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ORIGINAL RESEARCH

Combined Inflammatory Markers for Predicting Acute Exacerbations in Chronic Obstructive Pulmonary Disease With Respiratory Failure

Xiao-Hua Zhang[1,2], Ming-Feng Han[2], Xiao-Bao Teng[2], Jing-Feng Shi[2], Xiao-Ling Xu[1,3]

[1]Cheeloo College of Medicine, Shandong University, Jinan, 250000, Shandong, People's Republic of China; [2]Department of Respiratory and Critical Care Medicine, The Second People's Hospital of Fuyang City, Fuyang, Anhui, 236015, People's Republic of China; [3]Department of Respiratory and Critical Care Medicine, the First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui, 230001, People's Republic of China

Correspondence: Xiao-Ling Xu, Cheeloo College of Medicine, Shandong University, No. 44 of Wenhua West Road, Lixia District, Jinan, Shandong, 250000, People's Republic of China, Tel +86 18963789002, Email xxlahh08@163.com

Objective: This study aimed to assess the predictive value of the neutrophil-lymphocyte ratio (NLR), C-reactive protein/albumin ratio (CAR), and serum amyloid A (SAA) in predicting acute exacerbations of chronic obstructive pulmonary disease (AECOPD) complicated by respiratory failure (RF).

Methods: A retrospective study was conducted on 198 patients with AECOPD in the Respiratory Department of No. 2 People's Hospital of Fuyang City from December 2022 to May 2023. Patients were categorized into two groups: an experimental group with the presence of RF (n = 70) and a control group with no RF present (n = 128). Baseline characteristics and inflammatory marker levels were compared between the two groups, and their impact on the risk of readmission within one year was analyzed to assess the predictive value of NLR, CAR, and SAA in patients with AECOPD and RF.

Results: The experimental group exhibited significantly higher levels of white blood cells, neutrophils, C-reactive protein (CRP), SAA, NLR, and CAR compared to the control group. Additionally, the experimental group had a higher one-year readmission rate, with statistically significant differences. The areas under the receiver operating characteristic (ROC) curve for NLR, CAR, and SAA in predicting AECOPD with RF were 0.705, 0.659, and 0.656, respectively. When combined, the ROC area under the curve for these three markers increased to 0.717, which was statistically significant.

Conclusion: The combined assessment of NLR, CAR, and SAA offers a reliable reflection of systemic inflammation and holds predictive value for AECOPD with RF.

Keywords: acute exacerbation of chronic obstructive pulmonary disease, C-reactive protein/albumin ratio, neutrophil-lymphocyte ratio, predictive value, serum amyloid A

Background

Chronic obstructive pulmonary disease (COPD) is the most prevalent chronic respiratory disease, characterized by persistent respiratory symptoms and partially reversible airflow limitation. Although global data indicate a decline in prevalence and incidence rates in China and globally, the total number of COPD cases continues to rise, posing a persistent and significant public health concern. This rise in cases exceeds the global average decline in COPD prevalence and incidence rates.[1] During acute exacerbations of COPD (AECOPD), lung function deteriorates rapidly, resulting in hypoxemia and hypercapnia, which can lead to respiratory failure (RF).[2] Individuals with COPD and RF experience high mortality rates, poor prognosis, and significant economic costs, representing a considerable health threat. Early prediction of AECOPD with RF, along with timely disease assessment and prognosis forecasting, is critical for preventing RF and improving clinical outcomes.

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The pathogenesis of COPD is linked to both airway and systemic immune-inflammatory processes. Harmful particles such as smoking and air pollution activate the innate immune cells in the airways and lungs, releasing inflammatory mediators such as interleukin-8, tumor necrosis factor-α, prostaglandins, and leukotrienes, which cause inflammation. At the same time, adaptive immune disorders, T lymphocytes aggregate release cytokines, exacerbate the inflammatory response, resulting in airway and lung parenchyma damage. Continuous inflammation leads to the infiltration of a large number of inflammatory cells in the airway wall, the injury of airway epithelial cells, the proliferation of goblet cells, the increase of mucus secretion, and the thickening of airway smooth muscle, resulting in airway stenosis and obstruction. It can also cause the imbalance of proteinase-antiprotease, enhance oxidative stress, destroy the elastic fiber and other structures in lung tissue, and form emphysema and other diseases. Blood biomarkers such as inflammatory mediators, immune cells, and chemokines providing insights into COPD severity and prognosis.[3] Among these, the neutrophil-Lymphocyte Ratio (NLR), C-Reactive Protein/Albumin Ratio (CAR), and Serum Amyloid A (SAA) have been identified as potential inflammatory markers, closely associated with the onset and progression of inflammation and tumors. However, limited evidence exists regarding the clinical correlation between NLR, CAR, and SAA in patients with AECOPD and RF. The aim of this study was to examine the relationship between these inflammatory markers, general patient characteristics, and the risk of readmission within one year in patients with AECOPD and RF, assessing the combined predictive utility of NLR, CAR, and SAA for clinical application in such cases.

Materials and Methods

General Data

The study included 198 patients with AECOPD treated at the Respiratory Department of No.2 People's Hospital of Fuyang City from December 2022 to May 2023. The patients were divided into two groups based on the presence of RF: the experimental group with RF (n = 70) and the control group without RF (n = 128). No statistically significant differences were observed between the experimental and control groups in terms of age, sex, smoking history, or comorbid conditions ($P > 0.05$).

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) Diagnosis of AECOPD consistent with the guidelines outlined in the 2019 GOLD Science Committee Report;[4] (2) Age range between 50 and 80 years; and (3) Absence of active tuberculosis, bronchiectasis, bronchial asthma, or lung abscess, with complete clinical data available.

The exclusion criteria were as follows: (1) Presence of severe functional insufficiencies in the heart, liver, kidney, or other organs; (2) Comorbid autoimmune diseases, malignant tumors, or long-term use of immunosuppressants; (3) Comorbid hematological diseases; and (4) Patients lost to follow-up.

This study was conducted in accordance with the requirements and standards of the hospital's medical ethics committee. Consent was obtained from all participants and their families, ensuring informed consent for study participation.

Methods

Upon admission, basic information for each patient diagnosed with AECOPD, including age, sex, smoking history, disease duration, hospital stay, and comorbidities, was collected. Within 24 hours of admission, routine blood tests were conducted, along with measurements of C-reactive protein (CRP), SAA, procalcitonin (PCT), interleukin-6 (IL-6), and albumin (ALB). The number of hospitalizations due to acute exacerbation within the past year was also recorded.

Statistical Methods

Data processing was carried out using SPSS 27.0 statistical software. Normally distributed quantitative data are expressed as mean ± standard deviation and t-tests were performed for inter-group comparisons. For non-normally distributed quantitative data, median (interquartile range) [M(P25, P75)] is used, and Mann–Whitney *U*-tests were applied for inter-group comparisons. Categorical data are presented as [n (%)], with chi-square tests used for inter-

group comparisons. Receiver operating characteristic (ROC) curve analysis was conducted to assess predictive value, with $P < 0.05$ considered statistically significant. All tests were two-tailed, with $P < 0.05$ indicating statistical significance.

Results

Comparison of General Patient Information Between the Two Groups

The study included 198 patients with AECOPD, consisting of 165 males and 33 females, aged between 50 and 80 years, with a mean age of 69.81 ± 7.10 years. Comorbidities among the patients included hypertension (55 patients), diabetes (17 patients), coronary heart disease (31 patients), and cerebral infarction (28 patients). The experimental group, which included 70 patients with RF, had an average age of 71.01 ± 5.62 years, with 57 males and 13 females. The control group, consisting of 128 patients without RF, had an average age of 69.16 ± 7.73 years, with 108 males and 20 females. There were no significant differences in sex, age, smoking history, or comorbidities such as hypertension, diabetes, and coronary heart disease between the experimental and control groups ($P > 0.05$). However, significant differences were found in the disease course, hospital stay, and the presence of comorbid pulmonary heart disease ($P < 0.05$). Additionally, the experimental group had a significantly higher proportion of patients readmitted within one year due to acute exacerbation, with statistically significant differences ($P < 0.05$) (Table 1).

Comparison of Inflammatory Markers Between the Two Groups

In the experimental group, the levels of white blood cells, neutrophils, CRP, SAA, NLR, and CAR were 7.89 (5.57–-10.68) × 10^9/L, 6.22 (4.28–8.25) × 10^9/L, 19 (4–51.7) mg/L, 22.8 (5.23–80.5) mg/L, 7.74 (4.29–13.70), and 0.59 (0.10–1.35), respectively. In comparison, the control group exhibited levels of 6.79 (5.37–8.88) × 10^9/L, 4.54 (3.68–6.22) × 10^9/L, 4 (4–13.05) mg/L, 4 (4–35.55) mg/L, 2.58 (1.98–4.52), and 0.11 (0.10–0.36), respectively. The experimental group exhibited significantly higher levels of white blood cells, neutrophils, CRP, SAA, NLR, and CAR compared to the control group ($P < 0.05$). The lymphocyte count in the experimental group was 0.94 (0.42–1.42) × 10^9/L, which was lower than that of the control group at 1.39 (1.16–2.02) × 10^9/L, with statistically significant differences ($P < 0.05$). However, no statistically significant differences were observed in ALB levels, IL-6, and PCT between the two groups ($P > 0.05$) (Table 2).

Table 1 Comparison of General Patient Information

Observational Indicators	Experimental Group (n = 70)	Control Group (n = 128)	Test Value (Chi-Squared or t-value)	P-value
Age (yearsEQN, $\bar{x}$ ± S)	71.01±5.62	69.16±7.73	1.939	0.054
Sex (Male/Female; No. Of cases)	57/13	108/20	0.283	0.595
Smoking History [n (%)]	43 (61.4)	82 (64.1)	0.135	0.713
Disease Duration (years,EQN $\bar{x}$ ± S)	11.56±7.10	8.33±8.24	2.768	0.006
Underlying Diseases				
Complicated Pulmonary Heart Disease [n (%)]	33 (47.1)	14 (10.9)	32.77	<0.001
Comorbid Hypertension [n (%)]	21 (30)	34 (26.6)	0.267	0.606
Comorbid Diabetes [n (%)]	7 (10)	10 (7.8)	0.276	0.599
Comorbid Coronary Heart Disease [n (%)]	14 (20)	17 (13.3)	1.547	0.214
Comorbid Cerebral Infarction [n (%)]	8 (11.4)	20 (15.6)	0.656	0.418
Hospital Stay (days, EQN $\bar{x}$ ± S)	10.39±5.82	7.24±2.22	4.349	<0.001
Acute Exacerbation Requiring Readmission within 1 Year [n (%)]	39 (55.7)	46 (35.9)	7.224	0.007

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Table 2 Inflammatory Marker Detection Results Across Groups

Observational Indicators	Experimental Group (n = 70)	Control Group (n = 128)	Test Value (t-value or Z-value)	P-value
White Blood Cell Count(*10^9/L)	7.89 (5.57–10.68)	6.79 (5.37–8.88)	−2.184	0.029
Neutrophil Count(*10^9/L)	6.22 (4.28–8.25)	4.54 (3.68–6.22)	−3.667	<0.001
Lymphocyte Count(*10^9/L)	0.94 (0.42–1.42)	1.39 (1.16–2.02)	−2.898	0.004
Albumin(g/l)	38.00±4.27	38.99±3.92	−1.632	0.104
Procalcitonin(ng/mL)	0.05 (0.01–0.11)	0.04 (0.01–0.07)	−1.627	0.104
IL-6 (pg/mL)	9.99(3–56.85)	7(3–22.7)	−1.873	0.061
CRP (mg/L)	19(4–51.7)	4(4–13.05)	−3.532	<0.001
SAA (mg/L)	22.8(5.23–80.5)	4(4–35.55)	−3.472	<0.001
NLR	7.74(4.29–13.70)	2.58(1.98–4.52)	−4.598	<0.001
CAR	0.59(0.10–1.35)	0.11(0.10–0.36)	−3.517	<0.001

Notes: IL-6, Interleukin-6; CRP, C-reaction protein; SAA, Serum Amyloid A; NLR, neutrophil-lymphocyte ratio; CAR, C-reaction protein /albumin.

Predictive Values of NLR, CAR, SAA Individually and in Combination for AECOPD With RF

The predictive values of NLR, CAR, and SAA, both individually and in combination, for AECOPD with RF was evaluated using a binary logistic regression model. ROC curves were generated to evaluate and compare their predictive values (Figure 1). The areas under the ROC for predicting AECOPD with RF using NLR, CAR, and SAA were 0.705 (95% CI: 0.575–0.743), 0.659 (95% CI: 0.625–0.784), and 0.656 (95% CI: 0.572–0.740), respectively, with sensitivities of 0.667, 0.594, and 0.464, and specificities of 0.725, 0.742, and 0.825. When compared to individual predictions, the combined ROC area under the curve for these three markers was 0.717 (95% CI: 0.64–0.794) (P<0.001), with sensitivities and specificities of 0.841 and 0.533, respectively (Table 3).

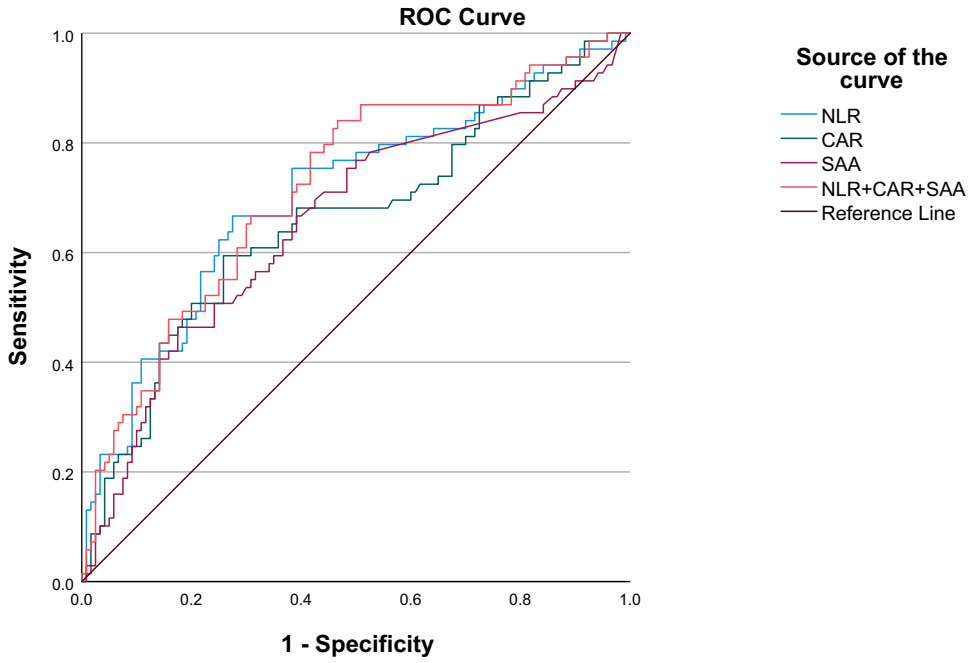

Figure 1 ROC Curves for Predicting AECOPD with RF using NLR, CAR, and SAA.

Table 3 Predictive Value of NLR, CAR, and SAA Alone and in Combination for AECOPD With RF

Test Result Variables	AUC	Standard Error	P	95% confidence Interval (*95% CI*)
CAR	0.659	0.043	<0.001	0.575–0.743
NLR	0.705	0.041	<0.001	0.625–0.784
SAA	0.656	0.043	<0.001	0.572–0.74
Predicted Probability	0.717	0.039	<0.001	0.64–0.794

Abbreviations: NLR, neutrophil-lymphocyte ratio; CAR, C-reaction protein /albumin; SAA,Serum Amyloid A; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; RF, respiratory failure; AUC, area under the curve; 95% CI, 95% confidence interval.

Discussion

COPD is characterized by partially reversible airflow limitation and a decline in lung function. AECOPD significantly contribute to the progression of the disease, leading to increased symptoms such as worsening cough, dyspnea, and difficulty breathing, along with a decline in lung function. These factors increase the risk of RF, complicating the clinical condition and severely impacting the quality of life.[5] Currently, diagnosing AECOPD with RF depends primarily on patient-reported symptoms, clinical signs, and blood gas analysis. However, there is a lack of objective markers for early assessment and prediction of RF onset. For patients with AECOPD and RF, it is crucial to closely monitor and identify early those risk factors that may lead to recurrent acute exacerbations and hospital readmissions.

Inflammatory responses are central to the pathogenesis of COPD, particularly the release of a large number of inflammatory cytokines. These cytokines directly damage the airway and alveolar structure, leading to functional changes in epithelial cells within the airways, increased mucus secretion, and airflow obstruction. As a result, airway narrowing occurs, and persistent inflammation can result in long-term structural changes, such as smooth muscle hyperplasia and fibrosis, causing airway remodeling. This leads to severe damage to lung ventilation and gas exchange functions, which may progress to RF. Inflammatory responses not only play a role in the onset of AECOPD but also contribute to its progression to RF.

Several studies have shown that an increase in levels of biomarkers such as C-reactive protein (CRP), fibrinogen, and white blood cell count is associated with a higher risk of frequent COPD exacerbations.[6] The ECLIPSE study identified six inflammatory markers—white blood cell count, fibrinogen, CRP, IL-6, interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α)—which are linked to the prognosis of AECOPD and can predict exacerbation frequency and mortality in patients with COPD.[7] NLR is a novel inflammatory biomarker that is easily measured, cost-effective, and highly practical, garnering significant attention. Both neutrophils and lymphocytes play critical roles in the immune system and defense mechanisms of the body.

A meta-analysis of 9 studies involving 5140 patients found that NLR may serve as an independent predictor for COPD exacerbations, with elevated NLR levels correlating to increased mortality, especially in Asian populations and those with higher average NLR values.[8] NLR has been linked to COPD severity and identified as an independent predictor of COPD-related mortality. It can also be used to monitor the prognosis of AECOPD, serving as a prognostic indicator for patients with COPD in intensive care settings.[9,10] Furthermore, NLR and platelet/lymphocyte ratio (PLR) are associated with 28-day mortality in patients with AECOPD and may function as prognostic biomarkers for short-term mortality in inpatients with AECOPD.[11] Another study confirmed an independent association between NLR and red blood cell distribution width (RDW) with RF in patients diagnosed with COPD. These findings suggest that elevated levels of NLR and RDW may play a role in the progression of COPD toward RF.[12]

This study found that the NLR ratio in the AECOPD with RF group (7.74 [4.29–13.70]) was significantly higher than that in the AECOPD group without RF (2.58 [1.98–4.52]), with statistically significant differences ($P < 0.05$). This suggests that AECOPD is associated with a systemic inflammatory response, and the elevated NLR in the AECOPD with RF group indicates the potential diagnostic value of NLR in the progression of COPD toward RF. In a related study, Lee et al used a linear regression model to examine the relationship between NLR levels and the severity of lung function, identifying

a significant negative correlation between NLR and airflow limitation.[13] Incorporating NLR into models with forced expiratory volume in the first second (FEV1) significantly improved the ability to predict exacerbations over a 1-year follow-up, supporting its role as a prognostic indicator for COPD deterioration.

The results of this study also indicated that the AECOPD group with RF experienced a significantly higher rate of readmissions due to acute exacerbations within one year, with statistically significant differences ($P < 0.05$). CAR is emerging as a valuable inflammatory marker for assessing inflammatory status and predicting disease prognosis. CRP, an acute-phase protein synthesized by the liver, increases significantly in response to inflammation or infection. CRP plays a role in the inflammatory response by activating the complement system and promoting phagocytosis by immune cells, and elevated CRP levels are linked to an increased risk of COPD exacerbations.[6] In patients with AECOPD, a hypermetabolic state often exists, which may be related to heightened inflammatory responses and increased metabolic demands.

ALB, a principal plasma protein, often exhibits reduced synthesis in inflammatory states due to the liver's increased production of CRP. This can lead to decreased serum ALB levels. Low ALB levels can indicate malnutrition, and excessively low ALB levels may suggest impaired immune function, making patients more vulnerable to infections, including bacterial, viral, and fungal infections, all of which can exacerbate the condition of AECOPD.

Prolonged infections drive up CRP levels, resulting in a negative nitrogen balance that subsequently lowers ALB levels and increases the CAR. CAR has been shown to have value in assessing the severity of conditions such as AECOPD, sepsis, and systemic inflammatory response syndrome (SIRS).[14,15] Elevated levels of NLR, CAR, and N-terminal pro-brain natriuretic peptide (NT-proBNP) may be useful clinical predictors of mortality in patients with AECOPD and heart failure.[16] Combining NLR, CAR, and NT-proBNP can enhance the accuracy of predicting 28-day mortality in these patients.

A study comparing the predictive value of body mass index (BMI), nutritional risk screening 2002 (NRS 2002), and serum ALB, three commonly used nutritional assessment tools, found that ALB levels are particularly valuable in predicting in-hospital mortality and 30-day readmission rates in patients with COPD and RF.[17] However, the role of CAR as a prognostic marker for patients with AECOPD and RF remains unclear. In our study, the CAR index in the AECOPD with RF group (0.59 [0.10–1.35]) was significantly higher than in the simple AECOPD group (0.11 [0.10–0.36]), with statistically significant differences ($P < 0.05$).

SAA, a non-specific acute-phase response protein, increases during both viral and bacterial infections and plays a role in enhancing chemokine production by inflammatory cells, contributing to immune regulation. It is also a biomarker for AECOPD, and has been found to be more sensitive than CRP alone or in combination with dyspnea for diagnosing AECOPD.[18] Lin et al demonstrated that SAA, with an area under the ROC of 0.931, can be used as an effective indicator for diagnosing and treating AECOPD.[19] The combination of serum Clara cell secretory protein 16 (CC16), plasma fibrinogen, and SAA has high sensitivity and specificity for predicting AECOPD prognosis.[20] SAA promotes pulmonary neutrophil accumulation by increasing Interleukin-17A (IL-17A) levels in the mucosa and γδT cells, thereby inducing chronic pulmonary inflammation in COPD.[21]

Although research on the role of SAA in patients with AECOPD and RF is limited, the results of our study indicate that the SAA index in the AECOPD with RF group (22.8 [5.23–80.5] mg/L) was significantly higher compared to the simple AECOPD group (4 [4–35.55] mg/L), with statistically significant differences ($P < 0.05$). These findings suggest that NLR, CAR, and SAA may have potential value in the progression of COPD to RF and could be involved in the development of RF in patients with AECOPD.

This study also evaluated the predictive value of NLR, CAR, and SAA, both individually and in combination, for AECOPD with RF. The areas under the ROC curve for predicting AECOPD with RF using NLR, CAR, and SAA were 0.705 (95% CI: 0.575–0.743), 0.659 (95% CI: 0.625–0.784), and 0.656 (95% CI: 0.572–0.740), respectively. The single detection of NLR, CAR and SAA all have certain predictive value for AECOPD with respiratory failure, among which the prediction accuracy of NLR is relatively high, which is consistent with the area under ROC curve of NLR in the study results being 0.705, which confirms that each single index has certain application significance in predicting the disease. The combined ROC area for these three markers was 0.717 (95% CI: 0.64–0.794) ($P < 0.001$), demonstrating superior diagnostic efficacy compared to the individual markers. Which is consistent with the conclusion of this study that combined detection can improve the predictive value. This finding confirms the significant value of using a combination

of NLR, CAR, and SAA for diagnosing AECOPD with RF, suggesting its potential for clinical application in improving diagnostic accuracy for physicians.

In clinical practice, changes in NLR, CAR, and SAA levels may precede significant respiratory failure symptoms in patients. By regularly detecting these indicators, early warnings can be given to high-risk patients, and the combination of these three indicators can also help doctors more accurately stratified patients' risk. For patients with significantly elevated indicators, it means that they are at a higher risk of worsening disease and respiratory failure, requiring closer observation and aggressive intervention, while for patients with little change in indicators, the risk is higher. The possibility of disease deterioration in the short term is relatively low. In terms of treatment, combined detection is helpful to judge the recovery of respiratory function of patients. When the indicators gradually improve, appropriate reduction of oxygen flow or attempt to withdraw the machine can be considered. To prevent the disease from getting worse again.

In summary, the combined detection of inflammatory markers NLR, CAR, and SAA holds significant value in assessing the condition of patients with COPD and RF. These markers can serve as predictive factors for readmission within one year in patients with AECOPD and RF, offering significant clinical insights for both diagnosis and prognosis. The convenience and accessibility of these markers make this approach feasible for broader application in primary healthcare settings. However, as this study is a single-center, retrospective study with a small sample size, further multi-center, large-sample prospective studies are necessary to confirm these findings.

Abbreviations

CPR, cardiopulmonary resuscitation; COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; RF, respiratory failure; NLR, neutrophil-lymphocyte ratio; CAR, C-reaction protein /albumin; SAA, Serum Amyloid A; GOLD, Global Initiative for Chronic Obstructive Lung Disease guidelines; CRP, C-reaction protein; PCT, Procalcitonin; ALB, albumin; ROC, receiver operating characteristics curve; SPSS, Statistical Package for Social Sciences; IL-6, Interleukin-6; IL-8, Interleukin-8; TNF-α, Tumor necrosis factor –α; RDW, red blood cell distribution width; FEV1, Forced expiratory volume in one second; NT-proBNP, N-terminal pro-brain natriuretic peptide; NRS, Nutritional Risk Screening; IL-17A, Interleukin-17A; 95% CI, 95% confidence interval; AUC, Area under the curve.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of the Second People's Hospital of Fuyang City (No.20221121070). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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Disclosure

The authors declare that they have no competing interests.

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