

Prognostic role of neutrophil–lymphocyte ratio and platelet–lymphocyte ratio for hospital mortality in patients with AECOPD

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Background and objectives: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is one of the leading causes of hospitalization and is associated with considerable mortality, for which clinicians are seeking useful and easily obtained biomarkers for prognostic evaluation. This study aimed to determine the potential role of the neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) as prognostic makers for hospital mortality in patients with AECOPD.

Methods: We included 303 patients with AECOPD in this retrospective study. Clinical characteristics, NLR, PLR, and serum levels of C-reactive protein (CRP) and other data were collected. Relationships between NLR/PLR and CRP were evaluated by Pearson's correlation test. Receiver operating characteristics curve and the area under the curve (AUC) were used to assess the ability of NLR and PLR to predict hospital mortality in patients with AECOPD.

Results: Mean levels of NLR and PLR of all patients with AECOPD were 7.92 ± 8.79 and 207.21 ± 148.47 , respectively. NLR levels correlated with serum CRP levels ($r=0.281$, $P<0.05$). The overall hospital mortality rate was 12.21% (37/303). Levels of NLR and PLR were significantly higher among non-survivors compared to survivors of AECOPD (both $P<0.05$). At a cut-off value of 6.24, the sensitivity and specificity of the NLR in predicting hospital mortality were 81.08% and 69.17%, respectively, with an AUC of 0.803. At a cut-off of 182.68, the corresponding sensitivity, specificity and AUC of PLR were 64.86%, 58.27%, and 0.639. The combination of NLR, PLR, and CRP increased the prognostic sensitivity.

Conclusion: NLR and PLR levels were increased in non-survivor patients with AECOPD, and the NLR may be simple and useful prognostic marker for hospital mortality in patients with AECOPD. More studies should be carried out to confirm our findings.

Keywords: acute exacerbation of chronic obstructive pulmonary disease, neutrophil–lymphocyte ratio, platelet–lymphocyte ratio, hospital mortality, prognosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic airway inflammatory disease characterized by persistent respiratory symptoms and airflow limitation.¹ COPD is associated, worldwide, with high morbidity and mortality. In China, the overall incidence of COPD was 8.2% in residents older than 40, based on a cross-sectional survey in seven provinces/cities;² in the USA, COPD was the third leading cause of mortality in 2011.³ Acute exacerbation of COPD (AECOPD) is associated with an acute worsening of respiratory symptoms that result in additional therapy.¹ AECOPD has an independent and significant negative influence on the prognosis of patients with COPD, it increases the frequency of further severe

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exacerbations, reduces health status and physical activity, speeds the decline of lung function, increases mortality, and places great economic burden on patients – with both high direct and in-direct medical costs.⁴⁻⁶

AECOPD is one of the leading causes of hospitalization, and contributes significantly to mortality among patients with COPD.⁷ Considering the important role of AECOPD in the prognosis of patients with COPD, early and accurate individual mortality risk assessment during exacerbation is of critical importance for clinical management, and is helpful for optimal allocation of limited medical resources. Clinicians are seeking clinically meaningful predictors of mortality following AECOPD admission, especially for biomarkers which can be easily obtained upon admission.⁸

AECOPD is associated with increased systemic and airway inflammation, and enhanced inflammation worsens clinical symptoms and decreases lung function of patients, necessitating hospitalized treatment.^{9,10} The neutrophil-lymphocyte ratio (NLR) is an marker of inflammatory status, representing both the neutrophil and lymphocyte counts;¹¹ the platelet-lymphocyte ratio (PLR) is also accepted as a novel marker in many systemic inflammatory disorders.¹² Both NLR and PLR are indicators of general immune response to various stress stimuli, and play an important role in the prognostic evaluation of a series of diseases, including malignant cancers, myocardial infarction, community-acquired pneumonia, and acute pulmonary embolism.¹³⁻¹⁷ However, limited data have been presented on the relationship between NLR/PLR and clinical outcomes of hospitalized patients with AECOPD. This study sought to investigate the prognostic role of NLR/PLR on in-hospital mortality of patients with AECOPD.

Methods

Patients

Patients with AECOPD who were admitted in Yongchuan Hospital, Chongqing Medical University from March 2014 to June 2016 were retrospectively enrolled in this study. All patients signed an informed consent for scientific research of clinical data during hospitalization, and ethics approval was obtained from the Yongchuan Hospital Ethics Committee.

Patients were included this study if they met the following criteria: 1) primary diagnosis of AECOPD, defined as an acute worsening of respiratory symptoms such as dyspnea, cough, or sputum purulence severe enough to warrant hospital admission;¹ 2) a COPD diagnosis supported by spirometric data of airflow obstruction even with bronchodilator (forced expiratory volume in 1 second [FEV₁]/forced

vital capacity [FVC] <0.70) when clinically stable at least for 3 months;¹ and 3) age ≥40 years, and admitted from their primary residence. For patients with multiple hospital admissions, only the first admission was recorded. A patient was excluded if AECOPD was not the primary diagnosis, the patient had other acute events such as acute myocardial infarction, or the patient had other end-stage diseases. The treatment plan for each patient was not influenced by participation in current study.

Data collection

Demographic and clinical data were collected from all subjects, including: age, gender, smoking history, lung function test results (FEV₁, FEV₁%Pred, FVC, and FEV₁/FVC), arterial blood gas on admission (SpO₂, PaO₂, PaCO₂, and pH value), serum C-reactive protein (CRP) levels (immunofluorescence and i-CHROMA Reader), routine blood test results on admission before antibiotic treatment (white blood cell, platelets, neutrophils, lymphocytes; Sysmex XN1000), length of hospital stay, and in-hospital mortality. Data collection was completed by two independent authors.

Statistical analysis

Data are represented as mean ± standard deviation. Categorical data are represented as frequencies and percentages. Differences between the survivor and non-survivor groups were compared by chi-squared test for categorical variables and an unpaired *t*-test for continuous variables. Relationships between NLR/PLR and CRP were evaluated by Pearson's correlation test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the sensitivity and specificity of different potential predictors of in-hospital mortality. In addition, we assessed the ability of two- or three-marker combinations to predict in-hospital mortality with methods recommended by Creaney et al.¹⁸ Data on NLR, PLR, and CRP were transformed with the natural logarithm and then standardized relative to controls; a logistic regression to predict AECOPD death/alive status was used to determine the weight given to each standardized marker. Markers were multiplied by their logistic regression coefficients and added to give a combined marker value, which was used to calculate sensitivity and specificity. The area under the curve (AUC) was used to assess prognostic accuracy, which ranges from 0.5 to 1.0 – with higher values indicating higher discriminatory ability.¹⁹ Data analysis was conducted using SPSS 18.0 for Windows (IBM, Chicago, IL, USA). The level of significance for all statistical tests was set as a two-sided *P*-value of 0.05.

Results

Characteristics of included subjects

Finally, 303 patients with AECOPD met our inclusion criteria and were included in this study. There were 200 men and 103 women, and the mean age was 61 years. The numbers of patients for each class of the Global Initiative for Chronic Obstructive Lung Disease classification were: 44, 132, 102, and 25 for classes I, II, III, and IV, respectively; the mean FEV₁%predicted value was 56%, suggesting most patients presented with moderate airflow limitation. Overall, 273 (90%) patients with AECOPD underwent a chest X-ray or chest CT scan examination. The mean length of hospitalization was 15 days, and 33 patients died during hospitalization, corresponding to an in-hospital mortality of 12.21%. The clinical characteristics, lung function data, and main laboratory findings of survivors and non-survivors are listed in Table 1.

NLR and PLR levels

The mean NLR and PLR levels across all patients with AECOPD were 7.92 and 207.21, respectively. NLR levels correlated positively with serum CRP levels ($r=0.281$, $P<0.001$), whereas the correlation between PLR and serum

CRP levels did not demonstrate a linear association ($r=0.219$, $P<0.001$; Figure 1). As shown in Table 1, levels of NLR and PLR were significantly higher among patients who died in hospital than among those who survived (both $P<0.05$).

Predictive ability of NLR, PLR, and CRP

ROC curve analysis for using NLR alone to predict in-hospital mortality indicated an optimal cut-off NLR of 6.24, AUC of 0.803, sensitivity of 81.08%, and specificity of 69.17% (Figure 2). This predictive ability exceeded that of CRP or PLR individually. Next, we investigated the predictive accuracy of different biomarker combinations: combining NLR with other markers increased predictive sensitivity, with the best AUC of 0.800 obtained using a combination of NLR and PLR (Figure 3). The predictive accuracy of a single marker or a marker combination is listed in Table 2.

Discussion

AECOPD is an acute event during the clinical course of COPD, and is significantly associated with the clinical outcomes of patients with COPD by worsening clinical symptoms, declining lung function, and increasing mortality.²⁰ Identifying a simple and reliable biomarker that

Table 1 Clinical summary of patients with AECOPD

Clinical characteristic	Overall (n=303)	Survivor (n=266)	Non-survivor (n=37)	P-value
Age (year)	61±10	60±10	67±10	<0.001
Gender, n (%)				
Male	200 (66%)	175 (66%)	25 (68%)	0.831
Female	103 (34%)	91 (34%)	12 (32%)	
Smoking status, n (%)				
Current/ever smoker	202 (67%)	179 (67%)	23 (62%)	0.928
Never smoker	101 (33%)	87 (32%)	14 (38%)	0.535
FEV ₁ (L)	1.33±0.59	1.35±0.61	1.18±0.44	0.117
FEV ₁ %Pred (%)	56.12±21.48	56.97±21.78	50.01±18.29	0.065
FVC (L)	2.32±0.83	2.37±0.84	1.99±0.60	0.007
FEV ₁ /FVC (%)	53.54±11.77	53.74±11.78	52.08±11.74	0.421
GOLD staging (I/II/III/IV)	44/132/102/25	41/116/89/20	3/16/13/5	0.451
SpO ₂ (%)	94.67±6.43	94.87±6.56	93.22±5.31	0.143
PaO ₂ (mmHg)	86.62±31.28	87.06±29.54	83.47±42.12	0.514
PaCO ₂ (mmHg)	46.47±15.94	45.64±15.18	52.41±19.87	0.015
pH value	7.40±0.06	7.41±0.06	7.36±0.08	<0.001
WBC (×10 ⁹ /L)	8.35±4.37	7.90±3.75	11.63±6.64	<0.001
Platelet (×10 ⁹ /L)	194.95±90.99	196.60±90.84	183.05±92.51	0.397
Neutrophils (×10 ⁹ /L)	6.49±4.26	5.98±3.64	10.16±6.22	<0.001
Lymphocytes (×10 ⁹ /L)	1.20±0.60	1.25±0.59	0.87±0.63	<0.001
NLR	7.92±8.79	6.99±8.19	14.61±10.10	<0.001
PLR	207.21±148.47	198.10±140.80	272.76±184.28	0.004
CRP (mg/L)	44.29±65.44	39.21±59.22	80.76±92.49	<0.001
Hospital LOS (day)	15±9	15±11	15±8	0.642

Note: Data presented as mean ± SD.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LOS, length of stay; NLR, neutrophil–lymphocyte ratio; WBC, white blood cell; PLR, platelet–lymphocyte ratio.

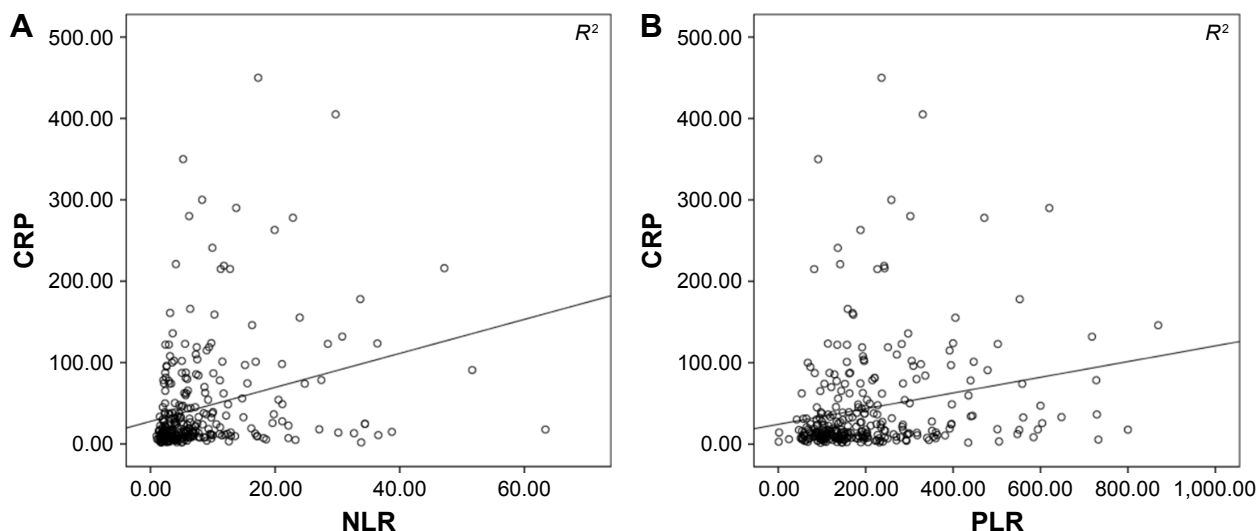


Figure 1 Correlations of the NLR and PLR with C-reactive protein (CRP).
Notes: Correlations between neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) levels in patients with acute exacerbation of chronic obstructive pulmonary disease and serum levels of C-reactive protein were assessed by Pearson’s correlation test, (A) NLR, $r=0.281$, $P<0.001$; and (B) PLR, $r=0.219$, $P<0.001$.

can accurately assess the mortality risk during AECOPD hospitalization is of great importance for the management of patients and rational allocation of medical resources. In this study, we found that NLR levels correlated with CRP – a systemic inflammation maker – in patients with AECOPD, and NLR and PLR levels were higher in non-survivors than in survivors who were patients with AECOPD; the NLR plays a valuable role in predicting the in-hospital mortality of patients with AECOPD.

COPD is associated with both enhanced airway and systemic inflammation and, during states of exacerbation, the severity of inflammation is significantly increased,²¹ and may stimulate the increase of the NLR and PLR, which may be used as markers of inflammation and as prognostic markers for patients with AECOPD. CRP is a classical inflammatory maker, and has been used to evaluate the systemic inflammation and prognosis of patients with COPD.²² In our

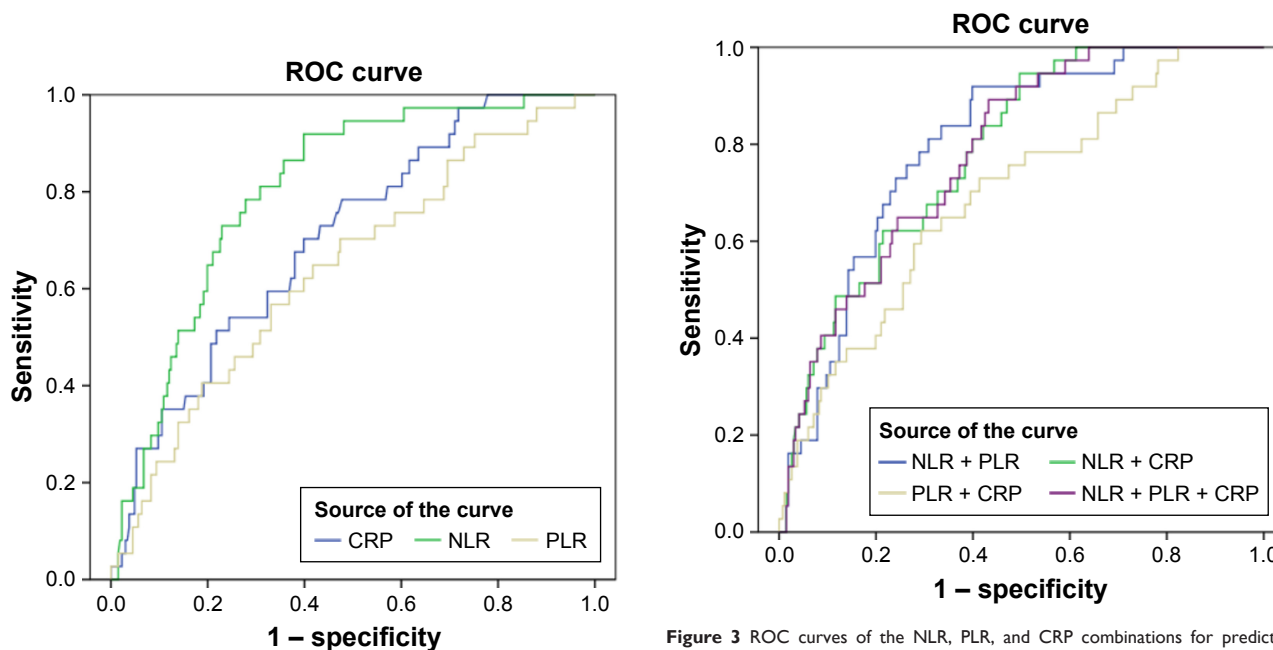


Figure 2 ROC curves of the NLR, PLR, or CRP for predicting in-hospital mortality of patients with acute exacerbation of chronic obstructive pulmonary disease. The receiver operating characteristic (ROC) curves for single predictors had the following areas: neutrophil–lymphocyte ratio (NLR), 0.803; C-reactive protein (CRP), 0.703; and platelet–lymphocyte ratio (PLR), 0.639.

Figure 3 ROC curves of the NLR, PLR, and CRP combinations for predicting in-hospital mortality of patients with acute exacerbation of chronic obstructive pulmonary disease. The receiver operating characteristic (ROC) curves for combined predictors had the following areas: NLR + PLR, 0.800; NLR + CRP, 0.785; PLR + CRP, 0.694; NLR + PLR + CRP, 0.783.
Abbreviations: NLR, neutrophil–lymphocyte ratio; CRP, C-reactive protein; PLR, platelet–lymphocyte ratio.

Table 2 Prognostic accuracy of the NLR, PLR, and CRP

Prognostic marker	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC
NLR	6.24	81.08%	69.17%	26.78%	96.34%	0.803
PLR	182.68	64.86%	58.27%	17.78%	92.27%	0.639
CRP	16.45 mg/L	78.39%	52.25%	18.59%	94.56%	0.703
NLR + PLR		91.89%	60.15%	24.29%	98.16%	0.800
NLR + CRP		89.19%	53.01%	20.89%	97.24%	0.785
PLR + CRP		70.27%	60.52%	19.85%	93.60%	0.694
NLR + PLR + CRP		89.19%	56.77%	22.29%	97.42%	0.783

Abbreviations: AUC, area under the curve; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; NPV, negative predictive value; PLR, platelet-lymphocyte ratio; PPV, positive predictive value.

study, we observed that serum CRP levels were significantly increased in non-survivor patients with AECOPD. Taylan et al reported that increased NLR is as useful as CRP in the evaluation of elevated inflammation in AECOPD, and the NLR is useful for the early identification of potential acute exacerbations in patients with COPD who have normal levels of traditional markers.²³ The NLR is a straightforward and valuable biomarker of AECOPD that may contribute as a predictor for respiratory hospitalization in patients with COPD.²⁴ In this study, we observed that levels of NLR were increased in patients with AECOPD and correlated positively with CRP levels, and NLR levels were higher in non-survivors than in survivor patients with AECOPD. At a cut-off value of 6.24, the sensitivity and specificity of NLR in predicting in-hospital mortality were 81.08% and 69.17%, respectively, with an AUC of 0.800. The results suggest that the NLR is useful as a prognostic biomarker for hospital mortality in patients with AECOPD. In addition, two studies supported that elevated NLR may be associated with long-term mortality in patients with COPD.^{25,26} Thus, the NLR plays multiple roles in AECOPD as a predictor of hospitalization, inflammation evaluation, and in-hospital/long-term mortality, and is helpful in the clinical management of patients with AECOPD.

Platelet activation is observed in patients with COPD and AECOPD, and represents a novel pathological mechanism in COPD.²⁷ Thus, the PLR, another inflammatory biomarker, is increased in COPD, and PLR levels were also significantly higher in patients with AECOPD compared to those with stable COPD.²⁸ In this study, for the first time, we evaluated the ability of the PLR to determine the clinical outcomes of hospitalized patients with AECOPD, and we found that, at a cut-off value of 182.68, the sensitivity and specificity of the PLR in predicting hospital mortality were 64.86% and 58.27%, respectively, with an AUC of 0.64, which suggests a lower predictive accuracy than with the NLR. In addition, the correlation between the PLR and CRP is not linear ($r=0.219$); thus, the predictive accuracy of the PLR alone

should be revisited and should be explained with caution. The combination of PLR and CRP with NLR increased the prognostic sensitivity for in-hospital mortality in patients with AECOPD. We suggest that results of the NLR and PLR should be explained with a traditional inflammatory marker such as CRP to ensure better prognostic accuracy.

Our study suggests that the NLR is a simple and useful biomarker for predicting in-hospital mortality in patients with AECOPD, as routine blood testing is available and affordable for each patient with AECOPD; the clinic utility of the NLR may be superior to that of other markers, which may need specific equipment or reagent. However, there were several limitations in our study. Our result in this Chinese cohort was from a single medical center, and it should be verified in larger studies with multiple centers and with different ethnic groups. More studies are needed to build a more definite conclusion on the prognostic accuracy of NLR and PLR in patients with AECOPD for both short- and long-term mortality. Second, future work should examine how the predictive power of the NLR and PLR relates to infection, to determine their ability of discriminating bacterial from nonbacterial AECOPD. Further studies with larger patient series are required to highlight the clinical significance of the NLR and PLR in the responses of patients with AECOPD to antibiotic therapy and further exacerbations.

Conclusion

This study suggests that NLR and PLR levels were increased in non-survivor patients with AECOPD, and the NLR is a simple, promising prognostic marker for assessing in-hospital mortality in patients with AECOPD. These findings justify further work into the role of the NLR and PLR in comprehensive management of patients with AECOPD.

Author contributions

CY and XL contributed to data collection, statistical analysis, and drafting the paper; ZT designed the study and revised the manuscript. All authors contributed toward data analysis,

drafting and revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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