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Original Research Article

DECOUPLING CATEGORICAL AND CONTINUOUS TRACKING OF CELL-COUNT RATIOS IN ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A PROSPECTIVE OBSERVATIONAL REANALYSIS FROM A TERTIARY CARE CENTRE IN NORTH INDIA

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ABSTRACT

Background: Systemic inflammatory progression is central to the pathogenesis of chronic obstructive pulmonary disease (COPD) and accelerates significantly during acute flares. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been proposed as accessible, cost-effective biomarkers to screen for acute inflammation. However, widespread inconsistencies in mathematical unit scaling and multi-collinearity in diagnostic regression models limit their use in clinical screening. This study evaluated the comparative prognostic utility of admission NLR and PLR for predicting disease severity and in-hospital outcomes in patients presenting with an acute exacerbation of COPD (AECOPD).

Materials and Methods: We conducted a prospective observational cross-sectional study among 153 consecutive adults aged ≥ 40 years admitted for AECOPD at Al-Falah School of Medical Sciences and Research Centre, Faridabad, India, between May 2024 and March 2026. Admission blood samples were processed via an automated 5-part hematologyanalyzer to calculate absolute leukocyte subsets and platelet counts. Exacerbation severity was categorized using the modified Medical Research Council (mMRC) dyspnea scale and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) definitions.Row-level master charts were re-analyzed to resolve unit scaling errors that distorted prior aggregate indices.

Results: The study population (N = 153) had a mean age of 63.87 ± 10.01 years, with a high concentration of current or former smokers (69.3%) and a clear male predominance (75.8%). Severe AECOPD was identified in 73.9% of patients. The corrected mean admission NLR was 6.12 ± 3.08, and the corrected mean PLR was 188.42 ± 95.16. Using a fixed baseline NLR cut-off (≥ 5.6), 43.1% of patients were classified as having high NLR. On univariate analysis, categorical high NLR showed no significant association with exacerbation severity (P = 0.782), oxygen flow requirements (P = 0.328), intensive care unit (ICU) admission (P = 0.234), hospital length of stay (P = 0.665), or in-hospital mortality (P = 0.540). Similarly, receiver operating characteristic (ROC) analysis showed limited diagnostic accuracy for binary thresholds (NLR Area Under the Curve [AUC] = 0.435; Platelet Count AUC = 0.569). However, when adjusting for age, sex, and cardiovascular

comorbidities in a stabilized multivariable logistic regression model that resolved cellular multi-collinearity, continuous baseline NLR emerged as a significant independent marker of severe AECOPD presentation (Wald χ^2 = 8.434, Odds Ratio [OR] = 1.34; 95% Confidence Interval [CI], 1.10–1.69; P = 0.004), alongside active smoking exposure (OR = 1.67, P = 0.017).

Conclusion: Admission NLR is a low-cost, widely accessible inflammatory marker that provides valuable prognostic information on AECOPD disease severity when tracked along a continuous numeric index.Conversely, the clinical utility of PLR remains limited by population-specific shifts.These ratios should be used alongside objective clinical metrics rather than as standalone diagnostic tests.

Key words: Chronic Obstructive Pulmonary Disease; Acute Exacerbation of COPD; Neutrophil-to-Lymphocyte Ratio; Platelet-to-Lymphocyte Ratio; Systemic Inflammation; Inflammatory Biomarkers; Disease Severity; Prognostic Biomarkers; Risk Stratification; Multivariable Logistic Regression

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents a major, progressive source of global chronic respiratory morbidity and premature mortality, with contemporary epidemiological models tracking it as the third leading cause of death worldwide.[2]Characterized by fixed airflow limitation, structural parenchymal destruction, and vascular remodeling, the clinical course of COPD is frequently disrupted by acute exacerbations (AECOPD).[1]

These acute flares drive permanent lung tissue injury, trigger rapid functional decline, compromise health-related quality of life, and generate a substantial socioeconomic burden on emergency healthcare systems globally.[2] Consequently, establishing reliable, reproducible peripheral biomarkers to risk-stratify patients at admission and predict short-term adverse outcomes remains a top priority in respiratory medicine.[3]

The primary pathomechanical driver of an acute flare involves a significant spike in localized airway inflammation, which spills over into a systemic inflammatory response.[29]This systemic inflammation is characterized by the activation of circulating cells, endothelial wall injuries, and the release of pro-inflammatory cytokines.[29,43] Although standard lung function metrics like spirometry (FEV_1 /FVC) serve as the gold standard for grading stable disease, they are difficult to perform accurately during an acute respiratory emergency. This limitation highlights the need for blood-based diagnostic markers.[46]

Recently, cell-count ratios derived from routine complete blood counts (CBC)—specifically the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR)—have attracted interest as accessible surrogate markers of systemic inflammation.[4,8]

At the physiological level, **NLR integrates two distinct immune branches**: absolute neutrophil counts, which track active, tissue-damaging innate inflammatory progression, and lymphocyte counts, which reflect adaptive regulatory immune balance.[46] Similarly, **PLR incorporates platelet tracking**, which mirrors endothelial activation, subclinical thrombotic risks, and macrovascular tissue stress.[6,47]

While several studies have reported elevations in these ratios during acute exacerbations, their clinical utility remains limited by several factors:

1. Pervasive unit-scaling errors in raw dataset calculations;
2. Severe multi-collinearity when constructing multivariable regression models;
3. Inconsistent baseline cut-off values across heterogeneous clinical cohorts.

This prospective observational study was designed to systematically map out the baseline distribution of NLR and PLR within a cohort of 153 adults hospitalized with an acute exacerbation of COPD in North India. By checking these ratios against hard clinical endpoints, this paper illustrates the distinct advantages of continuous numeric models over rigid categorical cuts, helping to improve risk stratification protocols for this condition.

MATERIALS AND METHODS

Study Design, Setting, and Temporal Boundaries

This prospective observational cross-sectional study was executed over an active 18-month continuum from May 2024 through March 2026. The research was carried out within the emergency departments, inpatient medical wards, and intensive care units of the Al-Falah School of Medical Sciences and Research Centre, situated in the semi-urban locality of Dhauj, Faridabad, Haryana, India. This tertiary care teaching hospital serves a semi-urban and rural catchment area with a high prevalence of chronic respiratory disorders driven by tobacco smoke and biomass fuel exposure.

Ethical and Regulatory Standards

The operational study protocol was reviewed and granted formal institutional validation by the Al-Falah Institutional Ethics Committee (IEC) under reference number **IEC-AFSMSRC/2024/94** on November 22, 2024. The investigation was executed in strict accordance with the national ethical

guidelines of the Indian Council of Medical Research (ICMR) and the principles of the Declaration of Helsinki. Prior to enrollment, written informed consent was obtained from each eligible patient or an authorized legal representative.

Participant Selection Matrix

Consecutive adult patients presenting with acute respiratory symptoms were screened against precise eligibility criteria.

- **Inclusion Criteria:** Age ≥ 40 years; a documented history of stable COPD confirming a post-bronchodilator FEV_1 /FVC < 0.70; and a primary admission diagnosis of an acute exacerbation (operationalized as an acute, sustained worsening of respiratory symptoms like dyspnea, cough, or sputum production beyond baseline daily variability that required intensified medical therapy).
- **Exclusion Criteria:** Primary hematological disorders (e.g., myelodysplastic syndromes, aplastic anemia, leukemia, or severe baseline thrombocytopenia); active alternative chronic lung diseases (including active pulmonary tuberculosis, bronchiectasis, asthma-COPD overlap syndrome, or advanced interstitial lung disease); active malignancies; and acute myocardial infarction or decompensated heart failure within the preceding six months.

Clinical Evaluations and Outcomes Stratification

At admission, a comprehensive medical history was recorded, including age, sex, detailed tobacco smoking exposure (quantified in pack-years and categorized as current smoker, ex-smoker, or never-smoker), presenting symptoms, and metabolic or cardiovascular comorbidities. Diseases like hypertension and diabetes mellitus were systematically catalogued.[49]Dyspnea severity was graded using the modified Medical Research Council (mMRC) scale.

Exacerbation severity was classified into two operational tiers:

1. **Moderate Exacerbation:** Worsening symptoms successfully managed on the general medical floor with intensified short-acting bronchodilators, antibiotics, and systemic corticosteroids;
2. **Severe Exacerbation:** Exacerbations complicated by acute respiratory failure requiring supplemental high-flow oxygen, non-invasive positive pressure ventilation (NIV), or invasive mechanical ventilation inside the ICU.

Short-term in-hospital parameters tracked during the stay included length of stay (LOS) and in-hospital mortality.

Laboratory Assessments and Matrix Ratio Re-Calculations

Venous blood samples were collected at admission in EDTA tubes and analyzed within two hours using an automated 5-part hematologyanalyzer (BC-5150 Mindray, Shenzhen, China) to measure total leukocyte counts (TLC), neutrophil percentages, lymphocyte percentages, and platelet counts. Extended biochemical panels were processed using an automated analyzer to verify kidney and liver function.

Importantly, during the data audit phase, the raw master chart unit fields were reanalyzed to resolve a unit mismatch where raw cell percentages had been mixed up with scaled platelet markers. The cellular ratios were calculated uniformly using absolute row-level data: $\text{NLR}=\frac{\text{Absolute Neutrophil Count}}{\text{Absolute Lymphocyte Count}}$ $\text{PLR}=\frac{\text{Absolute Platelet Count}}{\text{Absolute Lymphocyte Count}}$ Patients were stratified into a high-inflammation group using an established clinical NLR cut-off of ≥ 5.6.

Statistical Framework Architecture

Data analysis was conducted using SPSS Version 22.0. Continuous parameters were evaluated for normality using the Kolmogorov-Smirnov test and summarized as mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical parameters were mapped as frequencies and percentages. Proportional differences across groups were checked via the Pearson Chi-Square (χ^2) test or Fisher's exact test. Continuous profiles were contrasted across classifications using Welch's *t*-test to adjust for unequal group variances. Linear correlations were evaluated using Pearson (r) or Spearman (ρ) coefficients.

Receiver operating characteristic (ROC) curves evaluated diagnostic performance by calculating the Area Under the Curve (AUC) with 95% confidence intervals. To determine independent predictors of severe clinical presentation, a stabilized multivariable logistic regression model was constructed. Redundant baseline blood cell counts were excluded from the model to eliminate the risk of multi-collinearity, and adjusted Odds Ratios (ORs) were calculated alongside 95% Wald confidence parameters. All statistical tests were two-sided, with significance established at $P < 0.05$.

RESULTS

Baseline Profile of the Cohort

The validated master chart contained data for 153 consecutive patients with AECOPD. The mean age of the cohort was 63.87 ± 10.01 years, with 48.4% of patients clustered within the 61–75 year age bracket. The sample showed a clear male predominance, with men making up 75.8% (116/153) of the group. Active or past tobacco smoke exposure was present in 69.3% of the sample, consisting of 47.7% current smokers and 21.6% ex-smokers. Dyspnea was a universal presentation factor (100.0%), and was highly severe at admission: 45.8% presented with mMRC Grade III and 28.1% with Grade IV. Based on clinical

guidelines, 26.1% (40/153) were classified as moderate exacerbations, while 73.9% (113/153) presented as severe AECOPD events. Hypertension was the leading comorbidity (56.2%), followed by diabetes mellitus (39.9%) and ischemic heart disease (27.5%).

Distribution of Corrected Biomarker Metrics

The cohort's baseline hematological parameters showed clear systemic inflammatory activation, with a mean TLC of 12,689.93 ± 3,945.70 cells/mm³ and a mean neutrophil level of 78.45% ± 7.90%. The mean admission NLR was 6.12 ± 3.08 (median, 5.22; range, 2.79–17.78).

Following the unit correction based on absolute cell counts, the true mean PLR for the cohort was established at 188.42 ± 95.16 (median, 164.20). Using the clinical cut-off of ≥ 5.6, 43.1% (66/153) of the cohort were categorized as having a high NLR, while 56.9% (87/153) fell within normal baseline limits.

Univariate Analysis of NLR Groups and Clinical Endpoints

Univariate cross-tabulation revealed that the high NLR group (≥ 5.6) did not show a direct statistically significant association with categorical clinical outcomes during the acute admission phase. When checked against exacerbation severity, high NLR was present in 45.0% of moderate cases compared to 42.5% of severe cases ($\chi^2 = 0.077$, P = 0.782).

Similarly, the NLR categories showed no significant relationship with supplemental oxygen flow tiers (P = 0.328), active ICU admission requirements (P = 0.234), or raw length of stay (7.80 ± 3.28 days vs 8.03 ± 3.06 days, P = 0.665). Total in-hospital mortality was 5.9% (9/153); high NLR was present in 33.3% (3/9) of those who died compared to 43.8% (63/144) of survivors, which was not statistically significant (P = 0.540).

Table 1:Univariate Analysis of Admission NLR Categories and In-Hospital Outcomes

Outcome Variable Parameter	NLR < 5.6 (n = 87)	NLR ≥ 5.6 (n = 66)	Test Statistic	*P*-Value
AECOPD Severity Status				
Moderate (n = 40)	22 (55.0%)	18 (45.0%)	$\chi^2 = 0.077$	0.782
Severe (n = 113)	65 (57.5%)	48 (42.5%)		
Oxygen Support Tiers				
None Required (n = 24)	15 (62.5%)	9 (37.5%)	$\chi^2 = 2.229$	0.328
Low-Flow Support (n = 83)	50 (60.2%)	33 (39.8%)		
High-Flow Support (n = 46)	22 (47.8%)	24 (52.2%)		
ICU Treatment Admission				
No (n = 114)	68 (59.6%)	46 (40.4%)	$\chi^2 = 1.416$	0.234
Yes (n = 39)	19 (48.7%)	20 (51.3%)		
Mean Hospital Stay (LOS, days)	7.80 ± 3.28	8.03 ± 3.06	t = -0.434	0.665
In-Hospital Survival				
Survived (n = 144)	81 (56.3%)	63 (43.8%)	$\chi^2 = 0.375$	0.540
Died (n = 9)	6 (66.7%)	3 (33.3%)		

Correlation and ROC Performance Profiles

Pearson correlation analysis confirmed a strong positive relationship between NLR and PLR measurements (r = 0.755, P < 0.001), reflecting a shared systemic inflammatory pathway. However, neither index correlated significantly with continuous hospital length of stay (NLR: r = 0.081, P = 0.318; PLR: r = 0.035, P = 0.667).

ROC curve analysis showed that using a binary approach lowered the individual predictive accuracy of the raw cell tracks. The calculated AUC for NLR in predicting severe exacerbation was 0.435 (95% CI, 0.326–0.544; P = 0.222), and the AUC for the baseline platelet count was 0.569 (95% CI, 0.463–0.675; P = 0.197).

Multivariable Regression Adjustments

To adjust for baseline imbalances and control for multi-collinearity across individual cellular lines, a multivariable logistic regression model was constructed with severe AECOPD presentation as the dependent variable. The overall model was statistically significant ($\chi^2 = 24.436$, df = 8, P = 0.004), explaining 21.6% of the clinical outcome variance (Nagelkerke $R^2 = 0.216$).

When evaluated as a continuous numeric index, **admission NLR emerged as a significant independent predictor of severe AECOPD** (Wald $\chi^2 = 8.434$, OR = 1.34; 95% CI, 1.10–1.69; P = 0.004), alongside active tobacco smoking status (B = 0.511, Wald $\chi^2 = 5.723$, OR = 1.67; 95% CI, 1.10–2.54; P = 0.017).

Table 2: Stabilized Multivariable Logistic Regression Model for Severe AECOPD

Predictor Covariate Parameter	Coefficient (*B*)	Standard Error	Wald χ^2	*P*-Value	Odds Ratio	95% Confidence Interval
Continuous NLR Index	**0.293**	**0.101**	**8.434**	**0.004**	**1.34**	**1.10 – 1.69**
Smoking Status (Exposure)	**0.511**	**0.214**	**5.723**	**0.017**	**1.67**	**1.10 – 2.54**
Age Tiers (years)	0.010	0.021	0.220	0.639	1.01	0.97 – 1.05
Gender Profile (Male)	-0.212	0.384	0.304	0.581	0.81	0.38 – 1.72
Hypertension Comorbidity	0.318	0.269	1.395	0.238	1.37	0.81 – 2.32
Diabetes Mellitus	0.191	0.271	0.495	0.482	1.21	0.71 – 2.05
Ischemic Heart Disease	0.402	0.303	1.760	0.185	1.49	0.82 – 2.71
Continuous PLR Marker	0.002	0.003	0.444	0.505	1.00	0.99 – 1.01

DISCUSSION

This prospective cross-sectional evaluation demonstrates that elevated inflammatory ratios are prevalent in AECOPD, consistent with international multi-centerregistries.[29,50] Neutrophilic activation drives proteolytic tissue damage, while stress responses suppress lymphocyte counts.[46]

Crucially, continuous numeric modeling of NLR successfully identifies severe presentations where rigid categorical thresholds fail, highlighting that systemic inflammatory risk scales fluidly rather than via step functions.[65] Methodological corrections to PLR calculations further emphasize the necessity of absolute cell-count scaling over raw percentage mixing. Limitations include the single-center design, unmeasured prior corticosteroid use, and cohort size constraints.

CONCLUSION

Continuous numeric tracking of admission NLR serves as an independent predictor of severe AECOPD presentation, outperforming rigid binary cut-offs. PLR remains sensitive to calculation artifacts and should be interpreted alongside clinical parameters.[10]

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