



NEUTROPHIL-LYMPHOCYTE RATIO, PLATELET-LYMPHOCYTE RATIO, PROCALCITONIN AND C-REACTIVE PROTEIN AS PREDICTORS OF ACUTE EXACERBATION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A CASE-CONTROL STUDY

Dr Rajesh Kumar Sharma*

Senior Residents, Department of General Medicine, SMS Medical College and Hospital, Jaipur, Rajasthan, India *Corresponding Author

Dr Bhagirth

Senior Residents, Department of General Medicine, SMS Medical College and Hospital, Jaipur, Rajasthan, India

Dr Sandeep Khairwa

Senior Resident, Department of General Medicine, GMC Nagaur, Rajasthan, India

ABSTRACT

Background: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is associated with increased morbidity and mortality. Early identification of patients at risk for exacerbation is critical, particularly in resource-limited settings. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are simple, inexpensive inflammatory indices derived from routine complete blood count (CBC) that may serve as useful biomarkers for AECOPD. **Objectives:** To compare inflammatory markers — NLR, PLR, CRP and procalcitonin (PCT) — between AECOPD patients and stable COPD patients, and to evaluate their diagnostic accuracy in predicting acute exacerbation. **Methods:** A case-control study was conducted at SMS Medical College and Hospital, Jaipur. Fifty patients admitted with AECOPD (cases) were compared with 50 patients with stable COPD on outpatient follow-up (controls). CBC, NLR, PLR, ESR, CRP, PCT, and spirometry (FEV1, FVC) were measured. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal cut-off values. **Results:** The two groups were comparable in age (58.4 vs 59.0 years), sex, BMI, and disease duration. NLR was significantly higher in AECOPD than in stable COPD (4.78 ± 0.75 vs 2.26 ± 0.30 ; $p < 0.001$). PLR, CRP, PCT, and ESR were also significantly elevated in the AECOPD group (all $p < 0.001$). On ROC analysis, NLR had the highest discriminatory power (AUC 0.999; sensitivity 98%, specificity 96% at cut-off > 3.22), followed by PCT (AUC 0.900), PLR (AUC 0.842), and CRP (AUC 0.813). **Conclusion:** NLR, PLR, CRP, and PCT are significantly elevated in AECOPD and can serve as reliable, cost-effective inflammatory markers for identifying acute exacerbation. NLR demonstrated the highest sensitivity and specificity, making it a promising point-of-care tool for risk stratification of COPD patients, especially in resource-limited healthcare settings.

KEYWORDS : COPD, Acute Exacerbation, Neutrophil-lymphocyte Ratio, Platelet-lymphocyte Ratio, Procalcitonin, C-reactive Protein, Inflammatory Biomarkers, Spirometry

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable condition characterised by persistent respiratory symptoms and progressive airflow limitation due to airway and alveolar abnormalities, typically caused by prolonged exposure to noxious particles or gases. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is currently the third leading cause of morbidity and mortality worldwide, affecting approximately 2.5% of the global population.¹

Acute exacerbation of COPD (AECOPD) is defined as a sudden worsening of respiratory symptoms — increased dyspnoea, sputum volume, or purulence — beyond normal day-to-day variation, requiring a change in management. Exacerbations accelerate lung function decline, worsen quality of life, increase hospitalisation rates, and are independently associated with mortality. Bacterial and viral respiratory infections, as well as environmental pollutants, are the most common triggers.²

The systemic inflammatory response that underlies AECOPD results in elevated circulating levels of pro-inflammatory mediators and alterations in white blood cell differential counts. Established biomarkers such as C-reactive protein (CRP) and procalcitonin (PCT) have been studied as prognostic indicators in AECOPD, but require specific laboratory assays and incur additional cost and processing time.³

The neutrophil-to-lymphocyte ratio (NLR) — calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from a routine complete blood count (CBC) — is an emerging, cost-free inflammatory index that reflects the balance between innate and adaptive immune responses. A high NLR indicates a pro-inflammatory state. Similarly, the

platelet-to-lymphocyte ratio (PLR) — calculated as the absolute platelet count divided by the absolute lymphocyte count — reflects platelet-mediated inflammatory activity. Both indices can be obtained without additional cost from a standard CBC.⁴

Several studies have demonstrated that NLR and PLR are significantly higher in AECOPD compared to stable COPD, and that NLR is more sensitive than PLR for predicting acute exacerbation.⁵ Given the resource-constrained healthcare environment in India, identifying simple and affordable biomarkers for early risk stratification of COPD patients is of considerable public health importance. The present study was undertaken to compare NLR, PLR, CRP, and PCT between AECOPD and stable COPD patients, and to evaluate their predictive accuracy using ROC analysis.

MATERIALS AND METHODS

Study Design and Setting

This analytical, case-control study was conducted at the Department of General Medicine, SMS Medical College and Hospital, Jaipur, Rajasthan, India. Ethical approval was obtained from the Institutional Human Ethics Committee. Written informed consent was obtained from all participants prior to enrolment.

Participants

Cases: Fifty patients admitted to SMS Hospital with a diagnosis of AECOPD were enrolled. AECOPD was defined per GOLD 2023 guidelines as an acute worsening of respiratory symptoms requiring in-hospital treatment.

Controls: Fifty patients with stable COPD attending the outpatient clinic were enrolled as controls.

Inclusion Criteria: Patients with COPD diagnosed on the basis of GOLD 2023 guidelines; age > 40 years; both sexes.

Exclusion Criteria: Patients with bronchiectasis, pulmonary tuberculosis, bronchial asthma, myocardial infarction or stroke in the preceding 3 months, collagen vascular disease, or malignancy.

Sample Size

Sample size was calculated at $\alpha=0.05$ ($Z=1.96$) and 80% power ($Z=0.84$) using the formula for correlation between two quantitative variables, based on an expected correlation coefficient between NLR/PLR and AECOPD from prior literature. The minimum calculated sample size was 96, rounded to 100 (50 cases and 50 controls).

Clinical and Laboratory Assessment

All participants underwent detailed history, clinical examination, and standard investigations including CBC with differential count, ESR, CRP, PCT, kidney and liver function tests, ECG, chest X-ray, and spirometry. In the cases group, blood samples for NLR, PLR, PCT, CRP, and CBC were collected within 24 hours of hospital admission. In the control group, the same parameters were measured during the outpatient visit.

Spirometry was performed as per standard protocols. FEV1 and FVC were measured as percentage of predicted values. NLR was calculated as absolute neutrophil count ÷ absolute lymphocyte count; PLR was calculated as absolute platelet count ÷ absolute lymphocyte count.

Statistical Analysis

Data were entered in Microsoft Excel and analysed using standard statistical methods. Quantitative variables were expressed as mean $\pm$ standard deviation (SD). The independent samples t-test was used to compare means between the two groups. Chi-square (χ^2) test was used for comparison of categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal cut-off values, sensitivity, specificity, and area under the curve (AUC) for each biomarker. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Demographic and Baseline Characteristics

Of the 100 participants, 50 were in the AECOPD group (cases) and 50 were in the stable COPD group (controls). The two groups were well-matched on all baseline parameters, including age, sex, smoking status, residential background, disease duration, and anthropometric measurements (Table 1). The mean age was 58.70 ± 6.69 years overall, with no statistically significant difference between groups ($p=0.663$). A predominance of male patients was observed (77%), reflecting the higher prevalence of smoking in males. Sixty-eight percent of participants were current or past smokers, with an equal distribution between groups. The majority (74%) had a rural background.

Table 1. Baseline Demographic and Anthropometric Profile of Study Participants

Parameter	AECOPD (Cases) n=50	Stable COPD (Controls) n=50	Total n=100	p-value
Age (years), Mean $\pm$ SD	58.40 $\pm$ 6.67	59.00 $\pm$ 6.76	58.70 $\pm$ 6.69	0.663
Male sex, n (%)	39 (78.0%)	38 (76.0%)	77 (77.0%)	0.812
Smokers, n (%)	34 (68.0%)	34 (68.0%)	68 (68.0%)	1.000
Rural residence, n (%)	38 (76.0%)	36 (72.0%)	74 (74.0%)	0.648
Duration of COPD (years), Mean $\pm$ SD	8.98 $\pm$ 3.48	9.00 $\pm$ 3.46	8.99 $\pm$ 3.45	0.997

Weight (kg), Mean $\pm$ SD	66.92 $\pm$ 5.85	66.86 $\pm$ 5.76	66.89 $\pm$ 5.78	0.882
BMI (kg/m ²), Mean $\pm$ SD	24.32 $\pm$ 2.72	24.28 $\pm$ 2.88	24.30 $\pm$ 2.79	0.858

AECOPD = Acute Exacerbation of COPD; NS = Not Significant; values expressed as Mean $\pm$ SD or n (%) as applicable.

Pulmonary Function and Haematological Parameters

Spirometric parameters were significantly worse in the AECOPD group: mean FEV1 was $35.64 \pm 2.88\%$ vs $49.36 \pm 3.13\%$ in controls ($p<0.001$), and mean FVC was $74.92 \pm 5.30\%$ vs $89.68 \pm 5.08\%$ ($p<0.001$). Total leucocyte count (TLC) and absolute neutrophil count were significantly elevated in AECOPD, while lymphocyte counts were significantly reduced compared to stable COPD (all $p<0.001$). Platelet counts did not differ significantly between groups (Table 2).

Table 2. Pulmonary Function and Haematological Parameters in AECOPD and Stable COPD

Parameter	AECOPD (Cases) n=50	Stable COPD (Controls) n=50	p-value
FEV1 (%), Mean $\pm$ SD	35.64 $\pm$ 2.88	49.36 $\pm$ 3.13	<0.001
FVC (%), Mean $\pm$ SD	74.92 $\pm$ 5.30	89.68 $\pm$ 5.08	<0.001
TLC (μ L), Mean $\pm$ SD	9850.80 $\pm$ 1137.73	5988.00 $\pm$ 489.75	<0.001
Neutrophil count (μ L), Mean $\pm$ SD	6908.00 $\pm$ 1041.16	4532.00 $\pm$ 283.16	<0.001
Lymphocyte count (μ L), Mean $\pm$ SD	1450.00 $\pm$ 130.96	2036.20 $\pm$ 265.77	<0.001
Platelet count (μ L), Mean $\pm$ SD	279540.00 $\pm$ 56449.44	284660.00 $\pm$ 56996.82	0.484

Values expressed as Mean $\pm$ SD; $p<0.001$ = highly significant.

Inflammatory Markers: NLR, PLR, CRP, PCT, and ESR

All inflammatory markers were significantly higher in the AECOPD group compared to stable COPD (Table 3). The mean NLR was 4.78 ± 0.75 in cases vs 2.26 ± 0.30 in controls ($p<0.001$). PLR was 193.97 ± 41.05 in cases vs 142.12 ± 33.79 in controls ($p<0.001$). CRP was 6.52 ± 2.96 mg/L in cases vs 2.00 ± 2.26 mg/L in controls ($p<0.001$). PCT was 1.84 ± 0.17 ng/mL in cases vs 0.84 ± 0.63 ng/mL in controls ($p<0.001$). ESR was 21.22 ± 5.92 mm/hr in cases vs 9.46 ± 2.38 mm/hr in controls ($p<0.001$).

Table 3. Comparison of Inflammatory Markers Between AECOPD and Stable COPD

Inflammatory Marker	AECOPD (Cases) n=50	Stable COPD (Controls) n=50	Total n=100	p-value
NLR, Mean $\pm$ SD	4.78 $\pm$ 0.75	2.26 $\pm$ 0.30	3.52 $\pm$ 1.39	<0.001
PLR, Mean $\pm$ SD	193.97 $\pm$ 41.05	142.12 $\pm$ 33.79	168.04 $\pm$ 45.59	<0.001
CRP (mg/L), Mean $\pm$ SD	6.52 $\pm$ 2.96	2.00 $\pm$ 2.26	4.26 $\pm$ 3.47	<0.001
PCT (ng/mL), Mean $\pm$ SD	1.84 $\pm$ 0.17	0.84 $\pm$ 0.63	1.34 $\pm$ 0.68	<0.001
ESR (mm/hr), Mean $\pm$ SD	21.22 $\pm$ 5.92	9.46 $\pm$ 2.38	15.34 $\pm$ 7.42	<0.001

NLR = Neutrophil-Lymphocyte Ratio; PLR = Platelet-Lymphocyte Ratio; CRP = C-Reactive Protein; PCT = Procalcitonin; ESR = Erythrocyte Sedimentation Rate. All differences statistically significant ($p<0.001$).

ROC Curve Analysis

ROC curve analysis revealed that NLR had the highest discriminatory ability for predicting AECOPD among all

markers studied (AUC 0.999, 95% CI 0.997–1.001), with an optimal cut-off value of >3.22 , yielding sensitivity of 98.0% and specificity of 96.0%. PCT had the second highest AUC (0.900), followed by PLR (AUC 0.842) and CRP (AUC 0.813). The detailed ROC parameters are presented in Table 4.

Table 4. ROC Curve Analysis for Inflammatory Markers as Predictors of AECOPD

Marker	AUC	p-value	95% CI	Cut-off	Sensitivity (%)	Specificity (%)
NLR	0.999	<0.001	0.997 – 1.001	>3.22	98.0	96.0
PCT	0.900	<0.001	0.822 – 0.979	>1.58 ng/mL	88.0	86.0
PLR	0.842	<0.001	0.767 – 0.918	>158.07	82.0	68.0
CRP	0.813	<0.001	0.723 – 0.903	>1.55 mg/L	80.0	74.0

AUC = Area Under the Curve; CI = Confidence Interval; NLR = Neutrophil-Lymphocyte Ratio; PLR = Platelet-Lymphocyte Ratio; PCT = Procalcitonin; CRP = C-Reactive Protein.

Comparison with Published Literature

Table 5. Comparison of NLR Sensitivity, Specificity, and Cut-off Values with Published Studies

Study	Year	NLR Cut-off	Sensitivity (%)	Specificity (%)	AUC
Present Study	2024	>3.22	98	96	0.999
Aida M. Yousef et al.	2017	>3.12	86.7	76.7	—
Yao C et al.	2017	>6.24	81	69	0.803
Bhoor Singh et al.	2022	>6.11	72	90	—
Karan Sharma et al.	2023	>3.4	75.3	70.7	0.806

The cut-off value for NLR in the present study (>3.22) is consistent with the value reported by Yousef et al. (>3.12) but lower than those reported by Yao et al. (>6.24) and Bhoor Singh et al. (>6.11). The higher sensitivity (98%) observed in our study may reflect the more homogeneous patient population and the degree of airflow limitation in the AECOPD group.

DISCUSSION

The present case-control study systematically compared inflammatory markers — NLR, PLR, CRP, PCT, and ESR — between 50 AECOPD patients and 50 stable COPD patients at a tertiary care centre in North India. All five markers were significantly elevated in the AECOPD group ($p<0.001$), confirming the heightened systemic inflammatory burden during acute exacerbation. Spirometric parameters (FEV1 and FVC) were significantly lower in AECOPD, consistent with the pathophysiological deterioration that characterises exacerbations.

COPD is now recognised as a systemic inflammatory disease. Circulating inflammatory mediators, including pro-inflammatory cytokines, acute phase reactants, and altered leucocyte differential counts, are elevated even during stable COPD, and these levels surge dramatically during acute exacerbations.⁶ The TLC and its differential components are classical markers of systemic inflammation. Increased neutrophil activity and the relative lymphopaenia seen during exacerbations yield a markedly elevated NLR, reflecting the predominance of innate over adaptive immunity during the acute inflammatory state.

Our finding of a significantly higher NLR in AECOPD (4.78 ± 0.75) compared to stable COPD (2.26 ± 0.30) is consistent with multiple prior studies. Kurtipek et al. demonstrated significantly higher NLR and PLR values in AECOPD versus stable COPD patients, and concluded that

NLR was a superior predictor of AECOPD compared to PLR.⁷ Yao et al., in a retrospective study of 303 AECOPD patients, found mean NLR of 7.92 ± 8.79 and noted that NLR correlated with CRP levels and predicted hospital mortality.⁸ Ritumbhara et al., studying patients from North-West Rajasthan, reported mean NLR of 5.54 ± 2.12 in AECOPD vs 3.77 ± 0.22 in stable COPD.⁹ Bhoor Singh et al. reported significantly higher NLR in AECOPD cases ($n=50$) compared to controls, while PLR showed a trend toward elevation without statistical significance.¹⁰

On ROC analysis, NLR achieved the highest AUC (0.999) with sensitivity 98% and specificity 96% at a cut-off of >3.22 — markedly superior to PLR, PCT, and CRP. This exceptional discriminatory power underscores the utility of NLR as a bedside inflammatory index that can be rapidly derived without additional laboratory cost. The cut-off of >3.22 is similar to that identified by Erdal In et al. (>3.34) who reported sensitivity 78.7% and specificity 73.2% (AUC 0.863), and is close to the cut-off of >3.12 reported by Yousef et al. (sensitivity 86.7%, specificity 76.7%).¹¹ The higher AUC in the present study may reflect the clinical severity of AECOPD in the enrolled cases and the tight control of the stable COPD comparator group.

PCT, a well-established biomarker of bacterial infection, had an AUC of 0.900 (sensitivity 88%, specificity 86% at cut-off >1.58 ng/mL). Bhoor Singh et al. reported comparable PCT discriminatory performance (sensitivity 72%, specificity 88%, cut-off >1.2 ng/mL).¹⁰ Although PCT requires a specific assay, its high negative predictive value makes it useful for guiding antibiotic stewardship in AECOPD. PLR demonstrated moderate accuracy (AUC 0.842) with 82% sensitivity and 68% specificity, consistent with published literature suggesting its utility is limited compared to NLR. CRP (AUC 0.813; sensitivity 80%, specificity 74%) has established utility but requires additional assay time and cost.

The predominance of male patients (77%) and rural background (74%) in our study population reflects the epidemiology of COPD in Rajasthan, where tobacco use (bidi, hookah) and biomass fuel exposure are prevalent risk factors, particularly among rural males. The absence of significant demographic differences between cases and controls ensures internal validity.

From a clinical perspective, this study supports the integration of NLR — derived at no additional cost from a routine CBC — into the initial assessment of COPD patients presenting with respiratory deterioration. An NLR >3.22 warrants heightened clinical vigilance and may guide triage decisions, especially in settings where PCT and CRP assays are not immediately available. However, NLR is not disease-specific and may be elevated in other inflammatory states; hence clinical correlation remains essential.

CONCLUSION

This study demonstrates that NLR, PLR, CRP, and PCT are all significantly elevated in AECOPD compared to stable COPD, confirming their role as markers of acute systemic inflammation. Among the markers studied, NLR exhibited the highest diagnostic accuracy (AUC 0.999; sensitivity 98%, specificity 96% at cut-off >3.22) for identifying AECOPD. NLR is cost-effective, immediately available from routine CBC, and applicable in resource-limited settings across India and similar low-middle-income contexts. Pending larger prospective validation studies, NLR — combined with clinical assessment and, where available, PCT — may meaningfully improve risk stratification and management decisions in patients with COPD. The relatively lower specificity of PLR warrants further investigation before it can be recommended as a standalone predictor of exacerbation.

Limitations

This study has several limitations. The sample size of 100 was modest, which may limit the generalisability of findings and the power to detect associations with specific outcomes. The cross-sectional nature of the case-control design precludes causal inference. Different GOLD severity stages of COPD were not individually analysed, and the confounding effect of COPD severity on biomarker levels could not be fully excluded. Correlations with other inflammatory mediators (e.g., IL-6, TNF- α) were not assessed. Future prospective studies with larger, severity-stratified cohorts are warranted.

REFERENCES

1. Singh D, Agusti A, Anzueto A, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. *Eur Respir J*. 2019;53(5). doi:10.1183/13993003.00164-2019
2. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. *Lancet*. 2007;370(9589):786-96. PMID: 17765528
3. Emami Ardestani M, Alavi Naeini N. Evaluation of the prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in acute exacerbation of chronic obstructive pulmonary disease. *J Res Med Sci*. 2022;27:50. doi:10.4103/jrms.JRMS_512_20
4. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases. *Int J Mol Sci*. 2022;23(7):3636. doi:10.3390/ijms23073636
5. Kurtipek E, Bekci TT, Kesli R, Sami SS, Terzi Y. The role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in exacerbation of chronic obstructive pulmonary disease. *J Pak Med Assoc*. 2015;65:1283-7. PMID: 26519629
6. Pascual-González Y, López-Sánchez M, Dorca J, Santos S. Defining the role of neutrophil-to-lymphocyte ratio in COPD: a systematic literature review. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3651-3662. doi:10.2147/COPD.S178068
7. Kurtipek E, Bekci TT, Kesli R, Sami SS, Terzi Y. The role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in exacerbation of chronic obstructive pulmonary disease. *J Pak Med Assoc*. 2015;65:1283-7.
8. Yao C, Liu X, Tang Z. Prognostic role of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio for hospital mortality in patients with AECOPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2285-2290. doi:10.2147/COPD.S141760
9. Ritumbhara et al. Correlation of neutrophil to lymphocyte with acute exacerbation in chronic obstructive pulmonary disease at tertiary care hospital in North West Rajasthan. *Indian Journal of Immunology and Respiratory Medicine*. 2022;7(3):116-123.
10. Singh B, Kampani G, Lall B, Singh M. Study of Inflammatory Markers in Chronic Obstructive Pulmonary Disease. *J Assoc Physicians India*. 2022;70(12):11-12. PMID: 37355971
11. İn E, Kuluöztürk M, Öner Ö, Deveci F. The Importance of Neutrophil-to-Lymphocyte Ratio in Chronic Obstructive Pulmonary Disease. *Turk Thorac J*. 2016;17(2):41-46. doi:10.5578/ttj.17.2.009
12. Yousef M, Alkhiary W. Role of neutrophil to lymphocyte ratio in prediction of acute exacerbation of chronic obstructive pulmonary disease. *Egypt J Chest Dis Tuberc*. 2017;66(1):43-48.
13. 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. doi:10.1371/journal.pone.0204377
14. Gao X, Coull B, Lin X, et al. Association of Neutrophil to Lymphocyte Ratio with Pulmonary Function in a 30-Year Longitudinal Study of US Veterans. *JAMA Netw Open*. 2020;3(7):e2010350. doi:10.1001/jamanetworkopen.2020.10350
15. Paliogiannis P, Fois AG, Sotgia S, et al. Neutrophil to lymphocyte ratio and clinical outcomes in COPD: recent evidence and future perspectives. *Eur Respir Rev*. 2018;27(147):170113. doi:10.1183/16000617.0113-2017
16. 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. *J Thorac Dis*. 2017;9(6):1509-1516. doi:10.21037/jtd.2017.05.77
17. Sharma K, Garg K, Chopra V, Kundal R. Neutrophil-Lymphocyte Ratio as a Predictor of COPD Exacerbations: A Cross-sectional Study. *J Clin Diagn Res*. 2023;17. doi:10.7860/JCDR/2023/59293.17337