mechanical ventilation; ICU, intensive care unit; MIs, multiple imputations.

Data Sharing Statement

Due to patient privacy concerns, all data generated and analyzed during this study cannot be made publicly available, but they can be accessed by reasonable request from the author.

Ethics Approval and Informed Consent

The study was approved by the Ethics Review Committee of the First Affiliated Hospital of Sun Yat-sen University in April 2022 ([2022]-179). Because the present study was a retrospective design with anonymized data and patients' privacy were not violated, the Investigational Ethical Review Board agreed exemption applications of informed consent.

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Author Contributions

Fu-zhen Yuan and Chang-ran Zhang: study conception, design, collection of data, analysis, interpretation of results, figure design, writing the article draft, reviewing the article, and editing. Wei Shui, Yan-li Xing, Yuan-yuan Niu, Xin Zhang: study design, collection of data, analysis, interpretation of results and article draft writing. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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