

# Blood Neutrophil to Lymphocyte Ratio as a Predictor of Outcome of Acute Exacerbation of COPD

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## ABSTRACT

**Objective:** To look into the relationship of neutrophil-to-lymphocyte ratio with outcomes in patients presenting with acute exacerbation of COPD.

**Methodology:** This cross-sectional study was conducted at the Department of Medicine, Pakistan Atomic Energy Commission (PAEC) Hospital, Islamabad, over three months. A total of 105 adult patients presenting with acute exacerbation of COPD were enrolled in the study. Patients with significant comorbidities, concurrent infections, or immunocompromised status were excluded. The study investigated clinical outcomes such as mortality, ventilatory support, ICU transfer, and hospital stay. The data were analyzed using SPSS version 20.

**Results:** Elevated NLR was significantly associated with increased systemic inflammation, longer smoking and disease duration, prolonged hospital stay, higher need for ventilatory support, and increased early mortality. Multivariable analysis confirmed elevated NLR as an independent predictor of ventilator requirement and mortality.

**Conclusion:** NLR is a reliable, inexpensive, and readily available biomarker that correlates with disease severity and adverse outcomes in AECOPD and may aid early risk stratification and management decisions.

**Keywords:** Chronic obstructive; Lymphocytes; Mortality; Neutrophils; Pulmonary disease.

### Authors' Contribution:

<sup>1,2</sup>Conception; Literature research; manuscript design and drafting; <sup>2,3</sup>Critical analysis and manuscript review; <sup>3,4</sup>Data analysis; Manuscript Editing.

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## Introduction

Chronic obstructive pulmonary disease (COPD), is a lung condition with chronic respiratory symptoms. The condition is progressive and may be due to abnormalities in airways (bronchitis) or alveoli (emphysema) causing obstruction.<sup>1</sup> Patients of COPD sometimes present with acute exacerbation with symptoms of shortness of breath, coughing and chest tightness. A lot of inflammatory markers have been identified that are raised. These markers include White Blood Cell counts (WBCs), C- reactive

Proteins (CRP) and Erythrocyte sedimentation rate (ESR). Recently neutrophil to lymphocyte ratio (NLR) has emerged as an important marker of acute exacerbation of COPD. Studies in past have shown that patients can have normal ranges of CRP and ESR with elevated NLR.<sup>2</sup> Neutrophils to Lymphocyte ratio can help in early detection of potential acute exacerbations of COPD. The traditional markers may not be helpful in this regard, as they are usually raised late. NLR is also a cost-effective method that can be derived from complete blood count (CBC).<sup>3</sup> Other than inflammatory marker NLR can also act as

a predictor of in hospital and late mortality. Also, the ratio can be used for identifying bacterial infection. NLR is a significant marker for differentiating between stable COPD and acute exacerbation. Clinicians also use NLR for deciding admission in patients as well as a marker for recovery.<sup>4</sup> Researchers have shown linkage of NLR with mortality and used the ratio in many diseases including COPD. Individuals with prevalent lung diseases had a greater correlation with long-term lower respiratory disease mortality, whereas NLR exhibited favorable relationships with death from coronary and cerebrovascular disease.<sup>5</sup> AECOPD is caused by a variety of viral and noninfectious causes, although pharmacological treatment is common and includes antibiotics, glucocorticoids, and  $\beta$ -agonists. The absence of objective metrics for AECOPD has driven the hunt for innovative, easily measurable prognostic biomarkers to build more effective, patient-centered care regimens.<sup>1</sup> Numerous investigations have confirmed that NLR is a highly sensitive indication of infection, inflammation, and sepsis. Clinical studies validated NLR's strong predictive and prognostic value, as well as its sensitivity for diagnosing and classifying sepsis, bacteremia, and systemic infection. In order to better understand the biology of inflammation, the coupling and antagonistic relationship between innate and adaptive immunity, and its clinical implications for health and disease, NLR is a novel perspective marker of cellular immune activation and a reliable indicator of stress and systemic inflammation.<sup>6</sup> Early risk categorization upon emergency room presentation is essential because acute exacerbations of COPD are life-threatening emergencies that frequently require ventilatory support, have a high mortality rate, and require extended hospital stays. This study aims to assess the relevance of NLR in predicting mortality, duration of stay, and ventilator demand in AECOPD patients upon ER presentation because it is a straightforward and reasonably priced inflammatory marker that can be seen on routine CBC.

## Methodology

This cross-sectional study was conducted in the Department of Medicine at the Pakistan Atomic Energy Commission (PAEC) Hospital, Islamabad, over a period of three months after obtaining approval from the institutional ethical review board. The sample size was estimated using the WHO sample size calculator. Considering a 5% level of significance, 80% statistical power, and an anticipated correlation coefficient ( $r = 0.2752$ )<sup>2</sup>, a total of 105 adult patients of either gender with acute exacerbations of chronic obstructive pulmonary disease (AECOPD), were enrolled using non-probability convenient sampling. Patients with comorbid conditions, concurrent infections, or immunocompromised status were excluded. After obtaining written informed consent, laboratory data were recorded, including neutrophil and lymphocyte counts from complete blood count, as well as levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). The neutrophil-to-lymphocyte ratio (NLR) was calculated for each patient, and an NLR value greater than 2 was considered clinically significant. The following clinical outcomes were evaluated: length of hospital stay, transfer to the critical care unit, requirement for ventilator support, and mortality. The data was analyzed using SPSS version 20.

**Ethical approval** was taken from the institutional review board of Pakistan Atomic Energy Commission General Hospital [Ref No. PGHI-IRB (Dme)-Rcd-06-94] on 04-07-2024.

## Results

The age of the study population was 50-70 years. A total of 105 patients with acute exacerbation of COPD were included in the analysis. The mean age was  $54.04 \pm 6.03$  years. The mean duration of COPD was  $10.91 \pm 5.25$  years, while the mean duration of smoking was  $12.82 \pm 10.01$  years. The mean neutrophil-to-lymphocyte ratio (NLR) was  $6.38 \pm$

1.57. Mean CRP level was  $0.86 \pm 0.14$  mg/dL, and mean ESR was  $50.95 \pm 13.70$  mm/hr. Ventilator support within 7 days was required in 17% of patients, and 11% mortality was observed within 7 days of presentation. (Table 1)

Variable	Value
Age (years), mean $\pm$ SD	54.04 $\pm$ 6.03
Gender (Male), n (%)	97 (92.4%)
(Female), n (%)	8 (7.6%)
Smoking status (Active Smoker), n (%)	63 (60%)
Duration of smoking (years), mean $\pm$ SD	12.82 $\pm$ 10.01
Duration of COPD (years), mean $\pm$ SD	10.91 $\pm$ 5.25
Neutrophil–Lymphocyte Ratio (NLR), mean $\pm$ SD	6.38 $\pm$ 1.57
C-reactive protein (mg/dL), mean $\pm$ SD	0.86 $\pm$ 0.14
Erythrocyte sedimentation rate (mm/hr), mean $\pm$ SD	50.95 $\pm$ 13.70
Length of hospital stay (days), mean $\pm$ SD	7.13 $\pm$ 2.01
Ventilator support within 7 days, n (%)	18 (17.1%)
Mortality within 7 days, n (%)	12 (11.4%)

### Correlation of NLR with Inflammatory Markers and Clinical Variables

Spearman’s rank correlation analysis demonstrated a moderate positive correlation between NLR and CRP ( $\rho = 0.353$ ,  $p < 0.001$ ) and a strong positive correlation between NLR and length of hospital stay ( $\rho = 0.751$ ,  $p < 0.001$ ). NLR also showed a significant positive correlation with duration of COPD ( $\rho = 0.306$ ,  $p = 0.001$ ) and years of smoking ( $\rho = 0.228$ ,  $p = 0.020$ ). The correlation between NLR and ESR did not reach statistical significance ( $\rho = 0.182$ ,  $p = 0.064$ ). (Table 2)

Variable	Spearman’s rho ( $\rho$ )	p-value
C-reactive protein (mg/dL)	0.353	0.001
Erythrocyte sedimentation rate (mm/hr)	0.182	0.064
Years of smoking	0.228	0.020
Duration of COPD (years)	0.306	0.001
Length of hospital stay (days)	0.751	0.001

Spearman’s rank correlation was used due to non-normal distribution. p-value  $< 0.05$  is considered significant.

### Comparison of NLR Between Outcome Groups

Using the Mann–Whitney U test, patients requiring ventilator support had a significantly higher NLR compared to those not requiring ventilation (mean rank 92.36 vs 44.86,  $U = 74.5$ ,  $Z = -6.177$ ,  $p < 0.001$ ). Similarly, patients who died within 7 days had a significantly higher NLR compared to survivors (mean rank 97.17 vs 47.30,  $U = 28.0$ ,  $Z = -5.473$ ,  $p < 0.001$ ). (Table 3)

Outcome	Group	Mean Rank	Mann–Whitney U	Z value	p-value
Ventilator support	No	44.86	74.5	-6.18	0.001
	Yes	92.36			
Mortality	No	47.30	28.0	-5.47	0.001
	Yes	97.17			

Nonparametric Tests  $\rightarrow$  Mann–Whitney U p-value  $< 0.05$  is considered significant.

### Binary Logistic Regression Analysis

Binary logistic regression analysis demonstrated that NLR was a strong independent predictor of both ventilator requirement and 7-day mortality.

Outcome	Predictor	B	S.E.	Wald	Odds Ratio (Exp(B))	95% CI for OR	p-value
Ventilator support	NLR	2.201	0.477	21.309	9.03	3.55 – 22.99	0.001
Ventilator support	Constant	-18.009	3.825	22.161	—	—	0.001
Mortality within 7 days	NLR	2.510	0.838	8.982	12.31	2.38 – 63.57	0.003
Mortality within 7 days	Constant	-22.228	7.437	8.933	—	—	0.003

OR = Odds Ratio; CI = Confidence Interval  
 Dependent variables: Ventilator support within 7 days (0 = No, 1 = Yes); Mortality within 7 days (0 = No, 1 = Yes)  
 Interpretation: OR > 1 indicates increased likelihood of ventilator requirement or increased risk of mortality.

Each unit increase in NLR significantly increased the odds of requiring ventilatory support (OR = 9.03, 95% CI: 3.55–22.99,  $p < 0.001$ ) and also increased the odds of mortality within 7 days (OR = 12.31, 95% CI: 2.38–63.57,  $p = 0.003$ ). The ventilator model showed excellent predictive ability (Nagelkerke  $R^2 = 0.787$ ) with an overall classification accuracy of 97.1%, while the mortality model explained substantial variance (Nagelkerke  $R^2 = 0.753$ ) and correctly classified 93.3% of cases (Table 4).

## Discussion

An elevated neutrophil-to-lymphocyte ratio (NLR) was substantially linked to systemic inflammation, cumulative smoking exposure, longer disease duration, longer hospital stays, increased need for ventilatory support, and early mortality in this cohort of patients who were diagnosed with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). According to these results, NLR is a widely accessible biomarker that accurately represents the clinical severity and inflammatory burden of AECOPD, with significant short-term prognostic consequences.<sup>7–9</sup>

This study's high correlation between NLR and C-reactive protein (CRP) supports the idea that NLR acts as an independent marker of systemic inflammation. Recent research from 2021 to 2024 has repeatedly shown that higher NLR reflects the severity of the disease during stable stages and acute exacerbations of COPD and associated with higher levels of inflammatory biomarkers.<sup>9–11</sup> Recent cohorts have also demonstrated that NLR gradually rises as airway obstruction and inflammatory burden increase, emphasizing the pathophysiological significance of NLR in COPD.<sup>8,12</sup> Our study's correlation between raised NLR and adverse clinical outcomes is consistent with recent systematic reviews and meta-analyses that show elevated NLR levels are independently linked to higher overall mortality in COPD patients, especially in hospitalized AECOPD subgroups.<sup>13,14</sup> The usefulness of NLR in short-term risk assessment has been highlighted by updated meta-analytic data involving large patient populations, which show that it performs better as a prognostic indicator in acute exacerbations than in stable disease.<sup>13</sup> Recent multicenter observational studies have shown that NLR independently predicts in-hospital and early post-discharge mortality, which supports these findings.<sup>14,15</sup> Multivariable analyses verified NLR as an independent predictor of ventilator requirement, and patients in the current study who needed ventilatory support had considerably higher NLR

values. Elevated NLR has been associated with an increased risk of mechanical ventilation, intensive care unit admission, and extended hospitalization during AECOPD, according to recent clinical studies.<sup>16-18</sup> These findings imply that NLR can help physicians spot patients who are at risk of respiratory decline early in the course of the illness, enabling prompt care escalation. The substantial correlation found in this study between NLR and smoking duration and COPD is indicative of the cumulative inflammatory insult caused by long-term tobacco use and the advancement of disease pathology. Long-term smoking and prolonged disease duration have been linked to chronic neutrophilic inflammation, lymphocyte suppression, and consistently raised NLR values, which are linked to recurrent exacerbations and an increased risk of death, according to recent longitudinal investigations.<sup>12,19</sup> This bolsters the idea that in COPD, NLR incorporates both acute inflammatory reactions and persistent inflammatory load. Although the therapeutic relevance of NLR is generally supported by the body of evidence, there has been observed variation in appropriate cutoff levels and the intensity of connection among studies, most likely as a result of variations in study design, comorbidities, and population characteristics.<sup>14, 20</sup> However, its dependability and generalizability as a predictive biomarker are reinforced by the consistent relationships found between high NLR, systemic inflammation, and unfavorable outcomes across various healthcare settings.<sup>15,18</sup> This study contributes to the increasing number of recent research that supports NLR as an easy-to-use, affordable, and generally available biomarker for predicting risk in AECOPD. NLR, which is derived from routine complete blood counts, can be readily incorporated into clinical processes to help identify high-risk patients early and inform therapy choices, especially in settings with limited resources.<sup>16-18</sup> This study may have limited generalizability due to its observational and single-center approach. To establish standardized NLR

cutoff values, validate its prognostic accuracy across various populations, and evaluate its integration with physiological and radiological parameters in composite clinical prediction models, future prospective multicenter studies with larger sample sizes are required.<sup>20, 21</sup>

## Conclusion

In conclusion, increased systemic inflammation, longer smoking exposure and illness duration, a larger requirement for ventilatory support, and a higher early mortality rate in patients with AECOPD are all linked to elevated NLR. With the potential to improve risk classification and direct therapeutic methods in acute COPD exacerbations, these results lend support to the inclusion of NLR as a useful prognostic marker in regular clinical evaluation.

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