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ORIGINAL RESEARCH

Prognostic analysis of eosinophils and inflammatory index in acute exacerbations of chronic obstructive pulmonary disease

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is among the most frequent causes of Emergency Room (ER) visits due to its deteriorating symptoms. This study aimed to evaluate the association between eosinophil levels, systemic inflammation indices, and prognosis in patients presenting to the ER with acute exacerbations of COPD (AECOPD). **Methods**: This retrospective single-center study analyzed electronic health records of patients diagnosed with AECOPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines who presented to the ER between 2017 and 2022. Eosinophil levels and inflammatory parameters were measured in 549 patients meeting the inclusion criteria, and their associations with clinical outcomes were assessed. **Results**: The average age of the study population was 67.5 years, with male patients comprising 57.7% and current smokers accounting for 30.9%. The levels of inflammatory markers, including the systemic immune-inflammation index (SII), neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-platelet ratio (NPR) and platelet-to-lymphocyte ratio (PLR), were significantly elevated in patients with low eosinophil levels ($p < 0.001$). Patients with high levels of inflammatory markers and low eosinophil counts demonstrated increased rates of intensive care unit (ICU) admission and mortality. Receiver operating characteristic (ROC) analysis for mortality revealed a moderately high predictive value for lactate levels (Area under the curve (AUC): 0.805, 95% Confidence Interval (CI): 0.734–0.877) and SII (AUC: 0.785, 95% CI: 0.726–0.844). Among the parameters, lactate levels exhibited the highest specificity (89%), while SII and NLR showed the highest sensitivity (both 95%). **Conclusions**: High inflammation and low eosinophil levels were associated with worse outcomes, including increased mortality, in COPD patients presenting with acute exacerbations. Smoking status further influences the duration and rate of hospitalization. Aggressive management strategies could improve survival in patients with elevated lactate levels and inflammatory markers.

Keywords

COPD; Eosinophils; Inflammation index

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory lung disorder that represents a significant global public health challenge, ranking as the third leading cause of mortality worldwide [1]. The high prevalence and burden of COPD have led to research identifying factors associated with disease progression and prognosis [2]. Exacerbations, characterized by a worsening of respiratory symptoms requiring treatment modification, play an important role in disease progression. Acute exacerbations of COPD (AECOPD) are a major cause of emergency room (ER) visits, contributing to disease advancement, increased healthcare utilization, and diminished quality of life [1]. The definition of COPD exacerbation encompasses an event marked by worsening dyspnea, cough or sputum production over a period of $\leq$14 days, often accompanied by tachypnea or tachycardia. These episodes are typically associated with increased local and systemic inflammation triggered by airway infections, pollutants or other insults [3]. Severe exacerbations requiring hospitalization are linked to heightened mortality risk.

Efforts to elucidate the molecular mechanisms underlying AECOPD have shown that inflammatory changes in the proximal and distal airways and lung parenchyma are central to the disease's pathophysiology [4]. While neutrophilic inflammation predominates in AECOPD, a subset of patients exhibits

eosinophilic inflammation driven by a Th2-mediated immune response [4]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD2023) guidelines emphasize the utility of blood eosinophil counts in guiding the use of inhaled corticosteroids (ICS) to prevent exacerbations in patients with a history of recurrent exacerbations [5]. In addition, systemic inflammatory markers such as the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune-inflammation index (SII) have gained recognition for their prognostic value. Elevated NLR has been identified as a marker of systemic inflammation in AECOPD, while higher SII levels have been associated with increased mortality risk in chronic conditions, including cardiovascular diseases and malignancies [6].

In this study, we aimed to investigate the relationship between inflammatory indices, eosinophil levels, and clinical outcomes in COPD patients presenting to the ER with acute exacerbations.

2. Material and methods

2.1 Study cases and criteria

This retrospective single-center study was performed using electronic health records of patients diagnosed with AECOPD according to the GOLD guidelines. Patients who presented consecutively to the ER between 2017 and 2022 were included, which led to the assessment of data from a total of 2228 patients admitted to the ER with COPD exacerbation for eligibility (Fig. 1).

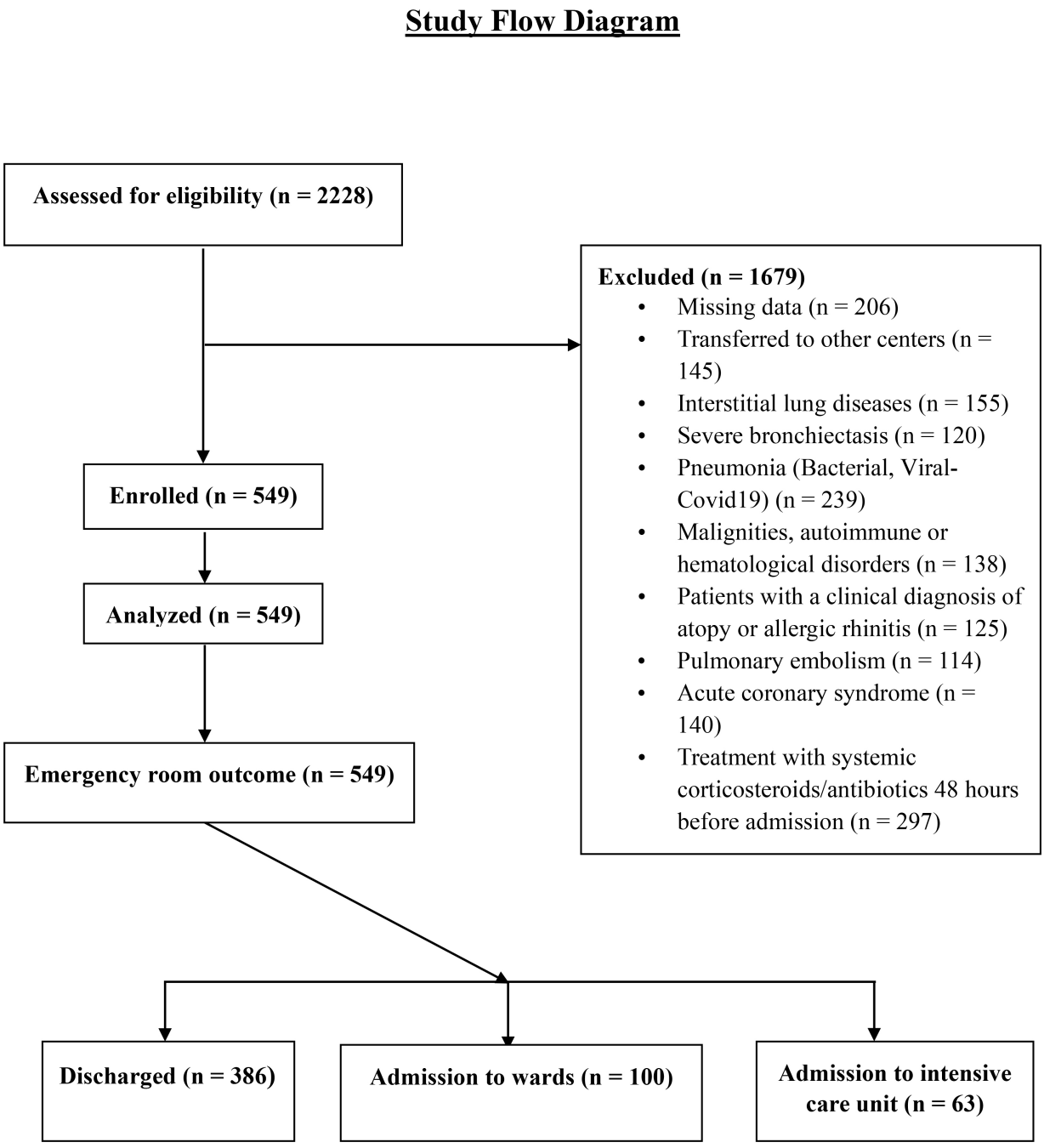

FIGURE 1. Flowchart of the study protocol and patient enrolment.

Baseline characteristics, including demographics, vital status, comorbidities and laboratory findings, were recorded prior to the administration of any treatments, such as antibiotics or systemic corticosteroids, in the Emergency Room (ER). Laboratory evaluations included inflammatory markers and arterial blood gas analyses. Blood samples were collected at the time of presentation to the ER with symptoms of exacerbation.

The inclusion criteria for this study were (1) patients over 40 years of age, (2) had a diagnosis of COPD confirmed by spirometry according to the GOLD criteria, which included predicted postbronchodilator forced expiratory volume in one second to forced vital capacity (FEV1/FVC) ratios of less than 70% and FEV1% values of less than 80%, (3) received maintenance therapy as documented in their medical records, and (4) presented to the ER with symptoms such as dyspnea, cough and sputum production.

To analyze the relationship between eosinophil counts and clinical outcomes, the patients were divided into three groups based on peripheral blood eosinophil counts: Group 1 included patients with eosinophil counts of less than 100 cells/μL, Group 2 included counts between 100 and 300 cells/μL, and Group 3 included counts of 300 cells/μL or higher. Systemic immune-inflammation index (SII), a recently developed marker of chronic inflammation that reflects increased blood neutrophil and platelet counts and decreased lymphocyte counts, was calculated along with other inflammatory indices. The inflammatory parameters were defined as follows: SII was calculated as platelet count multiplied by neutrophil count divided by lymphocyte count; neutrophil-to-lymphocyte ratio (NLR) as neutrophil count divided by lymphocyte count; neutrophil-to-platelet ratio (NPR) as neutrophil count divided by platelet count; and platelet-to-lymphocyte ratio (PLR) as platelet count divided by lymphocyte count.

The most recent pulmonary function test results obtained during the patients' stable periods were accessed from the hospital's databases. Clinical outcomes included discharge, ward admission, intensive care unit (ICU) admission, and survival.

2.2 Statistical analysis

Descriptive statistics for the data included mean, standard deviation, median, interquartile range (25th–75th percentiles), minimum, maximum, frequency and ratio values. The distribution of variables was assessed using the Kolmogorov-Smirnov test. For the analysis of quantitative independent variables, the independent samples *t*-test was applied to normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. Qualitative independent variables were analyzed using the chi-square test, and Fisher's exact test was applied when the assumptions of the chi-square test were not met.

For comparisons involving three-category dependent variables, the One-way Analysis of Variance (ANOVA) test was employed when normality conditions were satisfied, whereas the Kruskal-Wallis H test was used otherwise. *Post hoc* analyses utilized Tukey's test for homogeneous variances and Tamhane's T2 for non-homogeneous variances. A p-value of < 0.001 was considered statistically significant for *post hoc* comparisons. Correlations between continuous variables were examined using Spearman's correlation test for non-normally distributed data.

Univariate and multivariate logistic regression analyses were conducted to assess the effects of variables, with a p-value of < 0.05 considered statistically significant. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive ability of independent variables for categorical outcomes. Kaplan-Meier survival analysis was utilized to determine the impact of independent variables on mortality outcomes. All statistical analyses were conducted using SPSS software (version 28.0, IBM, Armonk, NY, USA).

3. Results

A total of 549 patients diagnosed with AECOPD were included in the study, as detailed in Table 1. The mean age of the participants was 67.5 years, with male patients comprising 57.7% of the study population. Among the patients, 30.9% were current smokers. Patients were classified into three groups based on their blood eosinophil counts: Group 1 (eosinophil count $<$100 cells/μL) included 282 patients, Group 2 (eosinophil count 100–300 cells/μL) comprised 179 patients, and Group 3 (eosinophil count $\geq$300 cells/μL) consisted of 88 patients.

The levels of inflammation parameters, including the SII, NLR, NPR and PLR, were significantly higher in Group 1 compared to Group 3 ($p < 0.001$). Additionally, the prevalence of current smoking was higher in Group 3 and showed a statistically significant difference compared to the other groups. Mortality rates were elevated in patients with low eosinophil counts (Group 1) compared to Groups 2 and 3, with this difference also reaching statistical significance ($p < 0.001$).

The correlation analyses between eosinophil count and inflammatory indicators are summarized in Table 2. A moderate negative correlation was observed between eosinophil count and systemic immune-inflammation index (SII) ($r = -0.425$, $p < 0.001$) as well as NLR ($r = -0.504$, $p < 0.001$). Weak negative correlations were identified with NPR ($r = -0.307$, $p < 0.001$), PLR ($r = -0.390$, $p < 0.001$), and WBC count ($r = -0.132$, $p = 0.002$). No significant correlation was found between eosinophil count and C reactive protein (CRP) levels ($r = -0.026$, $p = 0.550$). These findings suggest that lower eosinophil levels are associated with higher inflammatory markers, reflecting a systemic inflammatory state in patients with AECOPD.

Table 3 shows the demographic characteristics and laboratory findings of survivors based on clinical outcomes. Among the comorbidities, hypertension was the most prevalent (32%), followed by coronary artery disease (26%) and congestive heart failure (10%). Hospitalized patients were found to have significantly higher levels of inflammatory markers, including SII, NLR and PLR, compared to those who were not hospitalized ($p < 0.05$). Additionally, the proportion of current smokers was significantly higher in the hospitalized group ($p < 0.001$). Among hospitalized patients, the mean length of stay was significantly longer in current smokers (6.96 days) compared to non-smokers (5.35 days) ($p = 0.020$, data not shown in tables).

These findings highlight the impact of smoking on disease

TABLE 1. Analysis of demographics, pulmonary function tests and laboratory variables among the study groups based on the blood count of eosinophils.

Variables	Group 1 (n = 282)	Group 2 (n = 179)	Group 3 (n = 88)	*p*
	mean ± standard deviation (sd)*/ median (25–75)†	mean ± sd*/ median (25–75)†	mean ± sd*/ median (25–75)†	
Age	68.74 ± 10.96	66.55 ± 11.83	66.78 ± 10.74	0.035
Gender (male), n (%)	158 (56.0)	105 (58.7)	54 (61.4)	0.646‡
Current smokers, n (%)	30 (10.6)^a	60 (33.5)^b	80 (90.9)^b	<0.001‡
Mortality, n (%)	34 (12.1)^a	6 (3.4)^b	3 (3.4)^b	<0.001‡
FEV1% predicted	46.2 ± 12.0	46.5 ± 13.4	45.0 ± 12.3	0.674
FVC% predicted	56.0 (48.5–67.0)	56.5 (47.0–68.0)	56.0 (42.0–67.0)	0.780
SII	1587 (952–2860)^a	883 (517–1591)^b	831 (461–1429)^b	<0.001
NLR	7.3 (4.3–12.4)^a	3.8 (2.2–5.9)^b	3.1 (1.9–5.6)^c	<0.001
NPR	0.037 (0.026–0.049)^a	0.028 (0.019–0.038)^b	0.025 (0.019–0.037)^b	<0.001
PLR	201 (128–300)^a	138 (91–193)^b	129 (80–189)^b	<0.001
CRP	25.1 (9.1–87.1)	19.8 (8.1–57.1)	24.2 (11.4–64.7)	0.339
WBC	12.15 ± 5.18^a	10.95 ± 3.62^{a,b}	10.57 ± 2.85^b	0.006
Hgb	126.8 ± 61.5	126.9 ± 21.5	121.9 ± 26.7	0.891
Neutrophil	8.5 (5.9–11.6)^a	6.4 (4.8–9.5)^b	6.8 (5.1–9.1)^b	<0.001
Platelet	232 (177–310)	246 (196–301)	251 (202–299)	0.143
Lymphocyte	1.20 (0.75–1.69)^a	1.88 (1.25–2.66)^b	2.04 (1.44–3.10)^c	<0.001
pH	7.34 ± 0.09	7.33 ± 0.09	7.34 ± 0.01	0.343
PCO_2	55.8 ± 18.6	51.9 ± 16.1	54.8 ± 17.9	0.120
Lactate	1.9 (1.3–2.8)	1.7 (1.2–2.5)	2.0 (1.4–2.9)	0.032
Creatinine	0.95 (0.75–1.32)	0.94 (0.73–1.25)	0.95 (0.76–1.25)	0.843
Outcome				
Discharge	194 (68.8%)	123 (68.7%)	69 (78.4%)	0.055
Admission to wards	47 (16.7%)	41 (22.9%)	12 (13.6%)	
İntensive Care	41 (14.5%)	15 (8.4%)	7 (8.0%)	

**One-Way Anova, †Kruskal Wallis, ‡Chi-square, ^{a,b,c}Groups showing differences are marked with different letters.*
FEV1%: Forced expiratory volume in 1 second; FVC%: Forced vital capacity; SII: Systemic inflammation index; NLR: Neutrophil to lymphocyte ratio; NPR: Neutrophil to platelet ratio; PLR: Platelet to lymphocyte ratio; CRP: C reactive protein; WBC: White blood cell count; Hgb: Hemoglobin; PCO_2: Partial pressure of carbon dioxide.

TABLE 2. Correlation analysis between blood eosinophil count and inflammatory parameters.

Eosinophils	SII	NLR	NPR	PLR	WBC	CRP
r	−0.425	−0.504	−0.307	−0.390	−0.132	−0.026
p	<0.001	<0.001	<0.001	<0.001	<0.001	0.550
n	549	549	549	549	549	549

r: Correlation Coefficient Spearman's Rho.
SII: Systemic inflammation index; NLR: Neutrophil to lymphocyte ratio; NPR: Neutrophil to platelet ratio; PLR: Platelet to lymphocyte ratio; CRP: C reactive protein; WBC: White blood cell count.

severity and the associated healthcare burden in AECOPD

TABLE 3. Comparison of clinical outcomes based on demographics, pulmonary function tests and laboratory variables.

Variables	Discharged (n = 386)	Admission to wards (n = 100)	Admission to intensive care unit (n = 63)	*p*
	mean ± standard deviation (sd)*/ median (25–75)†	mean ± sd*/ median (25–75)†	mean ± sd*/median (25–75)†	
Age	69.0 (62.0–78.0)^{a}	64.0 (52.0–74.0)^{b}	67.0 (63.0–76.0)^{a}	<0.001
Current smokers, n (%)	101 (26.2)^{a}	52 (52.0)^{b}	17 (27.0)^{a}	<0.001‡
FEV1% predicted	47.2 ± 13.2^{a}	44.5 ± 12.2^{a,b}	41.9 ± 9.8^{b}	0.004
FEV1/FVC%	81.6 ± 10.6^{a}	81.2 ± 10.0^{a}	74.2 ± 12.4^{b}	<0.001
WBC	11.2 ± 4.1	11.5 ± 5.0	12.5 ± 4.1	0.079
SII	1071 (647–1932)^{a}	1229 (587–2346)^{a}	1630 (1098–4155)^{b}	<0.001
NLR	4.6 (2.6–8.2)^{a}	5.4 (2.7–9.9)^{a,b}	5.8 (3.9–14.2)^{b}	<0.001
NPR	0.031 (0.023–0.043)	0.030 (0.021–0.046)	0.031 (0.024–0.049)	0.643
PLR	151 (102–227)^{a}	172 (106–252)^{a}	214 (129–362)^{b}	<0.001
CRP	19.7 (7.2–75.6)	18.0 (6.4–56.0)	47.6 (23.4–83.1)	0.725
Eosinophils	0.105 (0.020–0.230)	0.120 (0.035–0.220)	0.070 (0.010–0.195)	0.091

**One-Way Anova, †Kruskal Wallis, ‡Ki Kare, ^{a,b}Groups showing differences are marked with different letters.*
FEV1%: Forced expiratory volume in 1 second; FEV1/FVC%: Forced expiratory volume in 1 second to forced vital capacity ratio; SII: Systemic inflammation index; NLR: Neutrophil to lymphocyte ratio; NPR: Neutrophil to platelet ratio; PLR: Platelet to lymphocyte ratio; CRP: C reactive protein; WBC: White blood cell count.

patients.

Next, we compared the demographics, pulmonary function tests and laboratory findings between survivors and deceased patients, as shown in Table 4. The findings indicate that the deceased group exhibited a significantly higher prevalence of comorbidities, including coronary artery disease, hypertension, and congestive heart failure, compared to the survivor group ($p < 0.05$). Additionally, inflammatory parameters, including SII, NLR, PLR, CRP and WBC count, were significantly elevated in deceased patients ($p < 0.001$). Furthermore, partial pressure of carbon dioxide, lactate levels, and heart rate were also significantly higher in the deceased group ($p < 0.001$).

Inflammatory parameters, including SII, WBC, CRP and lactate, were identified as significant predictors of mortality in the univariate logistic regression model for COPD patients presenting with exacerbations, as presented in Table 5. In the multivariable logistic regression analysis, SII and lactate levels remained significant independent predictors of mortality ($p < 0.001$).

In the Receiver Operating Characteristic (ROC) analysis conducted to evaluate the predictive utility of inflammatory markers and lactate levels for mortality, the Area Under the Curve (AUC) values indicated moderate predictive performance for lactate levels (AUC: 0.805, 95% CI: 0.734–0.877) and SII (AUC: 0.785, 95% CI: 0.726–0.844). Among the parameters analyzed, lactate levels demonstrated the highest specificity (89%), followed by WBC count (75%). In contrast, SII and the NLR showed the highest sensitivity (95%) (Table 6, Fig. 2).

The values for NLR, SII, PLR, WBC count, lactate, and eosinophil levels were classified as high or low based on the cut-off values identified in the ROC analysis. The impact of these categorical variables on survival was assessed using Kaplan-Meier survival analysis. The results showed that in patients with low blood eosinophil counts and elevated NLR, PLR and SII values, the median survival time was 13 days from admission. For patients with WBC counts above the cut-off value, median survival occurred on the 12th day. Among patients with elevated lactate levels, death occurred with a 50% probability by the seventh day ($p < 0.001$) (Fig. 3) (not shown in tables).

4. Discussion

This present study demonstrated that COPD patients admitted to the ER with exacerbating respiratory symptoms and a blood eosinophil count of <100 cells/μL had higher mortality rates and a greater likelihood of requiring intensive care unit (ICU) admission compared to those with eosinophil counts between 100–300 cells/μL and $\geq$300 cells/μL. Furthermore, the findings revealed that survival in patients with AECOPD was influenced by levels of lactate, WBC, and eosinophils, as well as by inflammatory markers such as NLR, PLR, and SII.

These results are consistent with previous research highlighting the association between lower blood eosinophil levels at admission and poor prognosis in AECOPD [7, 8]. COPD is recognized as a heterogeneous inflammatory disease, with approximately 20–40% of cases exhibiting eosinophilic airway inflammation in addition to the predominant neutrophilic inflammation [9].

In an epidemiological study, investigators followed-up the patients with COPD and showed that persistent blood eosinophilia was not identified as a risk factor for

TABLE 4. Analysis of demographics, pulmonary function tests, and laboratory variables based on in-hospital mortality.

Variables	Survive (n = 506)	Mortality (n = 43)	*p*
	mean ± standard deviation (sd)*/median (25–75)†	mean ± sd*/median (25–75)†	
Age	67.5 (59.7–76.3)	68.0 (65.0–86.0)	0.079
Gender (male), n (%)	289 (57.1)	28 (65.1)	0.390‡
Current smokers, n (%)	161 (31.8)	9 (20.9)	0.190‡
Heart rate	101 (80–124)	116 (96–130)	0.011
SO_2%	89.2 ± 6.6	87.7 ± 5.6	0.073
FEV1% predicted	46.6 ± 12.8	40.9 ± 9.3	0.003
FVC% predicted	57 ± 14	58 ± 15	<0.001
Comorbidities:			
Hypertension, n (%)	155 (30.6)	25 (58.1)	<0.001‡
CAD, n (%)	126 (24.9)	21 (48.8)	0.001‡
CHF, n (%)	49 (9.7)	9 (20.9)	0.034‡
SII	1084 (616–1991)	2356 (1287–5569)	<0.001
NLR	4.8 (2.6–8.6)	10.8 (4.8–19.7)	<0.001
PLR	156.5 (99–236)	259.0 (197–494)	<0.001
CRP	19.1 (7.1–65.0)	68.0 (27.3–91.0)	<0.001
WBC	11.21 ± 4.29	14.15 ± 5.37	<0.001
Eosinophil	0.11 (0.02–0.22)	0.04 (0.01–0.09)	0.001
pH	7.36 (7.30–7.41)	7.34 (7.13–7.41)	0.167
PCO_2	55 (50–63)	65 (59–78)	<0.001
Lactate	2.07 ± 1.23	3.72 ± 2.77	<0.001
Creatinine	0.95 (0.75–1.38)	1.13 (0.78–1.42)	0.521

†*Independent t test, *Mann Whitney U,* ‡*Ki Kare.*
SO_2%: oxygen saturation; FEV1%: Forced expiratory volume in 1 second; FVC%: Forced vital capacity; CAD: Coronary artery disease; CHF: Congestive heart failure; SII: Systemic inflammation index; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; CRP: C reactive protein; WBC: White blood cell count; PCO_2: Partial pressure of carbon dioxide.

TABLE 5. Binary logistic regression analysis of independent variables for mortality.

Variables	Univariate			Multivariate		
	Odds Ratio	95% Confidence Interval	*p*	Odds Ratio	95% Confidence Interval	*p*
SII	1.001	1.001–1.004	<0.001	1.000	1.001–1.002	<0.001
WBC	1.130	1.062–1.201	<0.001	-	-	-
CRP	1.004	1.001–1.008	0.045	-	-	-
Lactate	1.828	1.508–2.216	<0.001	1.901	1.533–2.358	<0.001
Eosinophil	0.028	0.002–0.458	0.012	-	-	-

SII: Systemic inflammation index; WBC: White blood cell count; CRP: C reactive protein.

TABLE 6. ROC analysis of predictors for mortality.

Variables	Cut off	Area Under the Curve	95% confidence interval Lower–Upper	Sensitivity	Specificity	*p*-value
Systemic inflammation index	1096.6	0.785	0.726–0.844	0.95	0.52	<0.001
Neutrophil to lymphocyte ratio	3.9	0.731	0.659–0.802	0.95	0.40	<0.001
Platelet to lymphocyte ratio	172.0	0.762	0.694–0.830	0.86	0.59	<0.001
White blood cell count	13.5	0.672	0.582–0.761	0.58	0.75	<0.001
Lactate	3.3	0.805	0.734–0.877	0.63	0.89	<0.001
Eosinophil	0.1	0.651	0.567–0.735	0.79	0.51	0.001

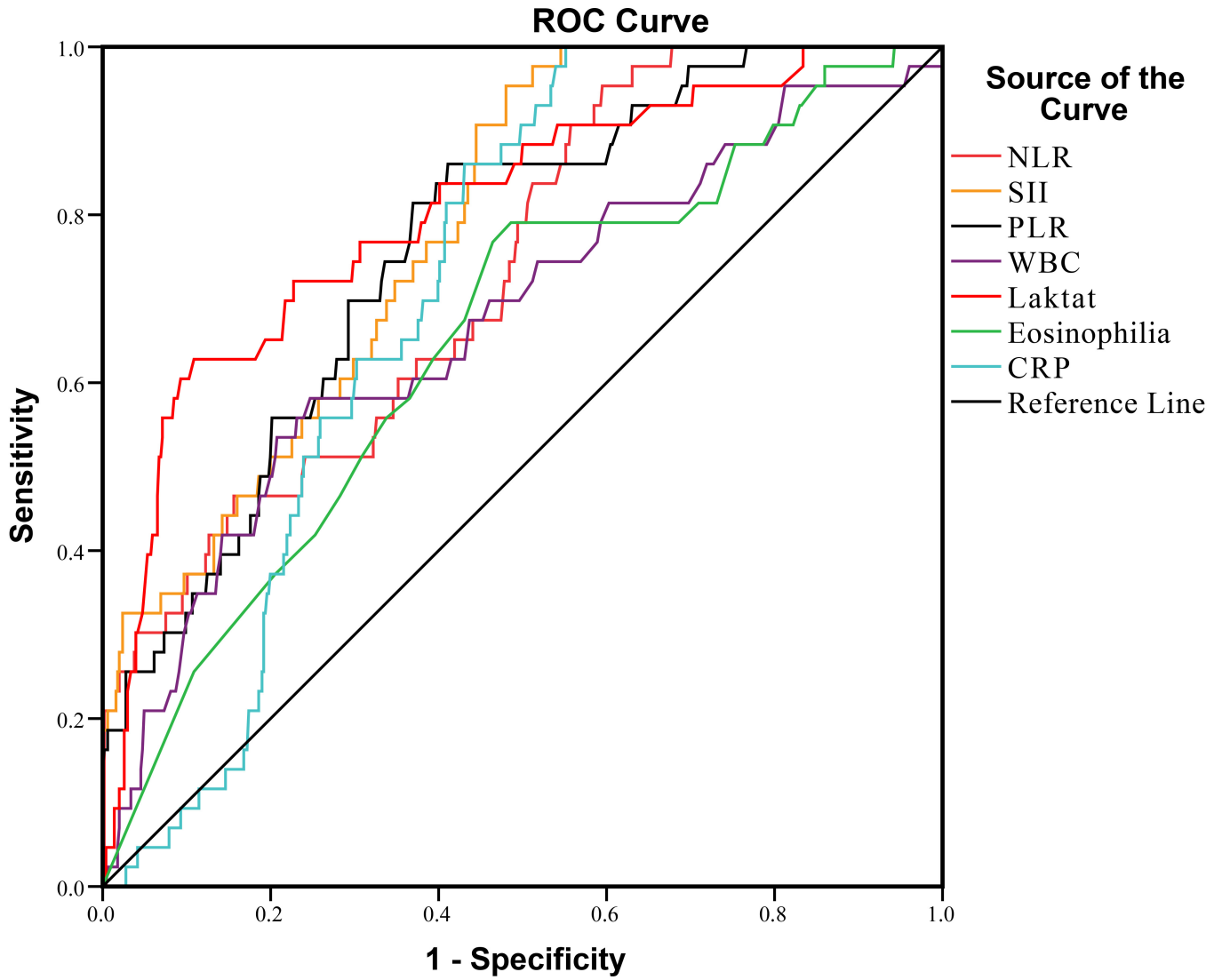

FIGURE 2. ROC analysis of inflammation markers and lactate levels for association with mortality. ROC: Receiver Operating Characteristic; NLR: Neutrophil to lymphocyte ratio; SII: Systemic inflammation index; PLR: Platelet to lymphocyte ratio; WBC: White blood cell count; CRP: C reactive protein.

exacerbation but was associated with improved survival outcomes in patients with COPD [10]. Although a blood eosinophil threshold of 2% or 150 cells/μL is commonly cited in the literature for eosinophil-related exacerbations, this cut-off remains subject to debate [11]. However, contradictory evidence exists, as some studies suggest that patients with higher eosinophil counts are at an increased risk of exacerbation, complicating the interpretation of eosinophil involvement in AECOPD progression [12]. These discrepancies may be explained by the diurnal variation of eosinophil counts, their fluctuation in response to viral infections or allergic conditions, and the observation that eosinophil-associated airway inflammation does not always manifest as systemic eosinophilia. Additionally, clinical characteristics of AECOPD may vary based on geographic and genetic factors [3].

The latest GOLD guidelines highlights the beneficial role of inhaled corticosteroids (ICS) in COPD patients with an eosinophilic component, thereby increasing clinical interest in the use of blood eosinophil count as a biomarker for COPD phenotyping [1]. However, several studies have reported an increased risk of exacerbation in patients with blood eosinophil counts exceeding 3%, adding complexity to the understanding of the relationship between eosinophil levels and AECOPD [13]. Despite ongoing research, there is currently no consensus on the optimal threshold for blood eosinophil counts in predicting outcomes or guiding treatment in AECOPD.

Moreover, in this study, blood eosinophil counts were found to be negatively correlated with inflammatory markers such as SII and NLR, which may reflect a dysfunctional immune response. Patients with higher blood eosinophil levels at admission exhibited better clinical outcomes. Notably, the rate of ICU admission was higher among patients with lower eosinophil counts ($<$100 cells/μL) compared to those with counts $>$100 cells/μL. These findings align with a recent study reporting that AECOPD patients with blood eosinophil levels $<$2% had elevated WBC, NLR, and CRP levels, longer hospital stays, and higher mortality rates compared to patients with eosinophil levels $>$2% [14]. However, contrasting evidence from Kang and Liu suggests shorter ICU stays and lower

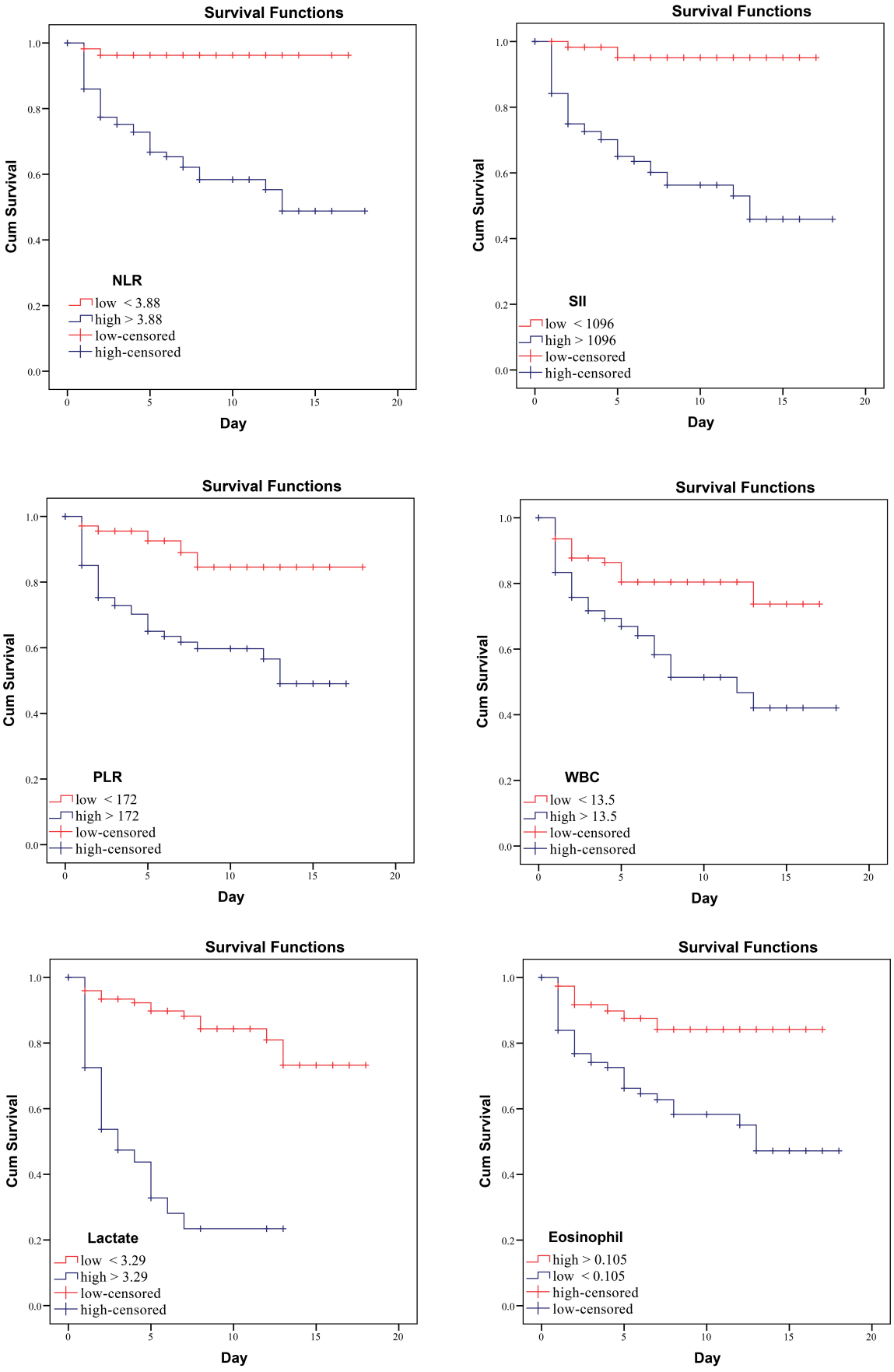

FIGURE 3. Effects of the investigated variables on patients' survival through Kaplan-Meier analysis. NLR: Neutrophil to lymphocyte ratio; SII: Systemic inflammation index; PLR: Platelet to lymphocyte ratio; WBC: White blood cell count.

mortality rates in patients with eosinophil counts <2% [15, 16].

As highlighted in the literature, eosinophilic COPD patients in a stable state tend to have reduced airway bacterial colonization compared to those with a neutrophilic phenotype [17]. Additionally, eosinophilic AECOPD patients have been shown to present with less purulent sputum and lower CRP levels compared to their non-eosinophilic counterparts [12]. Several studies indicate that AECOPD patients with lower eosinophil levels are more likely to have an infectious etiology than those with normal or elevated eosinophil counts [6]. Neutrophilia, often indicative of bacterial infection, was observed in eosinopenic patients in our study, who had elevated WBC, NLR, and neutrophil counts compared to patients with higher eosinophil levels, which are consistent with earlier research.

Eosinophils, when recruited to lung tissue, adhere to the endothelium and activate mediators such as eosinophilic peroxidase, eosinophilic cationic protein, and cytokines, which contribute to airway damage and inflammation [18]. Several studies have reported that glucocorticoid treatment is more effective in AECOPD patients with higher eosinophil levels [1]. In two separate cohort studies, patients with eosinophil levels >2% were predominantly male and included fewer smokers, but their FEV1% values did not differ significantly, findings that are consistent with our results [19, 20]. In contrast, our study showed that patients with low eosinophil counts were associated with poorer FEV1% values and lung function. From a clinical perspective, former smokers appeared to benefit from ICS therapy across all eosinophil count levels, whereas current smokers with lower eosinophil counts seemed to derive limited benefit from ICS therapy [11]. Consistent with previous studies, our findings revealed a higher proportion of current smokers among hospitalized patients compared to those discharged, underscoring the influence of smoking on disease severity and outcomes.

Patients presenting to the ER or requiring hospitalization are classified as experiencing “severe exacerbations”, according to the latest GOLD report [1]. Due to the variability in AECOPD outcomes, there is a growing need to identify an accessible and specific marker of lung inflammation. While CRP increases during various acute events, it lacks specificity for lung inflammation. Recent studies have highlighted SII as a marker of systemic inflammation and an independent risk factor for all-cause mortality in older patients with COPD [21]. Furthermore, SII has been proposed as a predictive tool for mortality in AECOPD, as research suggests it contributes to pro-inflammatory events by activating the release of mediators in the airways and lung parenchyma. NLR has also been widely recognized as a risk factor for mortality in patients with cardiovascular diseases, infectious diseases and sepsis in intensive care settings [22].

Elevated SII levels, which include increased platelet counts, underscore the role of platelets in the immune response, particularly in pathogen elimination. The inflammatory vascular comorbidities of hypertension, coronary artery disease and heart failure were significantly more prevalent among non-survivors in our study. In this regard, a study from China reported that lower blood eosinophil counts were associated with coronary heart disease and hypertension in COPD patients [7]. Taken together, these findings suggest that decreased eosinophil levels may alter vascular permeability and increase blood viscosity, which potentially exacerbates inflammatory vascular conditions.

Our findings suggest that SII and lactate levels represent valuable predictors of mortality risk in AECOPD. Kaplan-Meier survival analysis revealed that patients with lower eosinophil levels and higher SII, PLR and NLR values had a median survival of 13 days post-admission, which aligns with the understanding that inflammation in COPD is not limited to the lungs but also involves elevated circulating inflammatory markers, which are associated with worse outcomes during exacerbations [23, 24]. Moreover, our results are consistent with earlier studies indicating that higher PLR values correlate with reduced survival in AECOPD patients. As a marker reflecting both thrombocytosis and lymphopenia, PLR may indicate the degree of systemic inflammation in COPD, a condition frequently complicated by cardiovascular comorbidities that worsen clinical outcomes during exacerbations [25]. Hypoxemia in AECOPD may lead to the overproduction of immature platelets, which exhibit higher aggregation tendencies and increase thrombotic risk [26].

Lactate dehydrogenase is an enzyme that converts pyruvate to lactate, a process that reflects tissue hypoperfusion and hypoxemia [27]. During hypoxemia, pyruvate oxidation decreases, leading to increased lactate production. Several studies have demonstrated impaired lactate clearance in patients admitted to the ER with AECOPD who require hospitalization. In critical conditions such as respiratory failure or septic shock, elevated lactate levels in the early phases have been identified as a reliable indicator of short-term adverse outcomes and mortality [28]. Similar to this concept, our study found lactate levels to be a significant risk factor for mortality in both multivariable and ROC analyses, alongside inflammatory parameters, and in patients with high lactate levels, the probability of mortality was 50% within seven days of admission.

Our study had several limitations. It was conducted in a single center, and its retrospective design led to a reduced sample size due to missing data on medical history. Many patients lacked pulmonary function test results, which precluded the use of COPD combined assessment tools or dyspnea scales. Additionally, the variability in blood eosinophil levels limits their reliability as a biomarker in AECOPD. Despite these limitations, our study had notable strengths. The study design was robust and comparable to similar research. We minimized misclassification bias by excluding patients with asthma or allergic diseases and those who had received systemic corticosteroids before admission, which could have altered eosinophil levels. Furthermore, we reported 30-day mortality rates, providing valuable insights into short-term adverse outcomes. This finding is particularly relevant for clinicians managing patients with AECOPD.

5. Conclusions

COPD is a heterogeneous and chronic inflammatory disorder characterized by periods of exacerbation. Simple, cost-effective, and easily accessible markers such as WBC count,

NLR, PLR, SII and blood eosinophil counts may provide valuable insights into the prognosis and treatment strategies for patients with AECOPD presenting to the ER. Our findings indicate that AECOPD patients with blood eosinophil counts <100 cells/μL are more likely to exhibit severe clinical symptoms and heightened inflammatory responses. Furthermore, low eosinophil counts, in combination with elevated NLR, PLR, SII and lactate levels, are strongly associated with adverse clinical outcomes, including reduced short-term survival. These markers may serve as important tools for risk stratification and decision-making in the management of AECOPD.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available for sharing by the corresponding author upon request.

AUTHOR CONTRIBUTIONS

AM—provided the main framework, identified, and organized primary materials, and collaborated in writing the manuscript. MAÖ—identified appropriate references and collaborated on the writing of the manuscript. MÇ—reviewed and contributed to drafting sections of the manuscript. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was performed after the approval of institutional ethics committee (University of Health Sciences Şişli Hamidiye Etfal Training and Research Hospital Health Application and Research Center Clinical Research Ethics Committee, date: 04 April 2023, no: 3869) in accordance with the Declaration of Helsinki. Participation was voluntary and informed consent was obtained from all participants.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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