ORIGINAL RESEARCH

A Low Eosinophil to Platelet Ratio as a Worse Prognostic Index for Emergency Department Attendance in Acute Exacerbation of COPD

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Purpose: Identifying prognosis for patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is challenging. Eosinophils and platelet are involved in the development of COPD, which may predict adverse events. The objective of this study was to determine the effect of the eosinophil to platelet ratio (EPR) in predicting adverse events in patients with AECOPD who visited the emergency department.

Patients and Methods: The records of patients with AECOPD treated at Dalian Municipal Friendship Hospital from January 2018 to December 2020 were retrospectively reviewed. The relationship between the clinical characteristics and EPR, as cut-off value of 0.755, was evaluated.

Results: A total of 508 patients with an AECOPD (316 male, 192 female) were included. An optimal AUC cutoff of 0.755 for the EPR segregated the patients into 2 groups with significantly different mortality (25.3% vs 5.5%, $P < 0.001$). The same mortality risk with lower EPR was observed among the patients with emergency room attendance (35.6% vs 11.1%, $P < 0.001$). A model including EPR <0.755, exacerbation history, PaO_2 <60mmHg, $PaCO_2$ >50 mm Hg, hypoalbuminemia and age ≥80 was developed to predict death risk and showed good performance.

Conclusion: During severe COPD exacerbation, an EPR < 0.755 preceding therapy can predict worse outcomes in patients with an AECOPD.

Keywords: eosinophil, COPD, eosinophil to platelet ratio, emergency department

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability worldwide.[1] Acute exacerbation of COPD (AECOPD) is commonly described as a rapid increase in COPD symptoms outside of the normal daily variation, and requires changes to daily medication. Such exacerbations are often linked to poor health status, and high rates of hospitalization, readmission, and disease progression.[2]

The neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in peripheral blood are being increasingly studied as systemic inflammatory markers. Notably, they can be rapidly determined, are widely available, and are relatively inexpensive through routine blood count analysis. Xiong et al[3] in a retrospective study found that baseline NLR values were significantly higher in COPD patients who died than patients who survived, indicating that the NLR might predict mortality in hospitalized COPD patients. Kumar et al[4] reported that the PLR was associated with 90-day mortality in patients with COPD. In a recent retrospective study, Yao et al[5] reported that NLR and PLR values were significantly higher in non-survivor patients with COPD, and the NLR might be a useful prognostic marker for hospital

mortality in patients with an AECOPD. As such, the NLR and PLR, which are convenient and simple to calculate may be used to predict the prognosis of patients with COPD.

Studies have shown that a low levels of blood eosinophils may be a predictor of a poor prognosis in patients with COPD.[6–8] In addition, an eosinophil count <50 / μL may be a useful biomarker for detecting sepsis and be a predictor of mortality in patients with a critical illness.[6] MacDonald et al[9] found that a low eosinophil count may predict higher mortality in hospitalized patients with an AECOPD. Holland et al[7] reported that a blood eosinophil count <0.04×10^9/L was associated with higher in-hospital mortality in patients with an AECOPD. Chan et al[10] found that blood eosinophilia was associated with higher exacerbation risk in COPD patients. Prins et al[11] reported that blood eosinophilia ≥2% was associated with an increased risk of relapse.

Studies have shown that a platelet count may have a role in predicting disease prognosis. Several reports found that thrombocytopenia is an independent predictor of intensive care unit (ICU) mortality, with a relative risk (RR) ranging from 1.9 to 4.2.[12–14] In addition, recent studies have shown that a decrease in platelet count is associated with respiratory diseases, Lopez et al[15] performed an observational prospective study, and reported that thrombocytopenia is a marker of in-hospital mortality in ICU patients with respiratory failure due to H1N1 influenza. Ashraf et al[16] reported that in patients with stable COPD, a decreased platelet count was associated with increased risk of 3-year all-cause mortality. Conversely, Harrison et al[17] reported that thrombocytosis was associated with increased mortality in patients with COPD.

Taken together, the aforementioned studies indicate that eosinophil and platelet counts may be predictive of COPD outcomes. However, the conclusions of using eosinophil and platelet as biomarkers to predict the prognosis of COPD are inconsistent; therefore, we hypothesize that the eosinophil to platelet ratio can possibly be used to predict prognosis of COPD; moreover, there is a paucity of studies investigating the predictive effect of the EPR on COPD prognosis, of especially for patients seen in emergency department (ED) with an AECOPD. Thus, the purpose of this study was to investigate the relation between EPR and outcomes of patients with an AECOPD.

Materials and Methods

Patient Selection and Data Collection

Patients >45 years old with an AECOPD who were hospitalized at Dalian Municipal Friendship Hospital (a tertiary-A teaching hospital in Dalian, Liaoning Province, China), from January 2018 to December 2020 were identified using the electronic database, and followed up for 12 months. Medical records were reviewed by a respiratory physician to confirm an AECOPD and exclude alternative diagnoses. The follow-up period was from January 2021 to December 2022. During the follow-up period, patients underwent telephone visits (every 3 months) to collect detailed information. Ethics approval for the study was obtained from the Ethics Committees of Dalian Friendship Municipal Hospital [code number YY-LL-2021-050]. COPD was diagnosed according to the Global Initiative for Chronic Obstructive Lung Disease 2018. Patients taking oral corticosteroids (OCS) before admission were excluded from the study. Patients with ED attendance and non-ED attendance were analysed separately.

Outcomes and Covariates

All potential factors of interest were classified as demographic information, pre-existing co-morbidities, and clinical characteristics. Demographic variables were age, sex, complication (acute respiratory failure, ARF: including hypoxemic and hypercapnic), comorbidities (heart failure, hypoalbuminemia); clinical data included the history of exacerbations in the past 12 months, the presence of emphysema, laboratory blood test results (blood eosinophils absolute count, blood platelet count, calculated eosinophil to platelet ratio, neutrophil absolute count, blood lymphocyte count, calculated neutrophil to lymphocyte ratio and platelet to lymphocyte ratio), the presence of a lower respiratory tract infection (LRTI), spirometry results: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), length of hospitalization (LOH), severe exacerbations in the follow-up period, all-cause mortality, and all-cause readmission in 12-month after discharge from the index hospitalization. Severe COPD exacerbation was defined as worsening of respiratory symptoms that led to a COPD-specific hospitalization, an ED visit, or an ICU stay. All of the above-mentioned factors were reviewed and documented from the medical records. During the follow-up period, patients received telephone calls to collect detailed information about exacerbations and other clinical outcomes.

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Statistical Analysis

Normally distributed data are expressed as the mean ± standard deviation and nonnormally distributed data as the median (interquartile range [IQR], 25%, 75%). Categorical variables are summarized as numbers and percentages (n [%]). An independent t-test, χ^2 test, Yates continuity correction test, Fisher exact test, or Wilcoxon rank-sum test was used to assess the differences according to EPR groups, as appropriate. The predictive values of EPR were analysed with receiver operating characteristic (ROC) curve analysis, and area under the curves (AUCs) was calculated and compared. We used the least absolute shrinkage selection operator (LASSO) regression to screen the most useful variables associated with mortality. Multivariate logistic regression was employed to build a prediction model of prognosis by incorporating predictors selected from LASSO analysis. Time-to-event survival analyses were conducted using Kaplan–Meier methods and Log rank tests. These analyses were conducted using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism 8. In all statistical analyses, two-tailed values of $P < 0.05$ were considered statistically significant.

Results

The records of 858 patients treated in the study period were identified and reviewed. After excluding those patients discharged from ED directly (n = 178), receiving preadmission OCS use (n = 122) and lost followed up (n = 58). Thus, 508 patients with an AECOPD (316 male, 192 female) were included in the analysis. The median age of patients was 74 years (range, 46–97 years). In our data, 35.4% (n = 180) patients were hospitalized with ED visits, shown in Figure 1, others were admission without ED attendance (n = 328, 64.6%). The ROC analysis of EPR to predict mortality resulted in a cut-off point of 0.755 (AUC = 0.718, 95% CI: 0.585–0.785, Figure 2A). The patients with ED attendance were divided into 2 groups based on the EPR value: EPR ≥ 0.755 (n = 135, 75%) and EPR < 0.755 (n = 45, 25%).
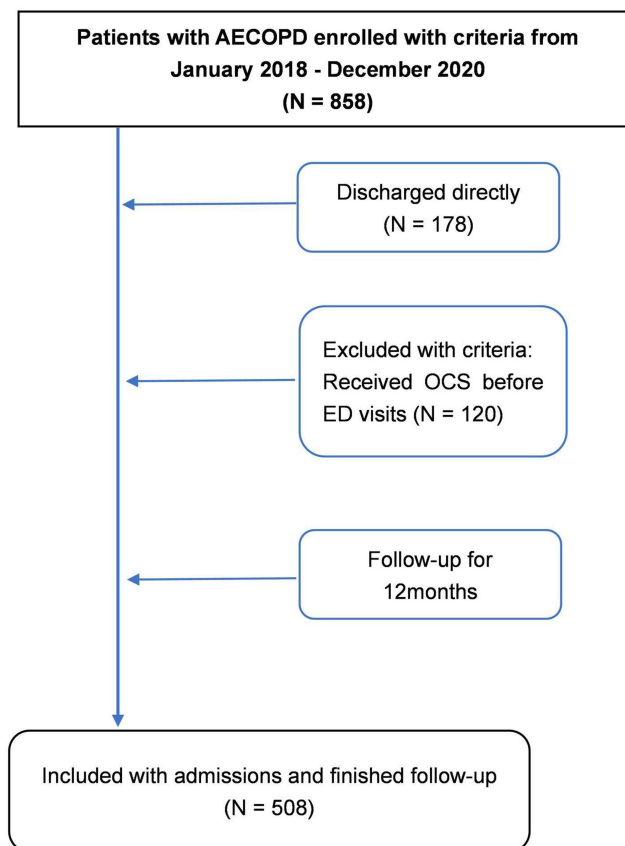
Patients with AECOPD enrolled with criteria from
January 2018 - December 2020
(N = 858)

Discharged directly
(N = 178)

Excluded with criteria:
Received OCS before
ED visits (N = 120)

Follow-up for
12months

Included with admissions and finished follow-up
(N = 508)

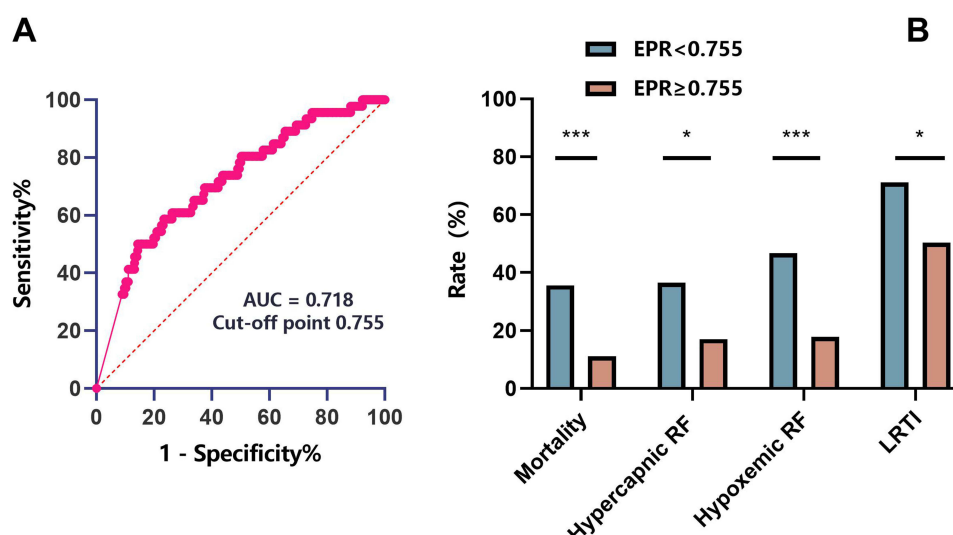**Figure 1** Flowchart of the cohort in the present research.

Figure 2 (**A**) ROC curve for eosinophils to platelet ratio predicts mortality, with cut-off points of 0.755, (**B**) clinical characteristics according to EPR groups in patients with ED visits. *$P < 0.05$, ***$P < 0.01$.
Abbreviation: RF, respiratory failure.

An EPR < 0.755 is Correlated with Unfavourable Outcomes

In all patients, an EPR < 0.755 was associated with a higher frequency of acute respiratory failure (hypoxemic: 41.6 vs 13.8%, $P < 0.001$, hypercapnic: 29.2 vs 11.7%, $P < 0.001$). Notably, in patients with ED attendance, most subjects were male (58.3%) and mean (IQR) age was 78 (68, 84) years, the rate of exacerbation was 35.5% (64/180), and the 1-year all-cause readmission rate was 45% (81/180). An EPR < 0.755 was associated with a higher frequency of acute respiratory failure (hypoxemic: 46.7 vs 17.8%, $P < 0.001$, hypercapnic: 35.6 vs 17%, $P = 0.016$), heart failure (55.6% vs 28.1%, $P = 0.002$), lower respiratory tract infection (71.1% vs 50.4%, $P = 0.024$), and had a longer length of hospital stay ($P = 0.013$), presented in Figure 2B. Those with an EPR < 0.755 had lower PaO_2 (62 [49, 78] vs 75 [65, 84], $P = 0.001$). However, there was no significant difference in baseline FEV1 ($P = 0.876$) and FVC ($P = 0.927$). The demographic characteristics and outcomes of patients seen in the ER are summarized in Table 1, details of all patients and those without ED attendance are presented in the Tables S1 and S2.

An EPR < 0.755 is Associated with a Higher Mortality Rate

The mortality rate for patients with an EPR < 0.775 was 25.8% (n = 23), and for those with an EPR ≥ 0.755 was 5.5% (n = 23, $P < 0.001$), and for patients with emergency room attendance the mortality rate was 11.1% (n = 15) in subjects with EPR ≥ 0.755 compared to 35.6% (n = 16) in the EPR < 0.755 group ($P < 0.001$). For patients without ED attendance, same results were observed, details are provided in Table S2.

Kaplan–Meier analysis confirmed that an EPR < 0.755 was associated with higher mortality in the ED. Similar results were observed in all patients and participants without ED visits, details are provided in the Figure S1.

Clinical Prediction Model

Six variables with non-zero coefficients in the LASSO regression model were included in the final multivariate logistic regression model (history of exacerbation in previous year, age ≥80, hypoalbuminemia, PaO2 <60mmHg, $PaCO_2$ >50 mm Hg, EPR < 0.755, Table 2). A model that including the abovementioned 6 predictors was developed and visualized as a nomogram (Figure 3). The model showed excellent discrimination in predicting mortality (C-index: 0.854, 95% CI: 0.795–0.912). The goodness-of-fit of the model was evaluated using the Hosmer–Lemeshow test and bias-corrected calibration curves (Figure S2). The Hosmer–Lemeshow test yielded a non-significant value ($P = 0.329$), which suggested that the model fit was acceptable. Evaluation of the bias-corrected calibration curves for the prediction model indicated good agreement. On internal validation, 10-fold cross-

Table 1 Demographics and Clinical Outcomes According to EPR Group in Patients with ED Attendance

	n1*	EPR ≥ 0.755 (n =135)	n2*	EPR < 0.755 (n =45)	t/χ^2/Z	P value
Sex					2.75	0.097
Male (n, %)		84 (62.2%)		21 (46.7%)		
Female (n, %)		51 (37.8%)		24 (53.3%)		
Age (median [IQR])	135	77 [67, 84]	45	84 [73, 86]	7.26	0.007
History of AE (n, %)	135	86 (63.7%)	45	27 (60%)	0.07	0.789
Inhaled corticosteroids	135	82 (67%)	45	24 (53.3%)	0.49	0.484
Readmission (n, %)	135	58 (43%)	45	23 (51.1%)	0.61	0.436
Exacerbation (n, %)	135	48 (35.6%)	45	16 (35.6%)	0.01	>0.99
Mortality (n, %)	135	15 (11.1%)	45	16 (35.6%)	12.48	<0.001
Heart Failure (n, %)	135	38 (28.1%)	45	25 (55.6%)	9.97	0.002
ARF- hypoxemic (n, %)	135	24 (17.8%)	45	21 (46.7%)	13.52	<0.001
ARF- hypercapnic (n, %)	135	23 (17.0%)	45	16 (35.6%)	5.77	0.016
LOH (median [IQR])	135	10 [8, 12]	45	12 [9, 16]	6.18	0.013
ICU admission (n, %)	135	2 (1.5%)	45	3 (6.7%)	1.71	0.101
Hypoalbuminemia (n, %)	135	52 (38.5%)	45	24 (53.3%)	2.45	0.117
LRTI (n, %)	135	68 (50.4%)	45	32 (71.1%)	5.07	0.024
Emphysema (n, %)	135	60 (44.4%)	45	26 (57.8%)	1.9	0.168
PaO$_2$ (median [IQR])	135	75 [65, 84]	45	62 [49, 78]	10.16	0.001
PaCO$_2$ (median [IQR])	133	41 [38, 46.5]	45	40 [37, 61]	0.87	0.352
FEV1 (L)	64	1.1 (0.8, 1.7)	4	1.3 (1.1, 1.4)	0.02	0.876
FEV1%	64	50.6 (35.6, 63.3)	4	48.1 (40.3, 59.4)	0.03	0.865
FVC (L)	64	2.0 (1.5, 2.6)	4	2.1 (1.7, 2.3)	0.79	0.927
FEV1/FVC (%)	64	62 (50.6, 65.8)	4	59.1 (53.5, 61)	0.008	0.383

Notes: n1* and n2* represent the total number of people actually assessed for each characteristic in the EPR > 0.755 group and the EPR < 0.755 group, respectively.
Abbreviations: AE, acute exacerbation; ARF, acute respiratory failure; LOH, length of hospitalization; ICU, intensive care unit; LRTI, lower respiratory tract infection; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Table 2 Predictors of All-Cause Mortality in AECOPD Participants

	Prediction Model		
	β-Coefficient	OR (95% CI)	P
Hypoalbuminemia	0.89	2.44(0.94–6.69)	0.07
PaCO$_2$ (> 50mmHg)	0.69	2.00(0.64–6.21)	0.22
PaO$_2$ (< 60mmHg)	0.16	1.17(0.35–3.76)	0.78
Age (≥ 80)	2.27	9.65(1.57–35.24)	<0.001
EPR (< 0.755)	1.12	3.08(1.16–8.27)	0.023
History of exacerbation	0.57	1.77(0.62–5.55)	0.29

Abbreviations: EPR, eosinophil platelet ratio; OR, odds ratio.

validation (bias-corrected C-index = 0.827) indicated that the model discrimination was good. The temporal validation cohort included 114 participants, and the AUC was 0.677 (95% CI: 0.368–0.986).

Predictors of Mortality in Patients Seen in ED with AECOPD

In order to evaluate the predictive ability of the model, we compared it with the DCEAF score[18] (including: dyspnea, eosinopenia, consolidation, acidaemia and atrial fibrillation), a predictor of mortality in patients hospitalized with an exacerbation of COPD. Compared to the DCEAF score, the new model had a higher accuracy (AUC of 0.854 vs 0.570, P = 0.012).
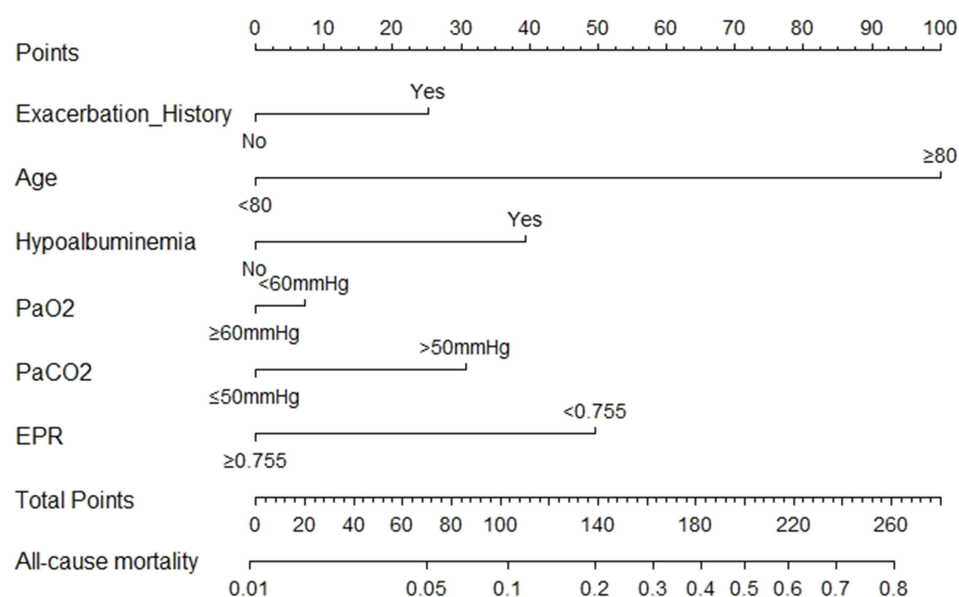
Figure 3 All-cause mortality Nomogram in patients with ED attendance.

The AUC of the eosinophil count for predicting mortality was 0.697, with a cut-off point of 0.045. Further analysis indicated that eosinophil count less than 0.045 was associated with higher mortality.

The AUC for platelet count for predicting mortality was 0.591, with a cut-off point of 175. Further analysis indicated that patients with a platelet count <175 an increased risk of death (14.9% vs 7%, $P = 0.01$).

The AUC of the prediction model, including history of exacerbation, EPR, hypoalbuminemia, PaO2 < 60mmHg, $PaCO_2$ > 50mmHg and age ≥ 80, for predicting mortality was 0.854. This was significantly higher than that of eosinophil ($P = 0.001$), platelet ($P < 0.001$) and EPR (AUC = 0.685, $P < 0.001$) predict mortality alone respectively, presented in Figure S3.

Discussion

To our knowledge, this is the first study to reveal that EPR is a worse prognostic index for emergency department attendance in acute exacerbation of COPD. In patients with ED visit, an EPR < 0.755 was associated with a 3.2 - fold increased risk of death compared to those with an EPR ≥ 0.755 (35.6% vs 11.1%). In addition, an EPR < 0.755 and 5 other variables were independent predictors of all-cause mortality in patients with AECOPD presented at the ED.

In patients seen in ED with AECOPD, we build a simple prognostic model, incorporating clinical information and laboratory results, which can accurately predict all-cause mortality, and performed more accurately than DCEAF scores.

Blood eosinophil count has been widely investigated in COPD.[19–22] And there is compelling evidence that a low eosinophil level is associated with worse outcomes of patients with an AECOPD.[23–25] Recently, Bartziokas et al[26] reported that in patients with AECOPD, those with eosinopenia had increased risk of noninvasive ventilation use. In the current study, the AUC of eosinophil count for predicting mortality was 0.697, with a cut-off point eosinophil count of 0.045. Further analysis indicated that patients with an eosinophil count <0.045 had higher mortality.

This finding is consistent with previous studies.[6,7,9] Lv et al[23] reported that patients with low eosinophils (<2%) had significantly longer length of hospital stay, and higher mortality than those with a higher eosinophil count. Wu et al[24] reported that patients with a low eosinophil count often experienced poorer clinical outcomes. Prudente et al[25] found that a decrease in number of peripheral eosinophils may be associated with a higher risk of death in COPD patients. In addition, a prior study reported that a low eosinophil level is associated with a higher mortality rate in patients with an AECOPD.[18]

Alterations of platelet count have also been reported to be related to COPD.[16] We found that the AUC for platelet count to predict mortality was 0.591, with a cut-off platelet count of 175. Further analysis showed that patients with a platelet count <175 had a greater risk of death (14.9% vs 7%, $P = 0.01$). A number of recent studies have reported

that thrombocytopenia is associated with ICU mortality.[12–14] Fawzy et al[16] reported that platelet count was associated with an increased risk of 3-year all-cause mortality in patients with COPD. Rahimi et al[27] reported that thrombocytopenia was associated with in-hospital mortality in AECOPD. Our findings are consistent with those of the afore-mentioned studies.

Blood eosinophil and platelet count have become an important management tool for patients seen in the ED with an AECOPD. Our results showed that in patients seen in ED with AECOPD, a lower EPR act as a predictor of death. Our findings highlight the potential usefulness of eosinophil to platelet ratio to predict prognosis in patients with AECOPD seen in ED. For patients with ED attendance due to AECOPD, those with eosinopenia and thrombocytopenia simulta-neously may have a poorer prognosis. Russell et al[28] reported that in patients with an AECOPD presenting to ED, a higher blood eosinophil count is associated with a shorter length of stay and reduced mortality. Prior research has indicated that eosinophils might have an anti-infection effect, Linch et al[29] reported that eosinophils might have anti-bacterial properties. In addition, in response to human rhinovirus and respiratory syncytial virus, eosinophil activation has been observed.[30,31] Thrombocytopenia was also associated with mortality in patients with an AECOPD.[27] A decreased platelet count might result from severe infection, which increases the risk of death. These findings may help explain why a low EPR is associated with increased mortality. Further studies are needed to better understand the role that EPR plays in AECOPD.

In this study, we demonstrated that NLR and PLR were not associated with mortality in patients with AECOPD. Consistent with our study, Aksoy et al[32] reported that in patients with AECOPD, the multivariate analysis showed that the NLR was not associated with mortality after adjusting for eosinophilia and other variables. In another study aimed to evaluate the association of the inflammation biomarker in patients with AECOPD with 90-day mortality, Kumar et al[4] demonstrated that NLR was not significantly associated with mortality ($P = 0.46$). In a retrospective study, Rahimiard et al[33] found that there is no significant difference in PLR values between the survival group and the non-survival group ($P = 0.75$), suggested that the PLR did not show significant relation to in-hospital death in AECOPD. In addition, another research[34] reported that in patients with AECOPD, the PLR value of non-survival patients was not significantly higher than that in survival participants ($P > 0.05$), and the diagnostic value of PLR in the prognosis of in-hospital mortality was found to be insignificant ($P = 0.18$), indicated that PLR was not associated with mortality. Therefore, the relationship between NLR, PLR and prognosis of AECOPD needed to be further clarified.

Chen et al[35] found that in patients presenting to the ED with an AECOPD and hypercapnic respiratory failure, respiratory rate, lactic acid, $PaCO_2$, blood urea nitrogen, haemoglobin, and platelet count were predictors of in-hospital mortality. Other study has reported that patients with an AECOPD and hypercapnia have an increased mortality rate.[36] Matkovic et al[37] found that hypercapnia in patients admitted for an AECOPD was an independent predictor of death. Our results are in line with prior study.

We also found that hypoalbuminemia was an independent risk factor for mortality. Chen et al[38] demonstrated that severe hypoalbuminemia was a strong risk factor for acute respiratory failure in patients with COPD. Additionally, a meta-analysis by Lomholt et al[39] found that hypoalbuminemia was associated with increased mortality in patients with COPD. A low albumin level may be a sign of worsening nutrition status or increased inflammation during an AECOPD.

There are some limitations of this study that should be considered. As a retrospective study, our study sample was relatively small and this can have an impact on the results. Second, multi-centre clinical trials with a larger sample size are still needed.

Conclusion

In conclusion, our data demonstrated that in patients with ED attendance due to AECOPD, an EPR <0.755 was associated with an increased risk of death.

Abbreviations

AECOPD, chronic obstructive pulmonary disease; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ICU, intensive care unit; RR, relatively risk; ARF, acute respiratory failure; EPR, eosinophil to platelet ratio; LRTI,

lower respiratory tract infection; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; forced expiratory rate of the 1st second (FEV1%); LOH, length of hospitalization; ED, emergency department; IQR, interquartile range; ROC, receiver operating characteristic curve; AUC, area under the curves; LASSO, least absolute shrinkage selection operator; OCS, oral corticosteroids; OR, odds ratio.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Dalian Friendship Municipal Hospital (protocol code YY-LL-2021-050, date of approval: 2021.12.31). Due to no specific patient identifiable information was used, patient consent was officially waived by the Ethics Committees of Dalian Municipal Friendship Hospital.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Disclosure

The authors report no conflicts of interest in this work.

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