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The Role Of Neutrophil-To-Lymphocyte Ratio In Predicting Mortality Of Chronic Obstructive Pulmonary Disease Exacerbations

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a prevalent condition and a leading cause of mortality worldwide. Acute exacerbations of COPD (AECOPD) are associated with heightened airway inflammation. The neutrophil-to-lymphocyte ratio (NLR) is recognized as a reliable marker of systemic inflammation and an independent predictor of outcomes in stable COPD. However, its predictive value for in-hospital mortality in AECOPD patients remains uncertain.

Objectives: This study aimed to determine the cut-off point, area under the curve (AUC), sensitivity, and specificity of the NLR for predicting in-hospital mortality in AECOPD patients, as well as to identify independent risk factors associated with mortality.

Methods: A hospital-based cohort study was conducted with follow-up during hospitalization. Patients aged ≥18 years with AECOPD admitted to Nguyen Tri Phuong Hospital between December 2023 and October 2024 were included, provided they met the inclusion criteria. Univariate and multivariate regression analyses were used to evaluate associations between in-hospital mortality and clinically significant risk factors. The receiver operating characteristic (ROC) curve was used to identify the NLR cut-off for predicting mortality.

Results: A total of 150 patients (mean age 67.60 ± 9.42 years) were included in the study. The median NLR was 7.80 (IQR 2.75–9.66), with significantly higher values in the mortality group (median NLR 16.01, IQR 6.33–21.28) compared to the non-mortality group (median NLR 7.12, IQR 2.46–9.12, $p<0.05$). The ROC curve analysis identified an NLR cut-off of 6.28 (AUC 0.793, p=0.001) for predicting in-hospital mortality, with a sensitivity of 81.80%, specificity of 62.70%, positive predictive value (PPV) of 15.26%, and negative predictive value (NPV) of 97.67%.

Univariate regression analysis revealed significant risk factors for in-hospital mortality, including ICU admission (OR=6.611, p=0.004), severe AECOPD (OR=3.825, p=0.036), mechanical ventilation (OR=14.743, p=0.001), increased pulse rate ≥95 beats/minute (OR=7.096, p=0.015), and NLR ≥6.28 (OR=7.56, p=0.012). Multivariate analysis identified a high NLR (≥6.28) as the only independent risk factor, increasing the risk of in-hospital mortality by 7.831 times (p=0.016).

Conclusions: Patients with AECOPD had a median NLR of 7.80 (IQR 2.75–9.66). An NLR cut-off of 6.28 demonstrated high sensitivity (81.80%) and specificity (62.70%) for predicting in-hospital mortality. Clinicians should closely monitor

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the NLR in AECOPD patients, particularly when it exceeds 6.28, to assess mortality risk and optimize treatment strategies.
Keywords: COPD, AECOPD, Neutrophil to Lymphocyte Ratio, mortality

INTRODUCTION

hronic obstructive pulmonary disease (COPD) is a prevalent condition and one of the leading causes of mortality worldwide. Acute exacerbations of COPD (AECOPD) significantly increase mortality, with reported in-hospital, three-month, six-month, and two-year mortality rates of 6.7%, 18%, 26%, and 31%, respectively[1,2]. AECOPD triggers acute airway inflammation. Hematological parameters, particularly the neutrophil-to-lymphocyte ratio (NLR), have been recognized as reliable indicators of systemic inflammation and independent predictors of outcomes in stable COPD[3,4]. The NLR is a biomarker reflecting neutrophilia and inflammation associated with tissue destruction, which results from an imbalance in protease/antiprotease activity and bacterial response. Concurrently, lymphopenia indicates impaired immune response due to severe inflammation, malnutrition, or overall poor health status. Hence, an elevated NLR reflects heightened inflammation and compromised immunity, which may contribute to worse clinical outcomes[4].

In AECOPD patients, an elevated NLR has been associated with increased risks of adverse in-hospital events, including admission to intensive care units, mechanical ventilation, prolonged hospital stay, infections, and pulmonary hypertension. Furthermore, it is linked to in-hospital mortality, early mortality (within 90 days)[5] and late mortality (at six months and 24 months)[6] following AECOPD.

This raises the research question of whether the NLR plays a role in predicting in-hospital mortality in AECOPD patients. Currently, there is limited research on this topic in Vietnam. Based on this rationale, we conducted the study titled "Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Predicting In-Hospital Mortality in Patients with Acute Exacerbations of Chronic Obstructive Pulmonary Disease."

OBJECTIVES

1. To determine the cut-off value, area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the neutrophil-to-lymphocyte ratio (NLR) in predicting in-hospital mortality among patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) at Nguyen Tri Phuong Hospital.
2. To identify risk factors for in-hospital mortality in patients with AECOPD at Nguyen Tri Phuong Hospital.

METHODS

Inclusion Criteria: All patients aged ≥18 years admitted to the Respiratory Department of Nguyen Tri Phuong Hospital with AECOPD.

Exclusion Criteria: Incomplete study data, patients lost to follow-up due to transfer to another facility for further treatment, patients with hematologic disorders affecting neutrophil and lymphocyte counts.

Study Design: A prospective cohort study.

Statistical Methods: Continuous variables were summarized as mean ± standard deviation. Relationships between categorical variables were tested using the χ^2 test or Fisher's exact test. Differences in mean values between two groups were analyzed using the Independent Samples T-test or the Mann-Whitney U test. The receiver operating characteristic (ROC) curve was used to determine the NLR cut-off value for predicting in-hospital mortality and calculate the area under the curve (AUC). Clinically significant risk factors for mortality were first analyzed using univariate logistic regression and subsequently included in a multivariate logistic regression model. A p-value ≤ 0.05 was considered statistically significant.

Variable Definitions Chronic obstructive pulmonary disease (COPD): Diagnosed based on chronic respiratory symptoms, history of exposure to risk factors and spirometry results consistent with irreversible airway obstruction, defined as a post-bronchodilator FEV1/FVC ratio < 0.7. AECOPD is defined as a condition in patients with a confirmed

diagnosis of COPD who experience worsening dyspnea and/or increased cough and sputum production within ≤14 days[7].

Severity of Acute Exacerbation: Based on the ROME proposal[8]

Mortality outcomes include the following two situations:

- In-Hospital Mortality: Patients with clinical deterioration leading to cardiac and respiratory arrest, unsuccessful resuscitation, and an isoelectric ECG confirmed in two symmetrical leads. This outcome is determined by two clinical physicians.
- Discharged in Critical Condition: Patients in a terminal stage, with a prognosis of death within 24 hours, whose families request discharge for cultural or spiritual reasons. Death is later confirmed via a follow-up call by hospital staff or verified through a local death certificate.

Other Variables**:**

Demographics and clinical characteristics: Age, gender, BMI, comorbidities, smoking history, number of exacerbations in the past year.

Symptom and severity scores: Modified Medical Research Council (mMRC) dyspnea scale, COPD Assessment Test (CAT) score, Visual Analog Scale (VAS) for symptoms.

Hospital-related factors: Admission to ICU or high-dependency unit.

Clinical and laboratory parameters: Vital signs at admission, mechanical ventilation, arterial blood gas analysis, neutrophil-to-lymphocyte ratio (NLR) at admission, blood C-reactive protein (CRP) levels.

Procedure: All patients aged ≥18 years with acute exacerbation of COPD (AECOPD) admitted to the Respiratory Department at Nguyen Tri Phuong Hospital from December 2023 to October 2024, who did not meet the exclusion criteria, were enrolled in the study. Data were collected at the time of admission through patient interviews and medical records. Patients were monitored daily until discharge or death.

RESULTS

A total of 145 patients aged ≥18 years with acute exacerbation of COPD (AECOPD) were enrolled in the study. These patients were admitted to the Respiratory Internal Medicine Department at Nguyen Tri Phuong Hospital between December 2023 and October 2024

Table 1: General Characteristics of Mortality and Non-Mortality Groups

Variable	Non-Mortality Group (n=134)	Mortality Group (n=11)	Total (N=145)	p-value
Age, years (mean ± SD)	67.78 ± 9.56	65.45 ± 7.36	67.60 ± 9.42	0.434
Age ≥65 (%)	65.70	54.50	64.80	0.458
Male gender (%)	86.60	90.90	86.90	0.682
BMI (kg/m²)	22.76 ± 1.78	23.18 ± 3.23	22.79 ± 1.91	0.489
Smoking history (%)	79.85	90.90	80.70	0.372
Pack-years (mean ± SD)	12.28 ± 9.31	14.27 ± 5.42	12.43 ± 9.08	0.485
Exacerbations in past year	1.27 ± 0.80	1.82 ± 0.87	1.31 ± 0.82	**0.032**
VAS score	4.19 ± 1.39	5.00 ± 1.89	4.26 ± 1.44	0.075
mMRC score	1.42 ± 0.68	2.00 ± 0.89	1.46 ± 0.71	**0.009**
CAT score	13.90 ± 4.54	15.09 ± 4.11	13.99 ± 4.50	0.485
ICU admission (%)	11.20	45.50	13.80	**0.002**
Severity				0.082
Mild (%)	1.49	0	1.40	

Variable	Non-Mortality Group (n=134)	Mortality Group (n=11)	Total (N=145)	p-value
Moderate (%)	74.63	45.45	72.40	
Severe (%)	23.88	54.55	26.20	
Vital Signs at Admission				
Heart rate (beats/min)	93.41 ± 14.95	104.64 ± 14.23	94.26 ± 15.14	0.018
Systolic BP (mmHg)	125.63 ± 16.02	121.82 ± 12.30	125.34 ± 15.77	0.442
Diastolic BP (mmHg)	73.90 ± 10.13	73.64 ± 9.24	73.88 ± 10.03	0.929
Respiratory rate (breaths/min)	20.05 ± 2.81	22.18 ± 4.23	20.21 ± 2.98	**0.022**
SpO_2 (%)	94.98 ± 7.69	92.18 ± 7.93	94.77 ± 7.72	0.250
Arterial Blood Gas				
pH	7.37 ± 0.08	7.38 ± 0.11	7.37 ± 0.08	0.708
$PaCO_2$ (mmHg)	43.57 ± 15.32	44.64 ± 21.38	43.65 ± 15.77	0.829
PaO_2 (mmHg)	78.80 ± 63.51	89.24 ± 38.31	79.60 ± 61.92	0.593
HCO_3^- (mmol/L)	24.16 ± 4.26	24.27 ± 4.44	24.17 ± 4.26	0.936
Sputum Culture				0.331
Negative (%)	49.30	27.30	47.60	
Positive (%)	16.40	18.20	16.60	
Not performed (%)	34.30	54.50	35.80	
Mechanical Ventilation	3.70	36.4	6.2	<0.001
Laboratory Findings				
WBC (G/L)	11.94 ± 4.36	11.38 ± 2.44	11.89 ± 4.24	0.677
Neutrophils (G/L)	8.56 ± 3.99	9.82 ± 2.88	8.65 ± 3.92	0.306
Lymphocytes (G/L)	**1.99 ± 1.33**	**0.89 ± 0.50**	**1.91 ± 1.32**	**<0.001**
Platelets (G/L)	255 ± 97.38	265 ± 91.59	256 ± 96.65	0.733
CRP (mg/L)*	46.02 (3.75–68.67)	69.83 (4–122)	47.82 (3.63–63.92)	0.268
Serum Creatinine (µmol/L)	94.39 ± 54.21	87.03 ± 34.26	93.83 ± 34.26	0.659

Table 2: Mortality Distribution by Neutrophil-to-Lymphocyte Ratio (NLR) Quartiles

Quartile (NLR)	Q1	Q2	Q3	Q4
Mean NLR	1.75	3.47	6.88	14.64
IQR	1.08–2.19	2.87–4.37	5.40–8.21	10.65–21.01
Mortality, n (%)	0 (0)	2 (5.41)	3 (8.33)	6 (16.67)

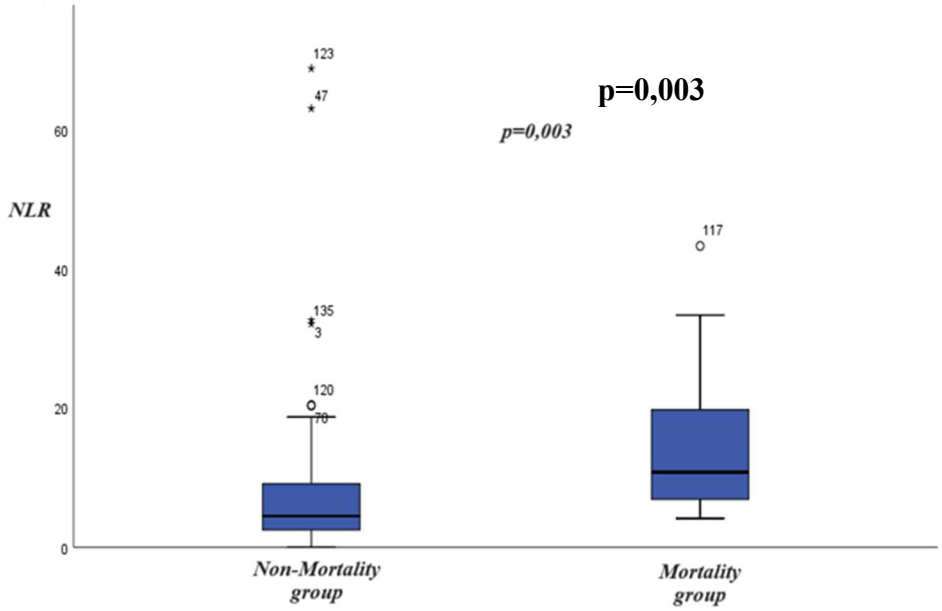

Figure 1: NLR Ratio Between Mortality and Non-Mortality Groups

ROC Curve for Predicting In-Hospital Mortality Using the NLR

Table 3: Predictive Value of NLR for In-Hospital Mortality

Variable	**High NLR (≥6.28) (n=59)**	**Low NLR (<6.28) (n=86)**
Mortality, n	9	2
AUC	0.793 (95% CI: 0.67–0.91)	
p-value	p=0.001	
Sensitivity (%)	81.80%	
Specificity (%)	62.70%	
Positive Predictive Value (%)	15.26%	
Negative Predictive Value (%)	97.67%	

Interpretation: The NLR cut-off value of 6.28 demonstrated a high sensitivity (81.80%) and a strong negative predictive value (97.67%) for predicting in-hospital mortality. The area under the ROC curve (AUC) of 0.793 indicates good predictive accuracy for NLR in assessing in-hospital mortality risk.

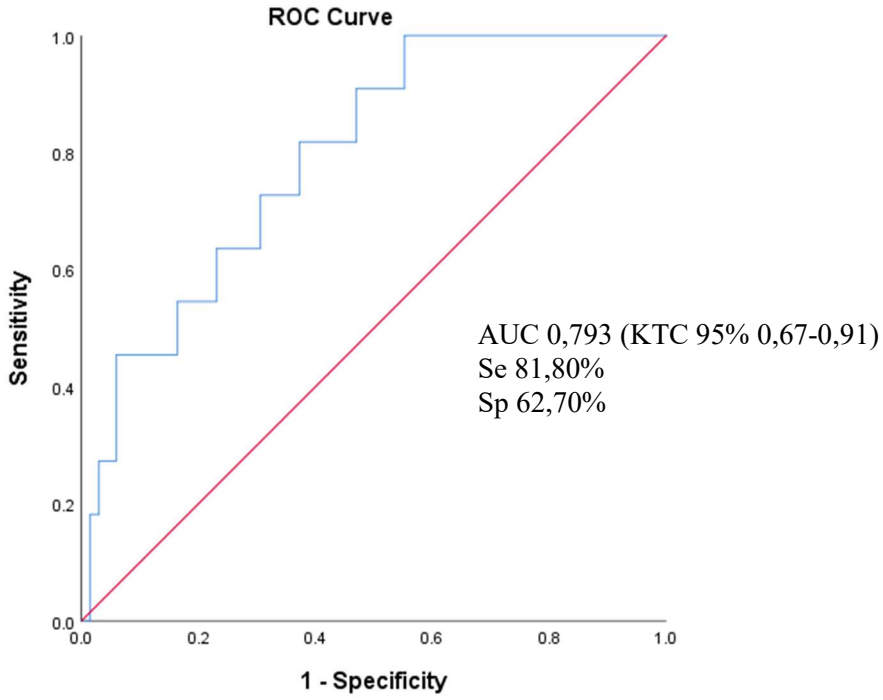

Figure 3: ROC Curve for Predicting In-Hospital Mortality Using the NLR

Univariate Regression Analysis of Risk Factors for In-Hospital Mortality in AECOPD

Table 4: Univariate Regression Analysis of Risk Factors for In-Hospital Mortality in AECOPD

Risk Factor	**OR**	**95% CI**	**p**
Age ≥65	**0.627**	**0.18–2.16**	**0.461**

Risk Factor	OR	95% CI	p
Male gender	1.552	0.18–12.86	0.684
Smoking history	2.523	0.30–20.57	0.387
Frequent exacerbation phenotype	2.540	0.73–8.78	0.141
ICU admission	6.611	1.79–24.32	0.004
mMRC score ≥2	2.032	0.56–7.27	0.275
Heart rate ≥95 beats/min	7.096	1.47–34.14	0.015
Mechanical ventilation	14.743	3.22–67.33	0.001
Severe exacerbation	3.825	1.09–13.37	0.036
NLR ≥6.28	7.560	1.57–36.39	0.012

Multivariate Regression Analysis of Risk Factors for In-Hospital Mortality in AECOPD
Table 5: Multivariate Regression Model for In-Hospital Mortality in AECOPD
Risk Factors Table (English Translation)

Risk Factor	OR	95% CI	p
Age ≥65	0.660	0.16 – 2.68	0.562
Frequent exacerbation phenotype	1.022	0.20 – 5.18	0.979
Mechanical ventilation	14.377	1.97 – 104.47	0.008
NLR ratio ≥6.28	8.204	1.51 – 44.63	0.015

Interpretation:
Univariate Analysis: Significant risk factors for in-hospital mortality include ICU admission (OR=6.611, p=0.004), heart rate ≥95 beats/min (OR=7.096, p=0.015), mechanical ventilation (OR=14.743, p=0.001), severe exacerbation (OR=3.825, p=0.036), and NLR ≥6.28 (OR=7.56, p=0.012).
Multivariate Analysis: After adjusting for other variables, NLR ≥6.28 and mechanical ventilation remains an independent risk factor for in-hospital mortality

DISCUSSION

NLR Ratio Between Mortality and Survival Groups

In this study, the median NLR ratio across the entire sample population was found to be 7.80 (IQR 2.75 – 9.66). Among patients who succumbed during hospitalization, the median NLR ratio was significantly elevated at 16.01 (IQR 6.33 – 21.28), compared to 7.12 (IQR 2.46 – 9.12) in those who survived (p=0.003). These results align closely with findings

from other studies. For instance, Cao Yuan Yao[9] reported a mean NLR ratio of 14.61 ± 10.10 in deceased patients versus 6.99 ± 8.19 in survivors ($p<0.001$), while Luo et al.[10] observed similar trends, with NLR ratios of 15.12 ± 12.99 and 8.51 ± 6.08 in deceased and surviving groups, respectively ($p<0.001$). The normal range for NLR is typically between 1 and 2 in healthy individuals and between 2 and 3 in patients with stable COPD[11]. However, during acute exacerbations, particularly in patients with adverse outcomes such as mortality, ICU admission, mechanical ventilation, or prolonged hospital stays, the NLR ratio tends to rise significantly.[12,13] This underscores its potential role as an inflammatory biomarker capable of reflecting the severity of systemic inflammation and predicting poor clinical outcomes in COPD exacerbation patients.

ROC Curve for In-Hospital Mortality Prediction Using the NLR Ratio

The analysis of the ROC curve in predicting in-hospital mortality highlighted the NLR ratio as a valuable biomarker. The optimal cutoff value was determined to be 6.28, with an AUC of 0.793 (95% CI: 0.67–0.91, $p=0.001$). This cutoff exhibited a sensitivity of 81.80%, specificity of 62.70%, a positive predictive value of 15.26%, and a negative predictive value of 97.67%. Comparable findings were reported by Cao Yuan Yao[14] who identified a slightly lower optimal cutoff of 6.24 (AUC 0.803, sensitivity 81.08%, and specificity 69.17%), demonstrating consistency across studies. Similarly, Ardestani proposed an NLR cutoff of 6.90 (AUC 0.7, sensitivity 60.87%, specificity 73.29%, $p<0.001$) for predicting in-hospital mortality. Further supporting these findings, a meta-analysis by Angelo Zinellu[15] demonstrated a strong association between the admission NLR ratio and adverse outcomes in patients with COPD exacerbations. The pooled data revealed an OR of 1.054 (95% CI: 1.016–1.093, $p=0.005$), with a standardized mean difference (SMD) of 0.82 (95% CI: 0.57–1.06, $p<0.001$). The analysis also reported a pooled sensitivity of 0.71 (95% CI: 0.64–0.77), specificity of 0.73 (95% CI: 0.65–0.80), and an AUC of 0.78 (95% CI: 0.74–0.81). These findings further solidify the clinical utility of NLR as a predictive biomarker.

The results underscore the significant potential of NLR in early risk stratification among patients with COPD exacerbations. Its ability to reflect systemic inflammation and immune balance makes it a convenient and effective tool for identifying patients at higher risk of adverse outcomes during hospitalization. As such, integrating NLR into routine clinical assessments could enhance decision-making and improve patient management strategies.

Risk Factors for In-Hospital Mortality in COPD Exacerbations

Univariate analysis identified several risk factors for in-hospital mortality, including ICU or high-dependency unit admission (OR=6.611, $p=0.004$), severe COPD exacerbations (OR=3.825, $p=0.036$), mechanical ventilation (OR=14.743, $p=0.001$), heart rate ≥95 beats per minute (OR=7.096, $p=0.015$), and an NLR ratio ≥6.28 (OR=7.56, $p=0.012$). However, multivariate regression analysis highlighted two independent predictors: an elevated NLR ratio ≥6.28, which increased the risk of in-hospital mortality by 8.204 times ($p=0.015$), and the use of mechanical ventilation, which raised the risk by a striking 14.377 times ($p=0.008$).

The high odds ratio for mechanical ventilation reflects its critical relationship with disease severity. Mechanical ventilation, often necessary in patients with acute respiratory failure, signifies a tipping point where the body's compensatory mechanisms are overwhelmed. While life-saving, its requirement indicates severe systemic inflammation, hypoxemia, and potential complications such as ventilator-associated infections, barotrauma, or multi-organ dysfunction, all of which may contribute to increased mortality.

Previous studies have corroborated the association between mechanical ventilation and poor outcomes in COPD exacerbations. This highlights the need for early identification of high-risk patients to implement preventive measures, reduce the need for invasive ventilation, and optimize management strategies. Mechanical ventilation not only serves as a treatment but also as a prognostic indicator for clinicians to assess patient trajectories during exacerbation episodes.

The NLR ratio has been reported as an independent predictor of adverse outcomes in severe COPD exacerbations, particularly in patients with the frequent exacerbation phenotype (≥2 episodes), according to the study by Fang-Ying

Lu.[16] Additionally, Fei Teng and colleagues identified the NLR ratio (OR=1.067, p<0.001) as a significant predictor of 28-day mortality following hospital admission for COPD exacerbations.[12] These findings demonstrate a consistent association between elevated NLR ratios and mortality, both in the short and long term, across multiple studies.

The peripheral blood NLR ratio reflects the balance between systemic inflammation and immune response. A higher NLR ratio indicates heightened inflammation relative to the body's immune capacity, suggesting a worse prognosis. This biomarker is particularly valuable due to its ease of measurement and its potential for widespread use in routine clinical settings. It serves as a reliable tool for prognostication in both stable COPD and during acute exacerbation episodes. Incorporating NLR into standard risk assessments could enhance the early identification of high-risk patients, guide therapeutic decisions, and improve overall outcomes in COPD management.

CONCLUSION

Patients with acute exacerbations of COPD (AECOPD) had a median NLR ratio of 7.80 (IQR 2.75 – 9.66). The optimal NLR cutoff value for predicting in-hospital mortality was 6.28, with a sensitivity of 81.80% and a specificity of 62.70%. Beyond cases requiring mechanical ventilation, clinical attention should be given to the NLR ratio at the time of hospital admission, especially when it exceeds the threshold of 6.28. This can aid in assessing mortality risk and guiding appropriate treatment strategies for AECOPD patients.

Declarations Conflict of Interest: The authors declare that they do not have a conflict of interest.

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Ethics delcarations: The study was conducted after being approved by the Ethics Committee in Biomedical Research of Nguyen Tri Phương Hospital. The research does not harm the health of patients and involves voluntary participation from patients after the researcher clearly explains the research. Patients can completely withdraw from the study at any time for personal reasons without affecting the patient's benefits. All personal and medical information is kept confidential through computer encryption, and documents are stored confidentially.

REFERENCES

1. Ko FW, Chan KP, Hui DS, et al. Acute exacerbation of COPD. *Respirology*. 2016;21(7):1152-1165.
2. Singanayagam A, Schembri S, Chalmers JD. Predictors of mortality in hospitalized adults with acute exacerbation of chronic obstructive pulmonary disease. A systematic review and meta-analysis. *Annals of the American Thoracic Society*. 2013;10(2):81-89.
3. Paliogiannis P, Fois AG, Sotgia S, et al. The neutrophil-to-lymphocyte ratio as a marker of chronic obstructive pulmonary disease and its exacerbations: A systematic review and meta-analysis. *European Journal of Clinical Investigation*. 2018;48(8):e12984.
4. Paliogiannis P, Fois AG, Sotgia S, et al. Neutrophil to lymphocyte ratio and clinical outcomes in COPD: recent evidence and future perspectives. *European Respiratory Review*. 2018;27(147)
5. Zinellu A, Zinellu E, Pau MC, et al. A comprehensive systematic review and meta-analysis of the association between the neutrophil-to-lymphocyte ratio and adverse outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease. *Journal of clinical medicine*. 2022;11(12):3365.
6. Pascual-Gonzalez Y, Lopez-Sanchez M, Dorca J, et al. Defining the role of neutrophil-to-lymphocyte ratio in COPD: a systematic literature review. *International journal of chronic obstructive pulmonary disease*. 2018:3651-3662.
7. Agustí A, Celli B, Criner G. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2023 report. GOLD executive summary. *European Respiratory Journal*. 2023;61(4):2300239.
8. Celli BR, Fabbri LM, Aaron SD, et al. An updated definition and severity classification of chronic obstructive pulmonary disease exacerbations: the Rome proposal. *American journal of respiratory critical care medicine*. 2021;204(11):1251-1258.

9. Yao C, Liu X, Tang Z. Prognostic role of neutrophil–lymphocyte ratio and platelet–lymphocyte ratio for hospital mortality in patients with AECOPD. *International journal of chronic obstructive pulmonary disease*. 2017:2285-2290.
10. Luo Z, Zhang W, Chen L, et al. Prognostic value of neutrophil: lymphocyte and platelet: lymphocyte ratios for 28-day mortality of patients with AECOPD. *International Journal of General Medicine*. 2021:2839-2848.
11. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. *Bratisl Lek Listy*. 2021;122(7):474-488.
12. Teng F, Ye H, Xue T. Predictive value of neutrophil to lymphocyte ratio in patients with acute exacerbation of chronic obstructive pulmonary disease. *PLoS One*. 2018;13(9):e0204377.
13. Kumar P, Law S, Sriram KB. Evaluation of platelet lymphocyte ratio and 90-day mortality in patients with acute exacerbation of chronic obstructive pulmonary disease. *Journal of thoracic disease*. 2017;9(6):1509.
14. Emami Ardestani M, Alavi-Naeini N. Evaluation of the relationship of neutrophil-to lymphocyte ratio and platelet-to-lymphocyte ratio with in-hospital mortality in patients with acute exacerbation of chronic obstructive pulmonary disease. *The clinical respiratory journal*. 2021;15(4):382-388.
15. Zinellu A, Zinellu E, Pau MC, et al. A comprehensive systematic review and meta-analysis of the association between the neutrophil-to-lymphocyte ratio and adverse outcomes in patients with acute exacerbation of chronic obstructive pulmonary disease. *Journal of Clinical Medicine*. 2022;11(12):3365.
16. Lu F-Y, Chen R, Li N, et al. Neutrophil-to-lymphocyte ratio predicts clinical outcome of severe acute exacerbation of COPD in frequent exacerbators. *International journal of chronic obstructive pulmonary disease*. 2021:341-349.