Article

Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Lymphocyte Ratio (NLR), and Monocyte-to-Lymphocyte Ratio (MLR), and Eosinophil-to-Lymphocyte Ratio (ELR) as Biomarkers in Patients with Acute Exacerbation Chronic Obstructive Pulmonary Disease.

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Abstract: The study comprehensively evaluated the prognostic roles of PLR, NLR, MLR, BLR, and ELR in patients with acute exacerbation chronic obstructive pulmonary disease (AECOPD). 619 patients with AECOPD and 300 healthy volunteers were retrospectively included into the study. The clinical characteristics containing laboratory findings of the AECOPD patients and the blood cell counts (CBCs) of the healthy volunteers were collected. Compared with the healthy volunteers, PLR, NLR, and MLR were elevated in COPD patients in stable condition, and were further elevated during exacerbation. ELR showed the opposite trend. PLR, NLR, and MLR were all positively correlated with hospital LOS as well as CRP. In contrast, ELR was negatively correlated with hospital LOS as well as CRP. Elevated PLR, NLR, and MLR were all associated with more serious airflow limitation in AECOPD. Elevated PLR, NLR, and MLR were all associated with increased in-hospital mortality while Elevated ELR was associated with decreased in-hospital mortality in AECOPD. A nomogram was construct to predict in-hospital mortality in AECOPD. The nomogram had a C-index of 0.850 (95% CI: 0.799 – 0.901) with good predictive value and clinical applicability. In summary, PLR, NLR, MLR, and ELR served as predictors for clinical outcomes in patients with AECOPD.

Keywords: Acute exacerbation chronic obstructive pulmonary disease (AECOPD); platelet-to-lymphocyte ratio (PLR); neutrophil-to-lymphocyte ratio (NLR); monocyte-to-lymphocyte ratio (MLR); basophil-to-lymphocyte ratio (BLR); eosinophil-to-lymphocyte ratio (ELR); in-hospital mortality; nomogram; decision curve analysis (DCA); clinical impact curve (CIC)

1. Introduction

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Chronic obstructive pulmonary disease (COPD) is a common chronic inflammatory disease worldwide, which is characterized by chronic airflow limitation accompanied by persistent respiratory symptoms such as dyspnea, cough, and sputum production [1]. COPD poses a huge health and economic burden for an individual, as well as society due to its high prevalence of approximately 10% in adult populations and rising incidence [2]. COPD had a high mortality worldwide, and was the fifth leading cause of death in the past, the ranking will rise to third by 2030. Acute exacerbations contribute substantially to hospitalization and mortality in COPD patients, and 46% of the patients experienced exacerbations at least once in the previous year [3].

Patients with acute exacerbation chronic obstructive pulmonary disease (AECOPD) have poor prognosis with a high mortality rate in hospital. It has been reported that the in-hospital mortality was in the range of 4% – 14% according to population-based surveys performed in Asia-Pacific territories [3]. Several clinical parameters were reported to be associated with in-hospital mortality in patients with AECOPD. For instance, cigarette smoking, as an extremely common risk factor for COPD, was associated with increased in-hospital mortality in patients with AECOPD [1, 4]; increased age and poor respiratory gas exchange served as risk factors for the in-hospital mortality [3]; raised C-reactive protein (CRP) levels were correlated with elevated risk for hospitalization and death in COPD as well as in-hospital mortality in AECOPD [5-7].

Recently, increasing studies found that platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and monocyte-to-lymphocyte ratio (MLR), as systemic inflammatory factors, played prognostic roles in various cancers, such as colorectal cancer [8], lung cancer [9], cervical cancer [10], breast cancer [11, 12], gastric cancer [13], pancreatic cancer [14], gallbladder cancer [15], and hepatocellular carcinoma [16]. In addition, PLR, NLR, and MLR were all predictors of in-hospital mortality in patients with COVID-19 [17]. Previous studies have demonstrated that both PLR and NLR were positively correlated with in-hospital mortality in AECOPD [7]. However, whether MLR also served as a risk factor for in-hospital mortality in AECOPD is unknown. Moreover, whether MLR was a better predictor for the in-hospital mortality compared to PLR as well as NLR is an exploratory issue.

In addition to the three systemic inflammatory factors, the basophil-to-lymphocyte ratio (BLR) and eosinophil-to-lymphocyte ratio (ELR) are identified to be reliable indicators of systemic inflammation [18-20]. The prognostic roles of BLR and ELR in cancers remain unclear due to rare published studies. Recently, it has been reported that elevated BLR was correlated with improved overall survival in patients with non-small cell lung cancer [21, 22]. In addition, BLR was identified to be an independent prognostic factor for distant recurrence-free survival in cervical cancer [23]. With respect to ELR, Ohkuma R, et a. [24] found that low ELR was an independent prognostic factor of clinical outcome in stage II resectable pancreatic cancer [24]. In AECOPD, ELR was a potential indictor of eosinophilic airway inflammation [25]. Whether BLE and ELR are predictors of in-hospital mortality in AECOPD is unclear.

This study comprehensively evaluated the prognostic roles of the systemic inflammatory factors (PLR, NLR, MLR, BLR, and ELR) in clinical outcomes of AECOPD patients. The levels of the systemic inflammatory factors between COPD patients in stable and exacerbation conditions were compared, and the levels between COPD patients and healthy volunteers were also compared. The correlations of the systemic inflammatory factors with airflow limitation, hospital length of stay (LOS), CRP, and in-hospital mortality in patients with AECOPD were analyzed. A nomograph was constructed to predict the in-hospital mortality, the practicability and accuracy of the predictive model were validated.

2. Materials and Methods

2.1. Patients

Patients with AECOPD admitted in the People's hospital of Guilin (Guilin, China) from February 2012 to November 2021 were retrospectively included in the study. In

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addition, 300 healthy volunteers from the Department of Laboratory Medicine of People's hospital of Guilin were also retrospectively included into this study. The study was carried out by a retrospective noninterventional way, and signed informed consent could be waived in accordance with Chinese guidelines and laws. The study protocol and waiver were approved by the Medical Ethics Committee of People's hospital of Guilin (No. 2022-011KY).

FEV1/FVC was calculated as the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC). Diagnosis of COPD was based on a post-bronchodilator FEV1/FVC < 0.70 combined with clinical manifestations such as dyspnea, chronic cough, or sputum production [1]. AECOPD was defined as an acute worsening of respiratory symptoms leading to additional treatment. The typical symptom of AECOPD was aggravated dyspnea accompanied by increased sputum purulence, cough, and wheeze [1]. Patients aged ≥ 18 years old with a primary diagnosis of AECOPD were included in the study. Exclusion criteria were malignancy, acute myocardial infarction, acute heart failure, and other end-stage diseases. For the patients admitted to hospital more than once, the baseline characteristics in the first admission was recorded.

2.2. Data Collection.

The clinical data of the patients were obtained from electronic medical records (EMRs). The demographic data included the age, gender, COPD history, height, weight, body mass index (BMI). The patients were classified using FEV1% predicted in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [1]. The pulmonary function parameters consisted of FEV1% predicted, FVC% predicted, and FEV1/ FVC. Arterial blood gas (ABG) analysis involved PH, PaO_2 (arterial oxygen tension), and arterial carbon dioxide tension ($PaCO_2$). Respiratory failure was a severe impairment of gas exchange functions in the respiratory system, leading to hypoxaemia (PaO2 < 60 mmHg) and/or hypercapnia ($PaCO_2$ > 50 mmHg) [26]. The common comorbidities of AECOPD comprised asthma, pneumonia, pulmonary heart disease (PHD), hypertension, diabetes mellitus, and cardiovascular disease. Blood routine examinations were also known as complete blood counts (CBCs), which referred to the counts of the white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), platelet, neutrophil, monocyte, lymphocyte, eosinophil, and basophil. PLR, NLR, MLR, BLR, and ELR were calculated using these counts. The other laboratory findings were composed of D-dimer, uric acid (UA), serum creatinine (Scr), blood urea nitrogen (BUN), albumin, and lactate dehydrogenase (LDH). Hospital length of stay (LOS) was calculated from the date of admission to the data of discharge from hospital or death. Stable COPD was a condition characterized as chronic symptoms and persistent airflow limitation without exacerbation in COPD [1].

For the healthy volunteers, the clinical data were derived from regular medical examinations and collected from the EMRs of the Department of Laboratory Medicine of People's hospital of Guilin. These clinical data consisted of age, gender, and CBCs.

2.3. Statistical analysis.

The normal distribution of continuous data was determined using Kolmogorov-Smirnov test. After Kolmogorov-Smirnov test, all of the continuous data were present as abnormal distributions. Thus, the value for each continuous variable represented the median (25th–75th centile). The comparison of continuous data between independent groups was performed by Mann–Whitney U test, and the paired comparison of the continuous data between groups was performed using Wilcoxon signed rank test [27]. The comparison of categorical variables between independent groups was performed using Chi Square test or Fisher's exact test. In addition, the comparison of the continuous data among multiple independent groups was performed using Kruskal-Wallis test [28]. Bonferroni's post hoc comparison test was used if the P value was < 0.05 through the Kruskal-Wallis test. The correlation between continuous clinical data was evaluated by Spearman's correlation coefficient, and the correlation between continuous and categorical variables

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was also evaluated by Spearman's correlation coefficient. The correlation between categorical variables was analyzed using phi or Cramer's V coefficient.

The association of clinical parameter with in-hospital mortality in patients with AECOPD was analyzed using binary logistic regression along with the corresponding odds ratio (OR) and 95% confidence interval (CI). Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive ability of clinical parameters for in-hospital mortality. A nomogram for predicting in-hospital mortality was established on the basis of the result of binary logistic regression analysis. R (version 4.1.0) analysis packages, including, PredictABEL_1.2-4, nricens_1.6, rmda_1.6, and rms_6.3-0, were used to plot the nomogram and perform the corresponding validation. All of the analyses were performed using SPSS version 26.0 (SPSS, Inc., Chicago, IL, USA), and $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Clinical characteristics of 619 patients with AECOPD.

A total of 619 patients with AECOPD were included into the retrospective study in accordance with the inclusion and exclusion criteria, and the baseline characteristics of these patients were summarized in Table 1. 55 patients died during hospitalization, reflecting an in-hospital mortality rate of 8.89%. The included patients consisted of 516 (83.4%) male patients and 103 (16.6%) female patients, with a median age of 70 years old. The median COPD history of the patients was 5.28 years, and 308 (49.8%) patients had no smoking history. The median height, weight, and body mass index (BMI) of the patients were 163 cm, 56 kg, and 21.4 kg/m^2, respectively. 11 (1.8%), 117 (18.9%), 330 (53.3%), and 161 (26.0%) patients with AECOPD were classified as GOLD stages Ⅰ, Ⅱ, Ⅲ, and Ⅳ, respectively. The median FEV1% predicted, FVC% predicted, and FEV1/FVC were 38.5%, 67.5%, and 58.5%, respectively. 92 (14.9%) patients were evaluated as respiratory failure. 72 (11.6%), 180 (29.1%), 199 (32.1%), and 168 (27.1%) patients with AECOPD had 0, 1, 2, and ≥ 3 comorbidities, respectively. 67 (10.8%), 250 (40.4%), 59 (9.5%), 187 (30.2%), and 42 (6.8%) patients were accompanied by asthma, pneumonia, PHD, hypertension, and diabetes mellitus, respectively. The median PLR, NLR, MLR, BLR, and ELR were 185.8, 4.712, 0.465, 0.022, and 0.087, respectively.

55 (8.89%) and 564 (91.1%) patients were divided into dead and survival groups, respectively. The age, $PaCO_2$, WBC, neutrophil, PLR, NLR, MLR, D-dimer, UA, Scr, BUN, and LDH were significantly higher in the dead group compared to the survival group (all $P < 0.05$). In contrast, the FEV1% predicted, FVC% predicted, FEV1/FVC, PH, PaO_2, lymphocyte, eosinophil, basophil, ELR, and albumin were significantly lower in the dead group compared with the survival group (all $P < 0.05$). In addition, the smoking history, GOLD stages, number of comorbidities, asthma, pneumonia, and PHD were related to in-hospital mortalities (all $P < 0.05$). The respiratory failure rate of the patients was marginally elevated in the dead group compared to the survival group ($P = 0.055$, Table 1).

Table 1. Comparison of baseline characteristics between survival and dead patients with AECOPD.

Clinical characteristics	Overall (n = 619)	Survival (n= 564)	Dead (n= 55)	P value
Age, years	70 (64 – 77)	70 (63 – 77)	71 (67 – 82)	0.025
Gender, n (%)				
Male	516 (83.4%)	466 (90.3%)	98 (95.1%)	
Female	103 (16.6%)	50 (9.7%)	5 (4.9%)	0.115
COPD history, years	5.28 (2.48 – 8.65)	5.17 (2.37 – 8.59)	5.99 (3.32 – 10.)	0.086
Smoking history, n (%)				
Current/ever	311 (50.2%)	270 (47.9%)	14 (25.5%)	
Never	308 (49.8%)	294 (52.1%)	41 (74.5%)	1.6×10^{-4}
Height, cm	163 (157 – 168)	163 (157 – 168)	165 (160 – 168)	0.127
Weight, kg	56 (50 – 64)	56 (50 – 64)	58 (50 – 64)	0.961

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BMI, kg/m2	21.4 (19.2 – 24.0)	21.4 (19.3 – 24.1)	21.3 (18.0 – 22.7)	0.177
GOLD stage				
GOLD stage Ⅰ	11 (1.8%)	11 (2.0%)	0 (0.0%)	
GOLD stage Ⅱ	117 (18.9%)	115 (20.4%)	2 (3.6%)	
GOLD stage Ⅲ	330 (53.3%)	305 (54.1%)	25 (45.5%)	
GOLD stage Ⅳ	161 (26.0%)	133 (23.6%)	28 (50.9%)	8×10^{-6}*
Pulmonary function				
FEV1% predicted, %	38.5 (29.7 – 48.0)	39.4 (30.8 – 48.5)	29.7 (23.8 – 36.8)	$1.88e^{-8}$
FVC% predicted, %	67.5 (57.7 – 77.9)	68.4 (58.6 – 78.3)	56.1 (45.6 – 67.5)	$1.30e^{-7}$
FEV1/FVC, %	58.5 (50.2 – 65.3)	59.0 (51.5 – 65.4)	51.9 (46.5 – 59.4)	2.6×10^{-5}
PH	7.41 (7.37 – 7.44)	7.41 (7.37 – 7.44)	7.38 (7.34 – 7.43)	0.006
PaO2, mmHg	74 (64 – 84)	74 (64 – 84)	68 (61 – 79)	0.015
PaCO2, mmHg	43 (38 -52)	43 (38 -50)	52 (40 – 58)	0.001
Respiratory failure				
Yes	92 (14.9%)	79 (14.0%)	13 (23.6%)	
No	527 (85.1%)	485 (86.0%)	42 (76.4%)	0.055
Number of comorbidities				
0	72 (11.6%)	71 (12.6%)	1 (1.8%)	
1	180 (29.1%)	168 (29.8%)	12 (21.8%)	
2	199 (32.1%)	178 (31.6%)	21 (38.2%)	
≥ 3	168 (27.1%)	147 (26.1%)	21 (38.2%)	0.023
Asthma				
Yes	67 (10.8%)	67 (11.9%)	0 (0.0%)	
No	552 (89.2%)	497 (88.1%)	55 (100.0%)	0.007
Pneumonia				
Yes	250 (40.4%)	215 (38.1%)	35 (63.6%)	
No	369 (59.6%)	349 (61.9%)	20 (36.4%)	2.3×10^{-4}
PHD				
Yes	59 (9.5%)	43 (7.6%)	16 (29.1%)	
No	560 (90.5%)	521 (92.4%)	39 (70.9%)	$2.28e^{-7}$
Hypertension				
Yes	187 (30.2%)	171 (30.3%)	16 (29.1%)	
No	432 (69.8%)	393 (69.7%)	39 (70.9%)	0.850
Diabetes mellitus				
Yes	42 (6.8%)	36 (6.4%)	6 (10.9%)	
No	577 (93.2%)	528 (93.6%)	49 (89.1%)	0.203
Cardiovascular disease				
Yes	95 (15.3%)	87 (15.4%)	8 (14.5%)	
No	524 (84.7%)	477 (84.6%)	47 (85.5%)	0.863
WBC, $\times 10^9$/L	8.28 (6.39 – 10.68)	8.21 (6.31 – 10.45)	9.50 (7.33 – 14.14)	0.002
RBC, $\times 10^{12}$/L	4.53 (4.10 – 4.92)	4.53 (4.10 – 4.92)	4.53 (4.10 – 4.96)	0.921
Hb, g/L	135 (124 – 146)	135 (124 – 146)	133 (122 – 146)	0.625
Platelet, $\times 10^9$/L	227 (183 – 283)	230 (183 – 283)	213 (166 – 290)	0.161
Neutrophil, $\times 10^9$/L	5.90 (4.26 – 8.51)	5.71 (4.19 – 8.31)	7.22 (4.90 – 12.48)	1.2×10^{-4}
Monocyte, $\times 10^9$/L	0.58 (0.43 – 0.81)	0.58 (0.43 – 0.80)	0.60 (0.47 – 0.96)	0.107
Lymphocyte, $\times 10^9$/L	1.23 (0.79 – 1.77)	1.25 (0.82 – 1.80)	0.77 (0.56 – 1.23)	2×10^{-6}
Eosinophil, $\times 10^9$/L	0.12 (0.03 – 0.24)	0.13 (0.04 – 0.25)	0.03 (0.01 – 0.10)	2×10^{-6}
Basophil, $\times 10^9$/L	0.03 (0.02 – 0.04)	0.03 (0.02 – 0.04)	0.02 (0.01 – 0.04)	0.022
PLR	185.8 (130.1 – 277.5)	183.6 (128.7 – 268.0)	268.7 (153.3 – 469.4)	2.4×10^{-4}
NLR	4.712 (2.747 – 8.730)	4.431 (2.644 – 8.259)	9.377 (4.667 – 22.761)	$1.30e^{-7}$
MLR	0.465 (0.315 – 0.756)	0.451 (0.306 – 0.709)	0.795 (0.464 – 1.239)	$6.02e^{-8}$
BLR	0.022 (0.014 – 0.036)	0.022 (0.014 – 0.035)	0.030 (0.013 – 0.054)	0.326

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ELR	0.087 (0.033 – 0.171)	0.094 (0.036 – 0.176)	0.037 (0.014 – 0.118)	4.1×10^{-4}
CRP, mg/L	10.3 (2.2 – 45.7)	8.9 (2.0 – 42.0)	28.2 (12.0 – 78.6)	2×10^{-6}
D-dimer, μg/mL	0.47 (0.28 – 0.93)	0.45 (0.27 – 0.88)	0.74 (0.44 – 1.32)	2.9×10^{-5}
UA, μmol/L	332 (268 – 407)	329 (266 – 402)	387 (282 – 468)	0.026
Scr, μmol/L	78.0 (67.0 – 95.9)	77.2 (66.8 – 92.8)	88.4 (73.0 – 122.2)	0.001
BUN, mmol/L	5.30 (4.30 – 6.70)	5.22 (4.27 – 6.52)	6.60 (4.95 – 9.61)	5.2×10^{-5}
Albumin, g/L	39.4 (36.4 – 42.1)	39.6 (36.6 – 42.4)	36.6 (33.9 – 39.6)	1.3×10^{-5}
LDH, U/L	198 (167 – 235)	198 (166 – 233)	225 (175 – 254)	0.045

* The P value was calculated after combination of GOLD stage I and GOLD stage II.

Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; PaO2, arterial oxygen tension; PaCO2, arterial carbon dioxide tension; PHD, pulmonary heart disease; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte; MLR, monocyte-to-lymphocyte ratio; BLR, basophil-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio; CRP, C-reactive protein; UA, uric acid; Scr, serum creatinine; BUN, blood urea nitrogen; LDH, lactate dehydrogenase.

3.2. The levels of systemic inflammatory factors in COPD patients during stable and exacerbation periods and healthy volunteers.

For the survival patients in hospital (n = 564), FEV1% predicted ($P = 2.69e^{-88}$), FVC% predicted ($P = 1.57e^{-81}$), and FEV1/FVC ($P = 4.73e^{-18}$) were dramatically elevated in the stable period compared to the exacerbation period. In the stable period, PaO_2 was significantly increased ($P = 4.64e^{-38}$) while $PaCO_2$ was significantly decreased ($P = 5.02e^{-19}$), as compared to the exacerbation period (Table S2). Among the survival patients, 410 COPD patients in stable condition performed blood routine examinations. Blood cell counts, Hb, PLR, NLR, MLR, BLR, and ELR in COPD patients between stable and exacerbation conditions were compared in Table 2. PLR ($P = 0.015$), NLR ($P = 5.11e^{-13}$), MLR ($P = 0.007$), and BLR ($P = 7.37e^{-16}$) were significantly decreased in stable condition compared to exacerbation condition, while ELR was significantly increased in stable condition compared with exacerbation condition ($P = 0.018$). In addition, demographic characteristics, blood cell counts, Hb, PLR, NLR, MLR, BLR, and ELR in patients with stable COPD and healthy volunteers were also summarized in Table 2. PLR ($P = 3.69e^{-38}$), NLR ($P = 1.00e^{-69}$), MLR ($P = 2.76e^{-66}$), BLR ($P = 4.48e^{-25}$) and ELR ($P = 1.18e^{-14}$) were dramatically decreased in the healthy volunteers compared to the patients with stable COPD.

Table 2. Comparisons of clinical characteristics among COPD patients during stable and exacerbation periods and healthy volunteers.

Clinical characteristics	Patients with AECOPD (n = 410)	Patients with stable COPD (n= 410)	Heathy volunteers (n= 300)	P value[a]	P value[b]
Age, years	69 (63 – 76)	69 (63 – 76)	51 (39 – 60)	—	1.27e-60
Gender, n (%)					
Male	340 (82.9%)	340 (82.9%)	137 (45.7%)		
Female	70 (17.1%)	70 (17.1%)	163 (54.3%)	—	$1.55e^{-25}$
WBC, ×109/L	8.17 (6.26 – 10.46)	7.29 (5.97 – 9.07)	6.64 (5.67 – 7.87)	$4.11e^{-17}$	1.5×10^{-5}
RBC, ×1012/L	4.49 (4.05 – 4.90)	4.40 (3.92 – 4.85)	4.92 (4.54 – 5.31)	$5.33e^{-9}$	$1.91e^{-26}$
Hb, g/L	134 (124 – 147)	131 (118 – 145)	144 (133 – 155)	$3.00e^{-11}$	$6.20e^{-20}$
Platelet, ×109/L	231 (184 – 284)	233 (187 – 290)	264 (230 – 301)	0.012	2.91e-7
Neutrophil, ×109/L	5.61 (4.10 – 8.37)	4.82 (3.59 – 6.58)	3.55 (2.82 – 4.45)	$1.04e^{-19}$	$9.42e^{-26}$
Monocyte, ×109/L	0.59 (0.43 – 0.80)	0.56 (0.44 – 0.73)	0.48 (0.37 – 0.59)	0.002	$2.11e^{-10}$
Lymphocyte, ×109/L	1.32 (0.89 – 1.82)	1.40 (1.01 – 1.84)	2.35 (1.97 – 2.83)	0.001	9.06e-62
Eosinophil, ×109/L	0.13 (0.04 – 0.25)	0.16 (0.07 – 0.30)	0.13 (0.08 – 0.21)	5×10^{-6}	0.095
Basophil, ×109/L	0.03 (0.02 – 0.04)	0.03 (0.02 – 0.04)	0.03 (0.02 – 0.04)	0.969	0.582
PLR	178.4 (128.3 – 260.9)	170.4 (126.6 – 244.9)	112.0 (90.5 – 136.2)	0.015	$3.69e^{-38}$

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NLR	4.228 (2.548 – 8.258)	3.391 (2.218 – 5.697)	1.506 (1.213 – 1.873)	$5.11e^{-13}$	$1.00e^{-69}$
MLR	0.448 (0.302– 0.687)	0.416 (0.281– 0.599)	0.204 (0.159 – 0.237)	0.007	$2.76e^{-66}$
BLR	0.023 (0.014– 0.035)	0.021 (0.013 – 0.032)	0.012 (0.008 – 0.017)	$7.37e^{-16}$	$4.48e^{-25}$
ELR	0.091 (0.034– 0.177)	0.109 (0.048– 0.223)	0.056 (0.035 – 0.092)	0.018	$1.18e^{-14}$

[a] The P value was calculation through comparison of clinical characteristics between patients with AECOPD and patients with stable COPD, and the comparison was performed using Wilcoxon signed rank test, in light of the abnormal distribution of difference values.
[b] The P value was calculation through comparison of clinical characteristics between patients with stable COPD and healthy volunteers, and the comparison was performed using Mann–Whitney U test, in terms of the abnormal distribution of clinical data.
Abbreviations: COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation chronic obstructive pulmonary disease; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte; MLR, monocyte-to-lymphocyte ratio; BLR, basophil-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio.

3.3. Relationships between systemic inflammatory factors and airflow limitation in pa-tients with AECOPD.

Kruskal-Wallis test was used evaluate the differences in PLR, NLR, MLR, BLR, and ELR among AECOPD patients with stages I, II, III, and IV. As a result, there were significant differences in PLR ($P = 0.003$), NLR ($P = 3 \times 10^{-6}$), MLR ($P = 1.4 \times 10^{-5}$), and ELR ($P = 0.025$) among AECOPD patients with stages I ~ IV. The median (25th–75th centile) PLR values were 136.3 (125.4 – 171.1), 171.6 (117.4 – 239.0), 184.3 (134.9 – 275.8), and 215.5 (138.4 – 323.1) in AECOPD patients with stages I, II, III, and IV, respectively. The patients classified as GOLD stage Ⅳ had significantly higher PLR than the patients classified as GOLD stage Ⅱ (Bonferroni's $P = 0.009$, Figure 1A). The median (25th–75th centile) NLR values were 3.405 (1.319 – 8.685), 3.631 (2.141 – 6.326), 4.635 (2.827 – 8.692), and 5.870 (3.465 – 12.457) in AECOPD patients with GOLD stages I, II, III, and IV, respectively. NLR were increased in patients with more severe airflow limitation (Figure 1B). The corresponding median (25th–75th centile) MLR values were 0.281 (0.232 – 1.023), 0.362 (0.262 – 0.563), 0.474 (0.322 – 0.820), and 0.560 (0.390 – 0.858), respectively. The patients classified as GOLD stage Ⅱ had significantly lower MLR compared to the patients classified as GOLD stage Ⅲ (Bonferroni's $P = 6.5 \times 10^{-4}$) as well as the patients classified as GOLD stage Ⅳ (Bonferroni's $P = 7 \times 10^{-6}$, Figure 1C). For ELR, the median (25th–75th centile) values were 0.043 (0.034 – 0.083), 0.105 (0.041 – 0.212), 0.090 (0.036 – 0.181), and 0.075 (0.021 – 0.155). The patients with stage Ⅳ had significantly lower ELR than the patients with stage Ⅱ (Bonferroni's $P = 0.037$, Figure 1D).

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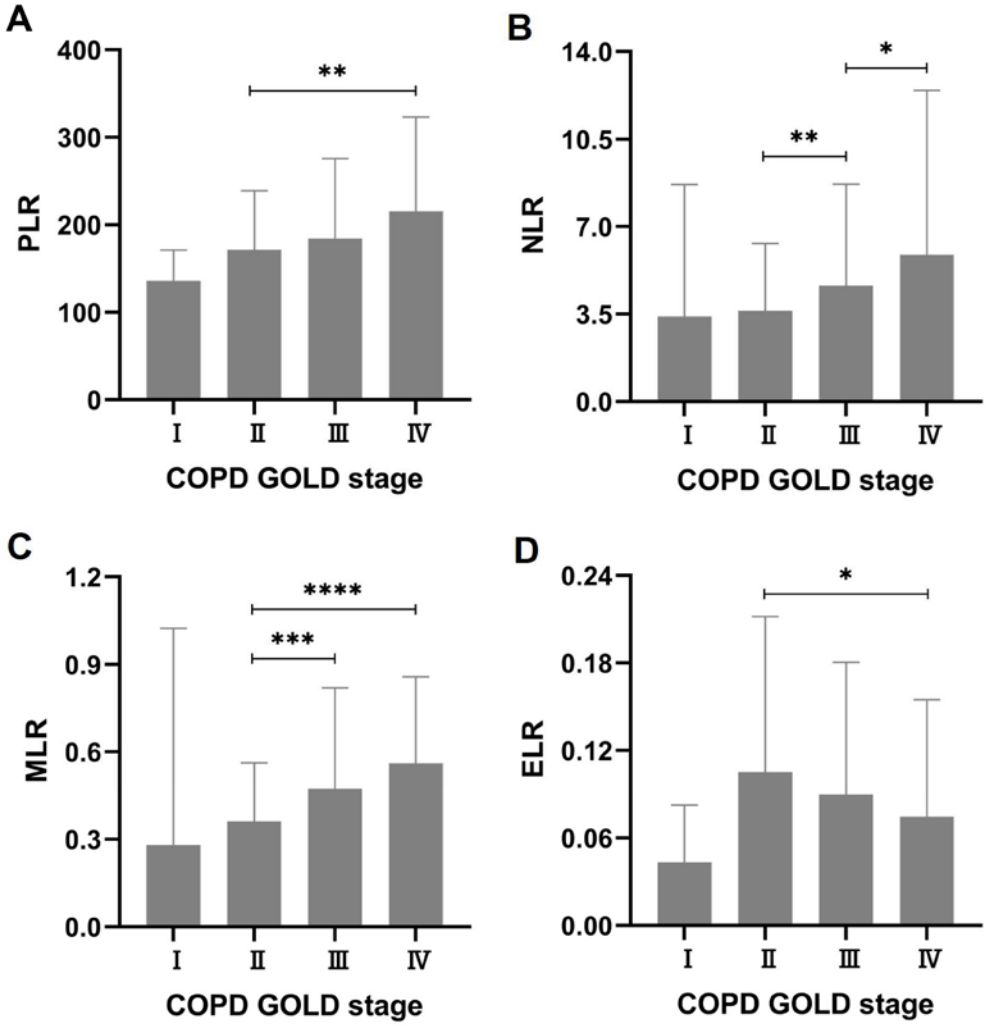

Figure 1. Relationships between systemic inflammatory factors and GOLD stages in patients with AECOPD. (A) PLR, platelet-to-lymphocyte ratio; (B) NLR, neutrophil-to-lymphocyte; (C) MLR, monocyte-to-lymphocyte ratio; (D) ELR, eosinophil-to-lymphocyte ratio. Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; AECOPD, acute exacerbation chronic obstructive pulmonary disease. Each value represents the median with interquartile range. *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$; ****, $P < 0.0001$.

In addition, FEV1% predicted negatively correlated with PLR (r = -0.166, $P = 3.2 \times 10^{-5}$), NLR (r = -0.223, $P = 1.99e^{-8}$), MLR (r = -0.197, $P = 7.69e^{-7}$), and BLR (r = -0.088, $P = 0.029$), whereas ELR presented a positive correlation with FEV1% predicted (r = 0.087, $P = 0.030$) (Additional file 2: Figure S1). With respect to FEV1/FVC, neither BLR (r = -0.073, $P = 0.068$) nor ELR (r = -0.077, $P = 0.055$) had significant correlations with FEV1/FVC. PLR (r = -0.129, $P = 0.001$), NLR (r = -0.117, $P = 0.003$), and MLR (r = -0.178, $P = 8 \times 10^{-6}$) all presented negative correlations with FEV1/FVC (Figure 2).

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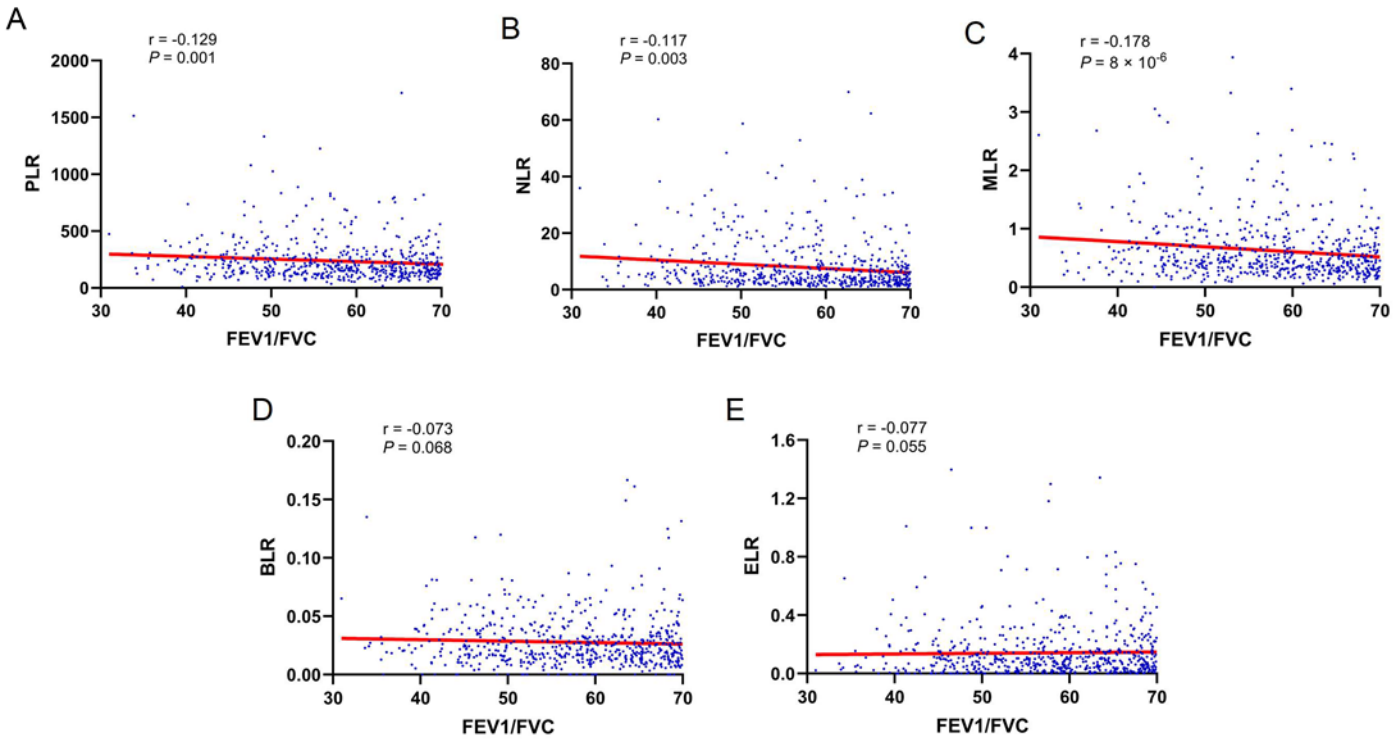

Figure 2. Correlations between systemic inflammatory factors and FEV1/FVC in patients with AECOPD. (A) PLR, platelet-to-lymphocyte ratio; (B) NLR, neutrophil-to-lymphocyte; (C) MLR, monocyte-to-lymphocyte ratio; (D) BLR, basophil-to-lymphocyte ratio; (E) ELR, eosinophil-to-lymphocyte ratio. Abbreviations: FEV1, forced expiratory volume in one second; FVC, forced vital capacity; AECOPD, acute exacerbation chronic obstructive pulmonary disease.

3.4. Influences of systemic inflammatory factors on the hospital length of stay and C-reactive protein in patients with AECOPD.

Spearman correlation coefficients were used to evaluate the correlations of systemic inflammatory factors (PLR, NLR, MLR, BLR, and ELR) with hospital length of stay (LOS) as well as CRP due to abnormal distributions of these clinical data. The median (25th–75th centile) hospital LOS was 8 (6 – 11) days. As shown in Figure 3, PLR (r = 0.152, $P = 1.5 \times 10^{-4}$), NLR (r = 0.279, $P = 1.52e^{-12}$), and MLR (r = 0.262, $P = 3.30e^{-11}$) were all positively correlated with hospital LOS, while ELR was negatively correlated with hospital LOS (r = -0.117, $P = 0.004$). BLR had no correlation with hospital LOS (r = 0.035, $P = 0.390$). The median (25th–75th centile) CRP was 10.3 (2.2 – 45.7) mg/L. As shown in Additional file 3: Figure S2, CRP positively correlated with PLR (r = 0.280, $P = 2.12e^{-12}$), NLR (r = 0.464, $P = 1.06e^{-33}$), and MLR (r = 0.456, $P = 1.88e^{-32}$), but negatively correlated with ELR (r = -0.166, $P = 4.1 \times 10^{-5}$). Moreover, BLR had no correlation with CRP (r = 0.039, $P = 0.332$).

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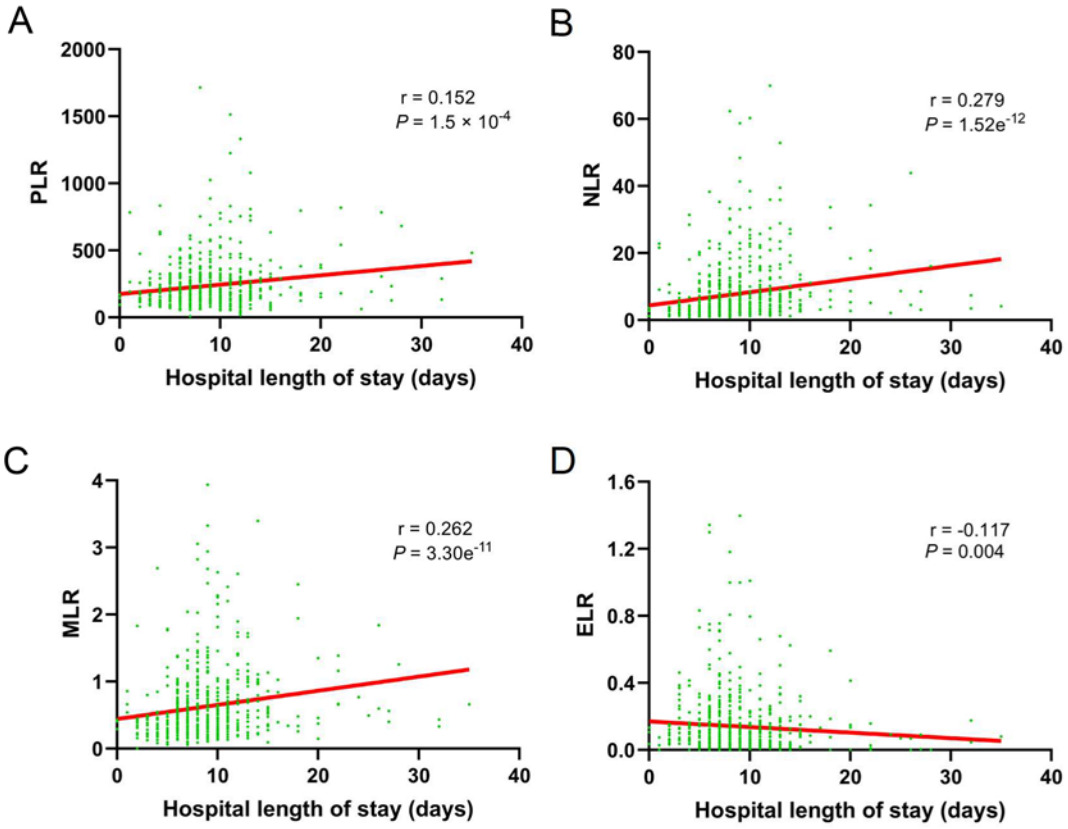

Figure 3. Correlations of systemic inflammatory factors with hospital length of stay in patients with AECOPD. (A) PLR, platelet-to-lymphocyte ratio; (B) NLR, neutrophil-to-lymphocyte; (C) MLR, monocyte-to-lymphocyte ratio; (D) ELR, eosinophil-to-lymphocyte ratio. Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease.

3.5. Receiver operating characteristic (ROC) curves for in-hospital mortality in patients with AECOPD.

ROC curves were plotted to assess the sensitivity, specificity, and accuracy of the systemic inflammatory factors in patients with AECOPD, and the area under the curve (AUC) was used to indicate the predictive ability for in-hospital mortality. The AUCs (95% CI) for PLR, NLR, MLR, BLR, and ELR were 0.650 (0.569 – 0.731), 0.715 (0.646 – 0.785), 0.721 (0.651 – 0.791), 0.540 (0.448 – 0.632), and 0.644 (0.568 – 0.720), respectively (Figure 4). The results indicated that both NLR and MLR had higher predictive value for in-hospital mortality compared to PLR as well as ELR. In addition, the results suggested that MLR had the highest predictive value for in-hospital mortality. The AUC for BLR was close to 0.5, implying that BLR almost had no predictive ability for in-hospital mortality. In addition, the AUCs (95% CI) for GOLD stages, FEV1% predicted, FVC% predicted, FEV1/FVC, and CRP were 0.677 (0.607 – 0.746), 0.729 (0.662 – 0.795), 0.714 (0.641 – 0.787), 0.679 (0.602 – 0.737), and 0.696 (0.638 – 0.753), respectively, suggesting that FEV1% predicted had the highest predictive ability for in-hospital mortality. The AUCs for NLR, MLR, FEV1% predicted, and FVC% predicted all exceeded 0.7, indicating that these clinical characteristics had good predictive ability for in-hospital mortality.

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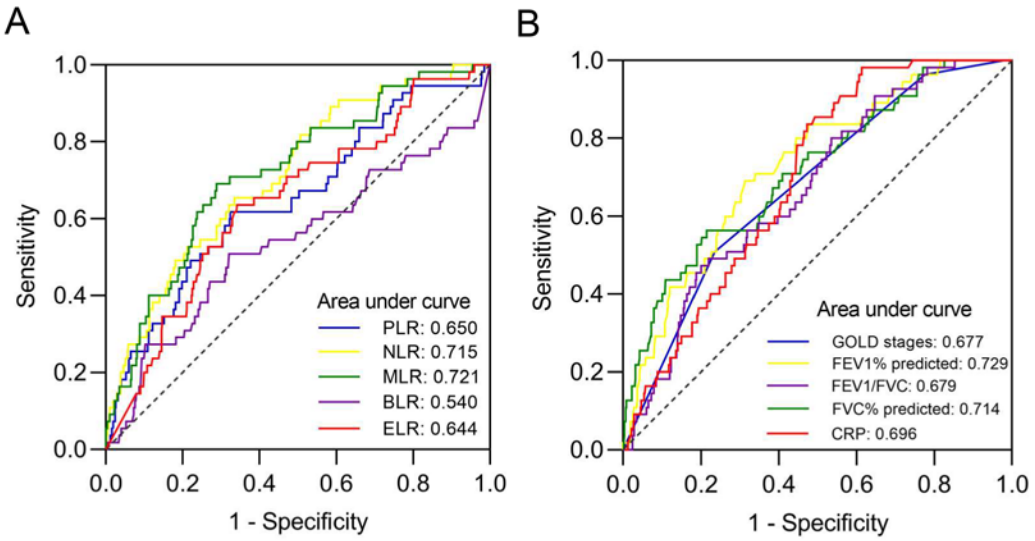

Figure 4. Receiver operating characteristic (ROC) curves for predictive ability of clinical characteristics in patients with AECOPD. (A) PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte; MLR, monocyte-to-lymphocyte ratio; BLR, basophil-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio; (B) GOLD, Global Initiative for Chronic Obstructive Lung Disease; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; CRP, C-reactive protein.

3.6. Association of clinical characteristics with in-hospital mortality in patients with AECOPD.

The age, FEV1% predicted, FVC% predicted, FEV1/FVC, PH, PaO_2, $PaCO_2$, WBC, neutrophil, lymphocyte, eosinophil, basophil, PLR, NLR, MLR, ELR, CRP, D-dimer, UA, Scr, BUN, albumin, and LDH as continuous variables had differences between survival and dead patients with AECOPD, and had potential to predict in-hospital mortality (Table 1). Association of the clinical parameters with in-hospital mortality of patients with AECOPD was analyzed using univariate binary logistic regression. As shown in Table 3, these clinical parameters, except for basophil and LDH, were significantly associated with in-hospital mortality in patients with AECOPD. Among these clinical parameters, the age, $PaCO_2$, WBC, neutrophil, PLR, NLR, MLR, CRP, D-dimer, UA, Scr, and BUN were all risk factors for in-hospital mortality in patients with AECOPD (all OR values > 1, Table 3).

Table 3. Univariate binary logistic regression analysis of clinical parameters associated with in-hospital mortality in AECOPD patients.

Clinical parameters	β	SE	Wald $\chi 2$	P value	OR	95% CI	
						Lower limit	Upper limit
Age	0.035	0.014	5.980	0.014	1.036	1.007	1.066
FEV1% predicted	-0.078	0.015	26.043	< 1 × 10-6	0.925	0.898	0.953
FVC% predicted	-0.061	0.012	28.114	1.14e-07	0.941	0.920	0.962
FEV1/FVC	-0.060	0.015	15.447	8.48e-05	0.942	0.914	0.970
PH	-8.005	2.399	11.131	8.5 × 10-4	0.000	0.000	0.037
PaO2	-0.020	0.009	5.008	0.025	0.980	0.963	0.998
PaCO2	0.030	0.009	10.915	0.001	1.030	1.012	1.048
WBC	0.125	0.030	16.894	4.0 × 10-5	1.133	1.068	1.203
Neutrophil	0.143	0.030	22.885	1.72e-06	1.153	1.088	1.223
Lymphocyte	-1.200	0.279	18.560	1.6 × 10-5	0.301	0.174	0.520
Eosinophil	-5.184	1.467	12.492	4.1 × 10-4	0.006	0.000	0.099
Basophil	-10.712	7.396	2.098	0.148	0.000	0.000	43.995
PLR	0.002	0.000	11.923	5.5 × 10-4	1.002	1.001	1.003
NLR	0.040	0.010	14.660	1.3 × 10-4	1.040	1.019	1.062

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MLR	0.965	0.193	25.107	1 × 10-6	2.625	1.800	3.828
ELR	-3.860	1.518	6.467	0.011	0.021	0.001	0.413
CRP	0.007	0.002	10.116	0.001	1.007	1.003	1.012
D-dimer	0.091	0.035	6.817	0.009	1.095	1.023	1.172
UA	0.003	0.001	10.315	0.001	1.003	1.001	1.006
Scr	0.008	0.003	10.097	0.001	1.008	1.003	1.014
BUN	0.148	0.034	18.415	1.78e-05	1.159	1.084	1.240
Albumin	-0.058	0.019	9.501	0.002	0.943	0.909	0.979
LDH	0.002	0.001	2.639	0.104	1.002	1.000	1.005

[a] The P value was calculation through comparison of clinical characteristics between patients with AECOPD and patients with stable COPD, and the comparison was performed using Wilcoxon signed rank test, in light of the abnormal distribution of difference values.
[b] The P value was calculation through comparison of clinical characteristics between patients with stable COPD and healthy volunteers, and the comparison was performed using Mann–Whitney U test, in terms of the abnormal distribution of clinical data.
Abbreviations: COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation chronic obstructive pulmonary disease; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte; MLR, monocyte-to-lymphocyte ratio; BLR, basophil-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio.

In view of the correlations between clinical characteristics (Additional file 4: Table S2), multivariate binary logistic regression analysis included the age, smoking history, FEV1% predicted, number of comorbidities, asthma, pneumonia, PHD, PH, $PaCO_2$, PaO_2, CRP, D-dimer, UA, Scr, BUN, albumin, WBC, NLR, MLR, and ELR. As shown in Table 4, smoking history, FEV1% predicted, pneumonia, PHD, UA, albumin, and MLR were significant independent predictors for in-hospital mortality in AECOPD patients. Through multivariate analysis, increased ELR was marginally associated with decreased in-hospital mortality ($P = 0.070$). Among these predictors, smoking history, pneumonia, PHD, UA, and MLR were all risk factors for in-hospital mortality.

Table 3. Binary logistic regression analysis of risk factors associated with in-hospital mortality in AECOPD patients.

Clinical parameters	β	SE	Wald χ2	P value	OR	95% CI	
						Lower limit	Upper limit
Smoking history[a]	-1.119	0.371	9.075	0.003	3.061	1.478	6.339
FEV1% predicted	-0.052	0.018	8.554	0.003	0.949	0.916	0.983
Pneumonia[a]	0.767	0.339	5.129	0.024	2.152	1.109	4.179
PHD[a]	0.843	0.388	4.729	0.030	2.324	1.087	4.970
UA	0.003	0.001	8.110	0.004	1.003	1.001	1.006
Albumin	-0.053	0.025	4.359	0.037	0.948	0.902	0.997
MLR	0.621	0.212	8.597	0.003	1.862	1.229	2.821
ELR	-2.522	1.391	3.288	0.070	0.080	0.005	1.226

[a] The patients without smoking history, pneumonia, or pulmonary heart disease served as the reference.
Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; PHD, pulmonary heart disease; UA, uric acid; MLR, monocyte-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio.

3.7. Establishment and validation of a predictive model.

The predictors, including smoking history, FEV1% predicted, pneumonia, PHD, UA, albumin, MLR, and ELR were used to establish a nomogram to predict in-hospital mortality in AECOPD patients (Figure 5). Each predictor reflected a designated score presented on the "Points" line (top line) of the nomogram. The total score of a patient with AECOPD was a summation of the scores for all the predictors. The probability of in-hospital mortality in a patient with AECOPD was estimated on the basis of the total score. The index of concordance (C-index) for the nomogram was 0.850 (95% CI: 0.799 – 0.901), indicating that the nomogram had high predictive ability. Moreover, the nomogram without MLR or ELR was also plotted with a C-index of 0.826 (95% CI: 0.772 – 0.879, Additional file 5: Figure S3).

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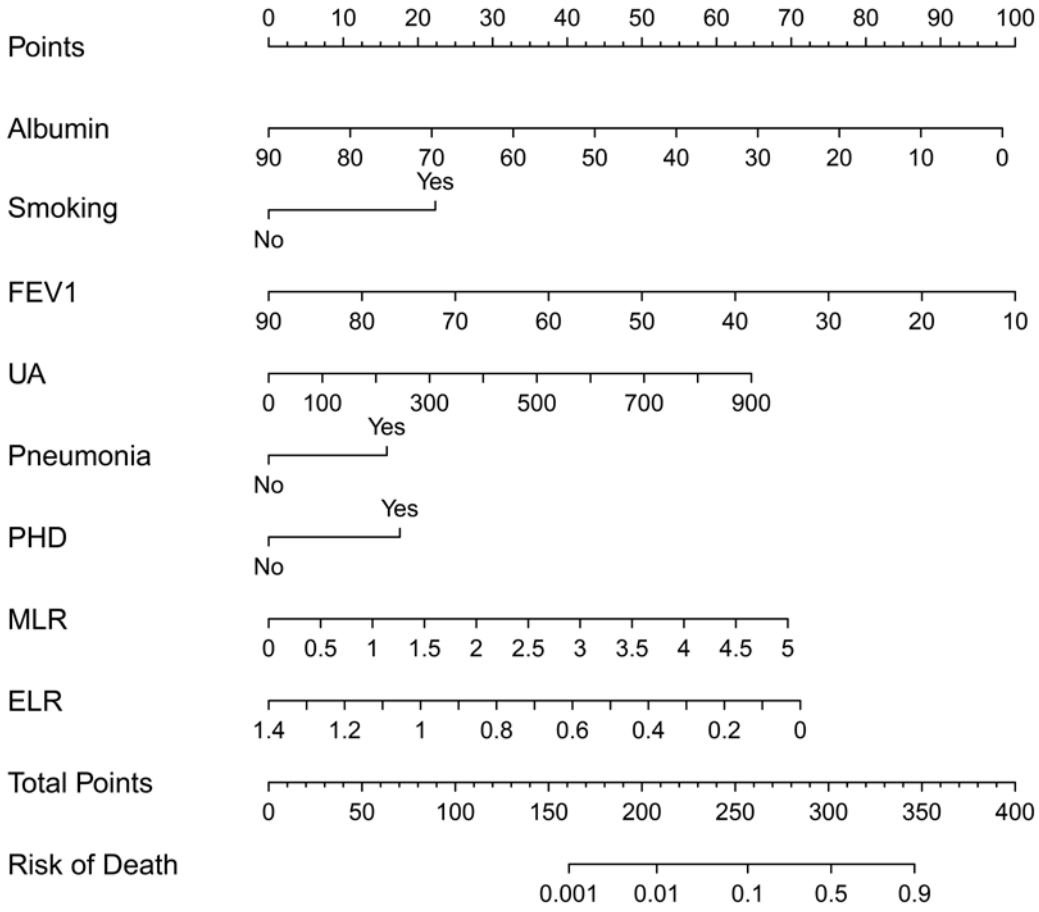

Figure 5. The nomogram for in-hospital mortality in patients with AECOPD. Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; UA, uric acid; PHD, pulmonary heart disease; MLR, monocyte-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio.

The C-index and predictive ability of the nomogram were validated by ROC curves (Figure 6A). The AUC for the nomogram with MLR and ELR was significantly higher than the AUC for nomogram without MLR or ELR ($P = 0.015$), indicating that the introduction of MLR and ELR significantly improved the predictive ability of the nomogram. Decision curve analysis (DCA) was performed to assess the clinical applicability of the nomogram as we previously described [29]. The nomogram with MLR and ELR added high net benefits within a wide range of threshold probabilities (Figure 6B). Calibration curves were plotted through bootstrap sampling 2000 times. The calibration curves for the nomogram with MLR and ELR and the nomogram without MLR or ELR were close to the reference lines, indicating that the predicted values by both the nomograms were consistent with the actual observed values (Figure 6C and 6D).

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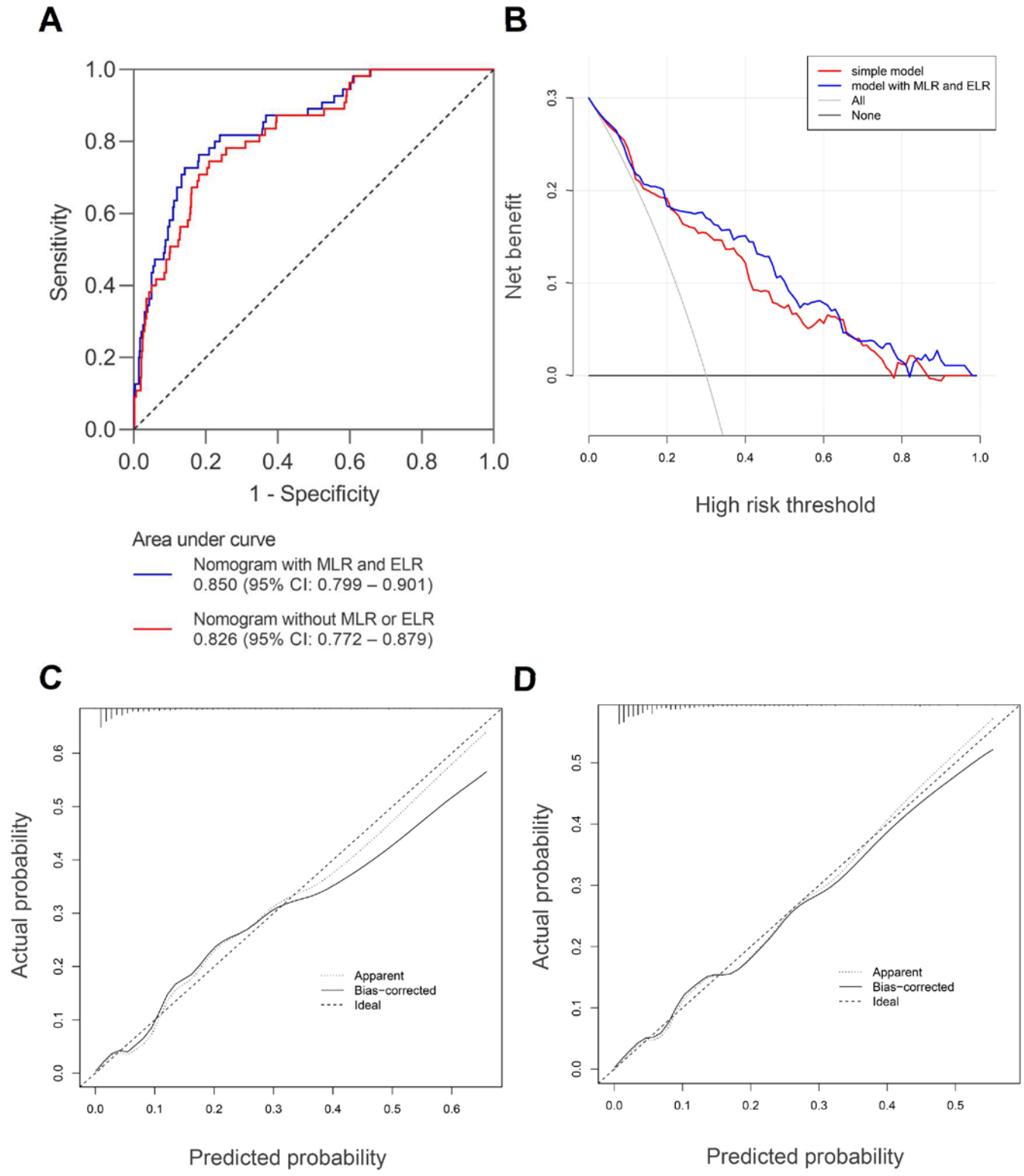

Figure 6. Validation of nomograms in AECOPD. (A) Receiver operating characteristic (ROC) curves for nomograms; (B) Decision curve analysis (DCA) of nomograms; the simple model referred to the nomogram without MLR or ELR; (C) The calibration curve for the nomogram with MLR and ELR; (D) The calibration curve for the nomogram without MLR or ELR; In panels (C, D), perfect prediction corresponded to the "ideal" line, the "Apparent" line represented the entire cohort (n = 619), and the "Bias-corrected" line was plotted through bootstrapping (B = 2000 repetitions), indicating observed nomogram performance. Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; MLR, monocyte-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio.

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A clinical impact curve (CIC) was used to further evaluate the predictive value and clinical applicability of the nomogram. As shown in Figure 7A, the nomogram with MLR and ELR had superior net benefits within a wide range of threshold probabilities. DAC and CIC analysis indicated that the nomogram with MLR and ELR possessed significant predictive value. Moreover, the nomogram without MLR or ELR also had good predictive value (Figure 7B). The net reclassification improvement (NRI) and integrated discriminatory index (IDI) were used to compare the predictive value of the two nomograms. Compared to the nomogram without MLR or ELR, the nomogram with MLR and ELR had a NRI of 0.323 (95% CI: 0.048 – 0.599; P = 0.022) and IDI of 0.048 (95% CI: 0.012 – 0.084; P = 0.009), indicating improved discriminatory performance.

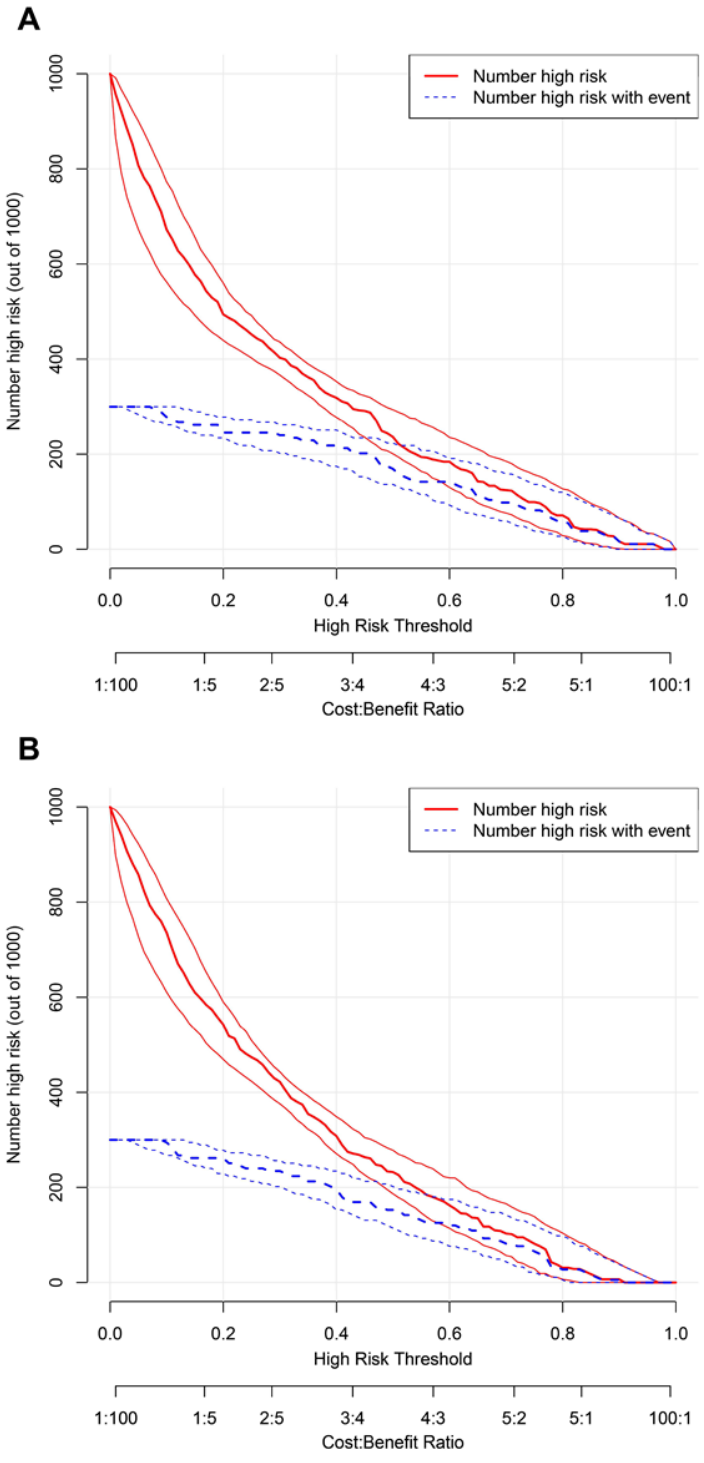

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Figure 7. Clinical impact curves of nomograms in AECOPD. (A) Nomogram without MLR or ELR; (B) Nomogram with MLR and ELR. The red curve and blue curve indicated the numbers of patients who were classified as high risk and true high risk by the model at threshold probabilities, respectively. True high risk denoted the high risk with events. The clinical impact curves indicated that both the nomograms had high net benefits, and suggested the high clinical predictive value of the nomograms. Abbreviations: AECOPD, acute exacerbation chronic obstructive pulmonary disease; MLR, monocyte-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio.

4. Discussion

To our best knowledge, this was the first to find that MLR and ELR were predictors of in-hospital mortality in AECOPD. In the present study, MLR independently predicted in-hospital mortality in patients with AECOPD, and increased MLR was associated with elevated in-hospital mortality, while increased ELR was correlated with reduced in-hospital mortality. Interestingly, PLR, NLR, and MLR were all risk factors for in-hospital mortality in AECOPD while ELR was a favorable factor for in-hospital mortality. Yang Z, et al [18] found that increased PLR, NLR, and MLR were all associated with enhanced systemic inflammation, while increased BLR and ELR were related to depressed systemic inflammation. These findings suggested that enhanced systemic inflammation was related to raised in-hospital mortality in AECOPD.

Compared with the healthy volunteers, PLR, NLR, MLR, BLR, and ELR were all elevated in COPD patients under stable condition. PLR, NLR, MLR, and BLR were further elevated while ELR was lowered during exacerbation. In AECOPD patients, elevated GOLD stages were associated with increased PLR, NLR, and MLR. Moreover, PLR, NLR, and MLR were all negatively correlated with FEV1% predicted as well as FEV1/FVC. These findings indicated that higher PLR, NLR, and MLR were all associated with more serious airflow limitation in AECOPD.

Mounting evidence indicated that prolonged hospital LOS was independently correlated with the increased severity of AECOPD [30-33]. In addition, serum CRP is a crucial indicator of the severity of AECOPD [34]. In the current study, PLR, NLR, and MLR were all positively correlated with hospital LOS as well as CRP. On the contrary, ELR was negatively correlated with hospital LOS as well as CRP. The results suggested that PLR, NLR, and MLR were all risk factors for the severity of AECOPD.

In the study, the number of comorbidities was related to in-hospital mortality in AECOPD. Among the comorbidities, asthma, pneumonia, and PHD were significantly associated with in-hospital mortality, there was no association of hypertension, diabetes mellitus, and cardiovascular disease with in-hospital mortality (Table 1). The results suggested accompanying with other respiratory disease was a risk factor for in-hospital mortality in AECOPD. PHD (cor pulmonale) refers to right ventricular hypertrophy with/without dilation induced by pulmonary hypertension that results in altered lung function and structure [35]. In fact, COPD is the leading cause of PHD, and PHD occurs in COPD patients due to loss of vascular bed and alveolar wall destruction [36]. It was the first time PHD was reported to be a risk factor for in-hospital mortality in AECOPD.

It was reported that raised UA was correlated with increased 30-day mortality as well as 1-year mortality in AECOPD [37]. Recently, Ogan N, et al. [38] revealed that UA was increased in AECOPD patients deceased during follow-up compared with alive AECOPD patients. For this study, it was the firstly found that UA was positively correlated with in-hospital mortality. Taken together, raised UA increased the risk of mortality in AECOPD.

A nomogram was established on the basis of the results of univariate binary logistic regression. As a result, smoking history, FEV1% predicted, pneumonia, PHD, UA, albumin, MLR, and ELR were chosen. The nomogram had a C-index of 0.850, indicating great predictive value for in-hospital mortality. The predictive value and clinical applicability of the nomogram were demonstrated through DCA, calibration curves, and CIC. Moreover, NRI and IDI showed that the nomogram with MLR and ELR had higher predictive ability than the nomogram without MLR or ELR, indicating that the introduction of MLR and ELR significantly improved the predictive ability of a nomogram.

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There were some limitations in the current study. This study was performed in a single center, leading to little contribution to generalize the findings. In the absence of a validation cohort to verify the practicability and accuracy of the nomogram, whether the nomograph have high predictive ability in other populations uncertain.

5. Conclusions

In the patients with AECOPD, elevated PLR, NLR, and MLR were all associated with aggravated airflow limitation, prolonged hospital LOS, increased CRP, and raised in-hospital mortality. On the contrary, elevated ELR was correlated with reduced hospital LOS, CRP, and in-hospital mortality. In addition, a nomogram was constructed on the basis of the clinical parameters related to in-hospital mortality, the nomogram had great predictive value for in-hospital mortality. The predictive value and clinical applicability of the nomogram were confirmed by DCA, calibration curves, and CIC. In addition, the introduction of MLR and ELR markedly improved the predictive value of a nomogram.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Comparison of clinical parameters between COPD patients in stable and exacerbation conditions; Figure S1: Correlations of systemic inflammatory factors with FEV1% predicted in patients with acute exacerbation chronic obstructive pulmonary disease. (A) PLR, platelet-to-lymphocyte ratio; (B) NLR, neutrophil-to-lymphocyte; (C) MLR, monocyte-to-lymphocyte ratio; (D) BLR, basophil-to-lymphocyte ratio; (E) ELR, eosinophil-to-lymphocyte ratio. Abbreviations: FEV1, forced expiratory volume in one second; Figure S2: Correlations of systemic inflammatory factors with C-reaction proteins in patients with acute exacerbation chronic obstructive pulmonary disease. (A) PLR, platelet-to-lymphocyte ratio; (B) NLR, neutrophil-to-lymphocyte; (C) MLR, monocyte-to-lymphocyte ratio; (D) ELR, eosinophil-to-lymphocyte ratio; Table S2: Correlations between clinical characteristics in patients with acute exacerbation chronic obstructive pulmonary disease; Figure S3: The nomogram without MLR or ELR for predicting in-hospital mortality in patients with AECOPD. Abbreviations: FEV1, forced expiratory volume in one second; UA, uric acid; PHD, pulmonary heart disease.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Medical Ethics Committee of People's hospital of Guilin (protocol code: 2022-011KY; date of approval: June 9, 2022).

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Data Availability Statement: The Data for the healthy volunteers are contained within the article and supplementary materials. The Data for the patients with AECOPD are available on request from the corresponding author.

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Conflicts of Interest: Author Ke-Wei Zhu is employed by the Office of Pharmacovigilance of Guangzhou Baiyunshan Pharmaceutical Holding Co., Ltd. Baiyunshan Pharmaceutical General Factory, Guangzhou, China. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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