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Assessing the Role of Neutrophil-To-Lymphocyte Ratio and Platelet-To-Lymphocyte Ratio to Evaluate the Severity of Chronic Obstructive Pulmonary Disease in Comparison With C-Reactive Protein

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KEYWORDS

Acute Exacerbation, Biomarkers, C-Reactive Protein, COPD, Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio.

ABSTRACT:

Background:

Chronic obstructive pulmonary disease (COPD) is a significant worldwide disease in terms of morbidity and mortality. Acute exacerbations (AECOPD) promote the development of the disease and a high level of healthcare demands. Although C-reactive protein (CRP) is a conventional measure of systemic inflammation, more affordable and accessible readily available hematological biomarkers are on the rise to help in immediate clinical evaluation.

Objective:

To consider the prognostic value of the Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) in patients with COPD compared to CRP.

Materials and methods:

This hospital-based, cross-sectional study recruited 142 study participants (n=71 in each group): the stable COPD (n=71) and the AECOPD (n=71) group. Spirometry (GOLD staging), clinical assessment and laboratory tests such as complete blood count and CRP were carried out. ROC curve analysis was used to calculate and compare NLR and PLR across the clinical states to determine the diagnostic accuracy.

Results:

During acute exacerbation, NLR and PLR were significantly higher than when the disease was stable (NLR:13.61 ± 4.90 vs. 2.47 ± 0.66; PLR: 255.18 ± 60.65 vs. 95.21± 27.17; $p < 0.001$). There were also positive relationships with a significant positive correlation between PLR and CRP (r=0.811) and NLR and PLR (r=0.911). It was found that ROC analysis has an excellent diagnostic performance in the classification of severity: NLR (AUC 0.963) at 6.28 and PLR (AUC 0.970) at 175, both with 93% sensitivity and 100% specificity. In addition, non-survivors with AECOPD had considerably higher mean NLR (23.29) and PLR (391.97) than those who survived.

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Conclusion:
NLR and PLR are cost-effective and universal inflammatory biomarkers that have prognostic sensitivity equal to that of CRP. By stratifying risks and triaging patients at greater risk of adverse outcomes and death, they can be incorporated into routine clinical practice, enabling rapid risk stratification and triage, especially in resource-limited environments.

INTRODUCTION:

COPD is one of the most enduring and debilitating respiratory diseases in various populations of the world due to the escalating airflow obstruction and chronic inflammation with severe effects on the functional capacity and the quality of life [1]. Though COPD was previously considered to be a disease of the airways, mounting data have demonstrated the systemic inflammatory character of the condition, with circulating immune markers increasing with pulmonary impairment and attacks [2].

With the global COPD burden expected to keep growing to pose a threat to over 200 million people and being among the leading causes of death, there is increased interest in finding easy, convenient, and efficient biomarkers to monitor disease activity, categorise disease severity, and foretell negative outcomes [3]. This requirement is especially applicable in acute exacerbations of COPD (AECOPD), which disproportionately contribute to hospitalization, worsening of lung function, and death [4].

In this clinical environment, the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) of the blood inflammatory ratios have gained considerable attention [5]. These ratios are composite images of an inherent and adaptive immune balance, which gathers the variations in neutrophil-mediated or platelet-mediated inflammatory activation and the decrease in lymphocyte-mediated control reactions [6]. As they are based on the routine complete blood counts, they do not demand any extra cost or specialized equipment to be measured, hence being especially useful in both the developed and limited-resource healthcare facilities [7].

A number of the studies that are incorporated in the current review support the potential of NLR and PLR as parameters that increase during inflammatory excess, particularly during COPD exacerbations. As an example, Bilir and co-authors proved that NLR rises remarkably during acute exacerbations and is strongly correlated with C-reactive protein (CRP), which is a common inflammatory biomarker; furthermore, the authors emphasized that high NLR indicates systemic inflammation in stable and exacerbated COPD conditions [8]. Their results indicated that NLR was positively correlated with CRP in the stable and AECOPD group, which supports the idea that neutrophilic and lymphocyte suppressive activity work in tandem with each other to reflect inflammatory load.

These observations have been furthered by other studies that compared NLR and CRP in healthy participants, stable COPD patients, and persons who experience acute exacerbations. According to Mahmoud et al., the gradients of rising NLR and CRP between the healthy controls and stable COPD and finally between the biomarkers and the AECOPD patients were distinct and showed that the gradients increased as the disease activity increased [9]. In their prospective analysis, NLR demonstrated good prognostic quality. In the hospitalized exacerbation cases, the values were significantly higher than in stable disease, and the NLR had a significant correlation with spirometric impairment [10]. CRP too showed a significant increase in exacerbation and confirms the systemic inflammatory measure related to deterioration of respiratory functions [11]. The researchers hypothesised that NLR with a cut-off of more than 3.26 has a high sensitivity and specificity to predict the occurrence of acute exacerbations, implying that it could be used as a first-line measure in identifying clinical deterioration early [12].

Although NLR and CRP have already been studied, the platelet-to-lymphocyte ratio (PLR) is now recognized as another marker that also indicates another aspect of systemic inflammation [13]. Besides their role in hemostasis, platelets are involved in both inflammatory signalling and immune modulation. They communicate with the leukocytes, discharge chemotactic mediators, and enhance the process of inflammation that defines the progression and exacerbations of COPD [14].

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The study of PLR is especially important due to the implication of platelet activation in COPD-related cardiovascular comorbidities and heightened thrombotic risk. The proposed assertion of a biological connection between platelet activity and systemic inflammatory burden.

The NLR and PLR significantly increased in AECOPD as compared to stable COPD patients in a study conducted by Sushma et al. Their results showed that the mean PLR in exacerbated cases (151.09) and stable patients (129.65) differ significantly and the CRP and procalcitonin levels increase significantly. In addition, PLR was negatively correlated with FEV1; thus, the higher the PLR levels, the greater the airflow limitation severity was [15]. This trend is comparable to that of NLR and supports the idea of PLR being an inflammation-related biomarker that is directly linked to the severity of the disease.

AIM:

To study the role of simple and inexpensive inflammatory indices like Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in COPD, as an early diagnostic predictor of severity of COPD when compared with C-Reactive Protein.

OBJECTIVES:

1. To study the role of Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) as inflammatory markers in assessing the severity of chronic obstructive pulmonary disease (COPD) in comparison with C-Reactive Protein (CRP).
2. To access the prognostic value of Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) in predicting in-hospital mortality among patients with acute exacerbation of chronic obstructive pulmonary disease.

METHODOLOGY:

Study design, setting, and duration:

This study is designed as a hospital-based, cross-sectional study conducted over a period of 18 months in the Department of Respiratory Medicine, Chettinad Hospital and Research Institute (CHRI).

Study population (Inclusion and exclusion criteria):

Patients aged above 40 years with a clinical diagnosis of **stable COPD** and **acute exacerbation of COPD (AECOPD)**, and individuals who provided informed consent to participate in the study and undergo necessary laboratory investigations were included.

Presence of comorbid conditions known to alter inflammatory markers, such as chronic liver disease, chronic kidney disease, autoimmune disorders, malignancies, or active non-pulmonary infections, history of recent major surgery, trauma, or hospitalization within the past four weeks, use of systemic corticosteroids, immunosuppressive drugs, or anticoagulant therapy that could significantly alter blood counts, pregnant or lactating women were excluded from the study.

Sampling technique and sample size:

A purposive sampling technique, where all eligible subjects who attended the outpatient and inpatient units within the study period were recruited.

A total of 142 patients were included in the study as it was predetermined by the researcher on the basis of feasibility and availability of the patients who were anticipated to attend the study site, and the number of cases who were supposed to be having COPD. This was sufficient to provide statistical comparison of stable COPD and AECOPD groups and to examine correlations between NLR, PLR, CRP, and severity of the disease. The representation of the participants in the two groups was sufficient to provide sufficient representation in order to compare it with the other sample and was statistically sound.

Study groups:

There were two groups of participants, depending on their clinical presentation, during the recruitment process:

Group 1: Stable COPD

The patients of this group were reviewed at a stable phase when they had not experienced exacerbation or altered treatment in the past four weeks. They were the controls of the inflammatory and hematologic status of COPD in the absence of acute attacks.

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Group 2: Acute Exacerbation of COPD (AECOPD)

This group included participants who came with an acute onset of COPD symptoms, of the nature of increased breathlessness, cough, or sputum. Such patients needed a treatment change and were offered a chance to test the change in NLR, PLR, and CRP in case of active inflammatory stress.

Procedure:

Patients visiting the Respiratory Medicine OPD and admitted in wards, ICU of the study setting were assessed in a structured way by standardized clinical and laboratory procedures. Demographic and clinical history were obtained after establishing eligibility according to inclusion and exclusion criteria. Physical examination was concerned with respiratory data like wheezing, breathing sounds, respiratory rate, and usage of accessory muscles. Spirometry was also done to categorize patients according to GOLD staging of stable COPD or to verify that they had obstructive patterns of AECOPD cases once the clinical possibility was achieved. After the clinical evaluation, aseptic collection of venous blood samples was carried out in order to conduct biochemical investigations.

A variety of demographic, clinical, and laboratory parameters used in the study are important to measure the severity of the disease and the relevance of the biomarkers.

1. **Demographic parameters:** Age, gender, smoking status (current, former, or non-smoker), and duration of illness.
2. **Clinical parameters:** Symptom profile, GOLD staging, presence of exacerbation, spirometric values such as FEV_1, FVC, and FEV_1/FVC ratio.
3. **Laboratory parameters:** Complete blood count including neutrophil count, lymphocyte count, platelet count, NLR, PLR, and CRP levels.
4. **Radiological parameters:** Chest X-ray findings, where applicable, to support diagnosis or rule out alternative causes.
5. **Exacerbation-related parameters:** Frequency of previous exacerbations, need for hospitalization, and severity of current episode.

These parameters enabled a comprehensive assessment of systemic inflammation and its correlation with the severity of COPD.

Statistical analysis:

Data were anonymized, coded, and entered into Microsoft Excel and analyzed using SPSS version 22.0. Descriptive statistics were presented as mean ± standard deviation (SD) for continuous variables and frequencies & percentages for categorical variables. **Independent t-test** and **Chi-square test** were applied to determine the association between demographic variables. To identify diagnostic accuracy and cut-off values that best predict exacerbations, receiver operating characteristic (ROC) curves were plotted to obtain diagnostic accuracy and optimal cut-off values of NLR and PLR. A p-value <0.05 was considered statistically significant.

Ethical consideration:

Ethical approval was obtained from the Institutional Human Ethics Committee of Chettinad Hospital & Research Institute before the commencement of the study (Ref no: IHEC-I/2639/24). All procedures were conducted after obtaining written informed consent, and confidentiality was maintained. Every laboratory experiment was conducted in line with safety and ethical requirements to protect the welfare of the participants. The research was least risky, and it included routine clinical studies that were conducted as a normal care of a patient.

RESULTS:

A total of 142 participants were recruited for the study.

Table 1: Distribution of socio-demographic profile of the participants (N=142)

Age distribution		
Age Group (Years)	**Stable n (%)**	**Exacerbated n (%)**
≤ 50	11 (15.5%)	5 (7.0%)
51-60	26 (36.6%)	14 (19.7%)
61-70	28 (39.4%)	35 (49.3%)
> 70	6 (8.5%)	17 (23.9%)
Total	71 (50.0%)	71 (50.0%)
Sex distribution		

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Sex	Stable n (%)	Exacerbated n (%)
Females	25 (35.2%)	22 (31.0%)
Males	46 (64.8%)	49 (69.0%)
Total	71 (50.0%)	71 (50.0%)

Table 1 presents the distribution of the socio-demographic profile of the participants. The 61-70 years formed 39.4% (n=28) and 51-60 years 36.6% (n=26) in the stable group and >70 years 8.5% (n=6). In the exacerbated group, 61–70 years formed 49.3% (n=35) and >70 years 23.9% (n=17), with ≤50 years 7.0% (n=5), indicating that the participants were predominantly in the 61-70 age category.

Regarding sex distribution, males accounted for 64.8% (n=46) and females 35.2% (n=25) among stable patients. Males were 69.0% (n=49) and females 31.0% (n=22) among exacerbated patients. Male predominance was observed in both groups, with a slightly higher male proportion in exacerbated cases.

Table 2: Occupational Distribution of the Study Population (N = 142)

Occupation	Frequency (n)	Percentage (%)
Bankers	3	2.1%
Casual Labour	6	4.2%
Driver	6	4.2%
Farmer	20	14.1%
Health Care Workers	5	3.5%
Home maker	38	26.8%
Hotel cook	7	4.9%
IT	5	3.5%
Office worker	7	4.9%
Other occupation	15	10.6%
Security	28	19.7%
Tailor	2	1.4%

Table 2 exhibits the distribution of occupation among the study participants. Occupation profile showed homemakers as the largest group (26.8%, n=38), followed by security personnel (19.7%, n=28) and farmers (14.1%, n=20). Other occupations formed 10.6% (n=15). Drivers and casual labourers were 4.2% each (n=6), while tailors were least represented (1.4%, n=2).

Table 3: Distribution of the exposure status of the study population (N=142)

Distribution by smoking		
Smoking status	**Frequency (n)**	**Percentage (%)**
Ever smoked	91	64.1%
Not smoked ever	51	35.9%
Total	142	100.00%
Distribution by biomass fuel exposure		
Biomass	**Frequency (n)**	**Percentage (%)**
No	77	54.2%
Yes	65	45.8%
Total	142	100.00%

Table 3 shows the distribution of study participants by exposure status. Smoking status revealed that a larger proportion of ever smokers (n=91) (64.1%) and non-smokers (n=51) estimated 35.9%. Therefore, almost two thirds of all the participants in the study were exposed to smoking. Biomass exposure was noted to be in 45.8% (n=65), and in 54.2% (n=77). Hence, nearly half of the study population had an exposure to biomass fuel.

Table 4: GOLD Severity Distribution by Clinical Group (N=137)

GOLD Stage	Stable n (%)	Exacerbated n (%)
Mild	28 (39.4%)	4 (6.1%)
Moderate	41 (57.7%)	14 (21.2%)
Severe	2 (2.8%)	47 (71.2%)
Very Severe	0 (0.0%)	1 (1.5%)
Total	71 (50.0%)	66 (46.47%)

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Table 4 compares the distribution of GOLD severity scores among the study population. In the stable group (n=71), moderate COPD prevailed (57.7%) (n=41) and mild COPD prevalence was the next highest (39.4% n=28), with severe COPD being the least prevalent (2.8%, n=2), and very severe being the least prevalent (0.0% n=0). Severe COPD was the most common in the exacerbated group (71.2%, n=47), then there was moderate (21.2, n=14), mild (6.1, n=4), and very severe (1.5, n=1).

Table 5: Distribution of laboratory parameters between groups (N=142)

Neutrophil-to-Lymphocyte Ratio (NLR)			
Group	**Mean**	**SD**	**p-value**
Stable	2.47	0.66	**< 0.001***
Exacerbated	13.61	4.90	
Platelet-to-Lymphocyte Ratio (PLR)			
Group	**Mean**	**SD**	**p-value**
Stable	95.21	27.17	**< 0.001***
Exacerbated	255.18	60.65	
C-Reactive Protein (CRP)			
Group	**Mean**	**SD**	**p-value**
Stable	5.79	2.31	**< 0.001***
Exacerbated	76.29	28.43	

*p-value < 0.05 – Statistically significant

Table 5 summarizes the distribution of laboratory parameters among the study population. The mean NLR of the stable group and exacerbated group was 2.47 ± 0.66 and 13.61 ± 4.90 respectively, and the exacerbation status of the former was significantly increased. The stable group had a mean PLR of 95.21 ± 27.17 and the exacerbated group had 255.18 ± 60.65; indicating the presence of higher values of PLR in exacerbated COPD. CRP of 5.79 ± 2.31 and 76.29 ± 28.43 in the stable and exacerbating groups respectively were highly significant and showed the picture of exacerbation with significantly high CRP. All the three parameters were statistically significant across both the groups ($p < 0.001$).

Table 6: Diagnostic Performance of Biomarkers for Severity Classification

Biomarker	**AUC**	**Cutoff**	**Sensitivity**	**Specificity**
NLR	0.963	6.28	93%	100%
PLR	0.970	175	93%	100%
CRP	0.975	25.06	94.4%	100%
Combined (NLR+PLR)	0.967	N/A	93%	100%

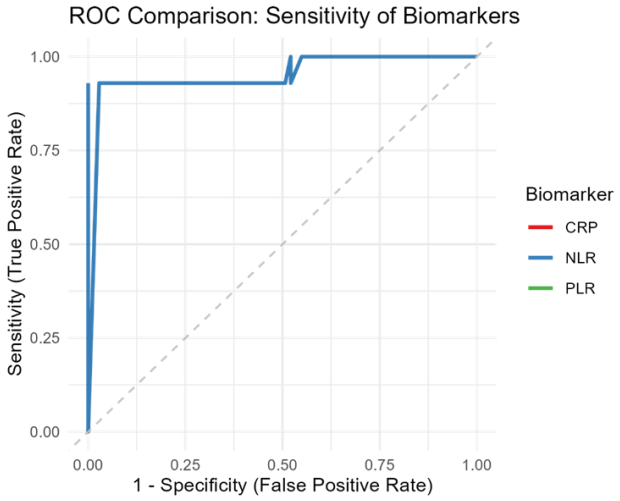

Figure 1: Diagnostic Performance of Biomarkers for Severity Classification

Table 6 & Figure 1 illustrates the Diagnostic Performance of Biomarkers for Severity Classification. Diagnostic accuracy showed high AUC values for all biomarkers: NLR AUC 0.963 (cutoff 6.28, sensitivity 93%, specificity 100%), PLR AUC 0.970 (cutoff 175, sensitivity 93%, specificity 100%), and CRP AUC 0.975 (cutoff 25.06, sensitivity 94.4%, specificity 100%). The combined model (NLR+PLR) showed AUC 0.967 with sensitivity 93% and specificity 100%.

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DISCUSSION:

Age group distribution by clinical status (stable vs exacerbated)

One-sample age distribution by clinical status (n=71 each) revealed a specific tendency of older age in exacerbated COPD. This trend indicates that the exacerbations in the present data were concentrated among the older population and is clinically reasonable due to the fact that an older age is related to lower physiologic reserve, increased exposure to infections, and a higher burden of comorbidities. Similar AECOPD cohorts described in the literature also depict older hospitalized patients; Hedhliabir et al. made use of mean age 66.9 ± 11.0 in hospitalized AECOPD [16], and Yao et al. used AECOPD admissions to predict mortality (no age-stratified percentages in the given summary) [17]. Combined, age enrichment during exacerbation in older age helps to be interpreted that the extremely elevated mean inflammatory ratios during exacerbations (NLR 13.61; PLR 255.18; CRP 76.29) may in part be due to more vigorous systemic inflammatory activation in a more vulnerable age group, as is evident in the larger body of evidence related to the AECOPD.

Sex distribution by clinical status (stable vs exacerbated)

There was sex distribution by clinical status (n=71 each) that showed that both groups were dominated by males. The very small increased male proportion in the exacerbated group could be due to increased exposure burden in men (especially smoking and occupational exposures) and could be a source of exacerbation vulnerability; but both groups maintained a fairly similar overall sex distribution, which would not explain differences in biomarkers between stable and exacerbated COPD merely on the basis of sex imbalance. This has been consistent with COPD biomarker evidence in which the evidence of inflammatory markers increases significantly during exacerbation even in relatively homogeneous sex cohorts. Kurtipek et al. reported marked increases in CRP, NLR, and PLR during AECOPD compared with stable disease in an all-male sample (CRP: 57.68 ± 58.49 vs 5.04 ± 6.65; NLR: 7.99 ± 5.72 vs 2.75 ± 1.11; PLR: 231.18 ± 141.36 vs 137.39 ± 65.42) [18], supporting that exacerbation-associated biomarker escalation is robust even without sex variation. Similarly, Şahin et al. reported highest NLR and PLR values during exacerbation compared with stable COPD and controls [19]. Therefore, the current study's sex distribution by group supports valid comparisons of biomarkers across clinical status and is consistent with published exacerbation-linked inflammatory behaviour.

Occupation distribution

Occupation distribution (N=142) showed homemakers as the largest category (26.8%, n=38), followed by security personnel (19.7%, n=28) and farmers (14.1%, n=20). This distribution is clinically relevant for COPD because occupation can reflect chronic exposure to dust, fumes, and biomass-related particulate matter, especially in farming and certain service occupations. Although the given comparator studies pay more attention to the behavior of biomarkers, than to occupation, the exposure scenario is the one that facilitates the possibility of systemic inflammations differences between the stable and exacerbated disease conditions. It is reproducibly reported in the literature that systemic inflammatory biomarkers, including NLR and PLR, increase in AECOPD in comparison to stable COPD [18,19], correlate with CRP [16,20], and are prognostic of negative outcomes, including mortality and ventilation requirement [17,21]. Occupational exposure diversity in this case can be a source of baseline disease burden and exacerbation triggers (infectious and non-infectious) and indirectly affect the biomarker distributions. Based on this, occupation results can be used to explain the cohort as having mixed exposures rather than tobacco disease as is consistent with actual COPD populations where systemic inflammation and exacerbation risk is indicative of combined inhalational exposures and comorbidities.

Smoking status distribution

A large burden of exposure was observed with the smoking status (N=142): ever smokers 64.1% (n=91) and non-smokers 35.9% (n=51). This is in relation to male dominance and contributes to a significant tobacco-based causation of COPD in this population group. Comparison evidence in AECOPD biomarker studies generally uses smoking related COPD groups; Kurtipek et al. [18] have analyzed COPD patients who have been classified as stable and AECOPD by GOLD 2013 and have reported that the inflammatory biomarkers are notably higher during an exacerbation (NLR: 7.99 ± 5.72

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vs 2.75 ± 1.11; PLR: 231.18 ± 141.36 vs 137.3). CRP-NLR correlation in COPD was also proved by Bilir et al. (stable r=0.436; exacerbation r=0.534), and high NLR was associated with more pronounced inflammation and worse lung function [20]. Thus, two-thirds of the cohort ever smokers are correlated with the inflammatory biomarker model as is the present study with very high exacerbation-state NLR (13.61), PLR (255.18), and CRP (76.29). External consistency with COPD biomarker literature is supported by the distribution of smoking, and the possible basis of the systemic inflammatory activation of exacerbation is a reasonable baseline.

Biomass fuel exposure

Biomass exposure was found in 45.8% (n=65) and non-existent in 54.2% (n=77), so it was found that almost half the cohort had a pertinent non-tobacco inhalational exposure. This is significant in COPD populations in which biomass exposure is a factor in inflammation of the airways, chronic bronchitis phenotype and exacerbation risk, especially in homemakers and rural occupation. Although the provided comparator studies focus on NLR/PLR/CRP specifically, but not biomass exposure, there is an overall consistency in the biomarker behavior observed in AECOPD when there is exposure to a variety of inflammatory triggers. In Kurtipek et al., exacerbations featured much greater CRP, NLR, and PLR compared to stable COPD [18], which Bilir et al. confirmed that NLR is associated with CRP and has poorer respiratory functioning [20]. Zinellu et al. concluded that NLR can be used as an indicator of negative outcome such as ventilation need and death in AECOPD and that PLR demonstrates the same tendencies with lower reliability [21]. Hence, it is likely to be expected that a cohort having had a significant biomass exposure will manifest systemic inflammatory elevations during exacerbations as in the case seen here (NLR 13.61; PLR 255.18; CRP 76.29 in exacerbated COPD). The results of biomass exposure add to findings of mixed exposures indicating that systemic inflammation in this cohort could be a cost-effective inflammatory marker regardless of whether exacerbation pathways are tobacco-induced or biomass induced airway damage.

GOLD severity distribution by clinical group

GOLD stage showed significant variations among standard and worsened clinical conditions. The difference in the denominator (enhanced mentioned in other places as n=71) is due to the exclusion of five participants who died and therefore could not be assessed for GOLD severity staging. However, the trend is very strong on the severity enrichment in exacerbations. It is consistent with biomarker literature: Bilir et al. demonstrated that higher NLR was associated with lower respiratory performance and increased inflammation [20], and Hedhliabir et al. associated higher NLR/PLR with poorer physiologic and ventilation status [16]. Zinellu et al. concluded that invasive ventilation and mortality risk in AECOPD are predicted by NLR [21]. Thus, the current severity distribution can be interpreted to suggest that the extreme inflammatory biomarkers in exacerbations are not accidental laboratory results only, but rather indicate a more severe disease subset, which has been previously shown to have inflammatory ratios that increase with COPD severity and outcomes.

NLR comparison (stable vs exacerbated)

NLR showed a marked increase during exacerbation: 2.47 ± 0.66 in stable COPD versus 13.61 ± 4.90 in exacerbated COPD ($p < 0.001$). This large separation indicates strong discriminatory potential of NLR for identifying exacerbation-associated inflammation. Kurtipek et al. reported NLR 7.99 ± 5.72 in AECOPD versus 2.75 ± 1.11 in stable COPD (p=0.001) [18]; the stable-state NLR in the present study (2.47) is similar to Kurtipek et al. (2.75), while the exacerbation-state NLR is substantially higher (13.61 vs 7.99), suggesting a more intense inflammatory burden or more severe exacerbation spectrum. Bilir et al. showed CRP-NLR correlation in both stable (r=0.436) and exacerbations groups (r=0.534) and that high levels of NLR were associated with lower levels of FEV1 [20], which supports the use of NLR as a severity-related one. In AECOPD, Yao et al. found that NLR cutoff 6.24 predicts hospital mortality (AUC=0.803) [17]. The ROC-based cutoff used in the study under analysis (6.28) fits the mortality threshold zone by Yao et al. [17] well, which makes the plausibility of the cutoff range as a means to find clinically significant risk. All in all, the current NLR results are in line with COPD evidence that NLR increases during the exacerbation, is correlated with CRP, and has prognostic importance.

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PLR comparison (stable vs exacerbated)

PLR rose significantly in exacerbated COPD: in stable COPD it was 95.21 ± 27.17 and in exacerbated COPD it was 255.18 ± 60.65 ($p < 0.001$). Such near-threefold increase is a good indicator of a high inflammatory signal which is sensed by PLR during exacerbation. Kurtipek et al. reported PLR 231.18 ± 141.36 in AECOPD versus 137.39 ± 65.42 in stable COPD (p=0.001) [18]. The current exacerbation PLR is of the same magnitude as those values (255.18 vs 231.18), and the stable PLR is smaller (95.21 vs 137.39), which leads to the conclusion that there is more separation in clinical states among this cohort. According to Sahin et al., the PRL was increased during stable COPD and the greatest during exacerbation and CRP and PLR had a positive association [19], indicating that PLR is a suitable inflammatory marker during COPD progression/exacerbation. Yao et al. reported PLR was higher in non-survivors (PLR 207.21 ± 148.47) and combining NLR/PLR/CRP improved prognostic accuracy [17]. The present study similarly showed higher PLR among deaths in exacerbated COPD (391.97) versus survivors (244.82), reinforcing PLR association with worse outcomes. In the current study, the authors found that PLR is associated with an extended hospital stay, which was also reported by Hedhliabir et al., who reported that the highest NLR/PLR was in the ventilated patients [16], who received ventilatory support. Overall, the PLR findings support its role as a practical, CBC-derived inflammatory index comparable with CRP-linked inflammatory behavior reported in COPD literature.

CRP comparison (stable vs exacerbated)

CRP showed a drastic increase in the case of exacerbation: 5.79 ± 2.31 in stable COPD compared to 76.29 ± 28.43 in exacerbated COPD ($p < 0.001$). This intensity facilitates a vigorous response of acute-phase inflammatory in exacerbations. Other works, such as Kurtipek et al., demonstrated a statistical significance of CRP of 57.68 ± 58.49 in AECOPD compared to 5.04 ± 6.65 in stable COPD (p=0.001) [18]. The stable CRP of the current study (5.79) is very close to that of Kurtipek et al. (5.04), whereas the exacerbation CRP is higher (76.29 vs 57.68), which indicates a greater amount of the inflammatory burden in the exacerbated group. Bilir et al. have shown strong correlation between CRP and NLR in stable and exacerbation COPD groups (r=0.436 and r=0.534) [20], and that CRP is correlated with hematologic ratios (Sahin et al., 2017) which strengthens the findings that CRP acts in parallel with hematologic ratios [19]. The same applies to the non-COPD inflammatory conditions: Lee et al. found CRP-NLR correlation (r=0.4, p<0.001) [22], and Ozgonul et al. found CRP-NLR correlation (r=0.461, p=0.002) [23]. Combined, the current CRP findings confirm the anticipated exacerbation-related inflammatory increase, and justifies the interpretation of NLR/PLR as cost-effective inflammation proxies, which change in the same direction as CRP in instances of acute inflammation.

Diagnostic performance (ROC) for severity classification

All biomarkers had a good prognostic performance. NLR had a cutoff of 6.28 and AUC 0.963 (sensitivity 93%, specificity 100%), PLR had a cutoff of 175 and AUC 0.970 (sensitivity 93% and specificity 100%), and CRP had a cutoff of 25.06 and AUC 0.975 (sensitivity 94.4 and specificity 100%). Combination model (NLR+PLR) was 0.967 (AUC) (sensitivity 93% specificity 100%). These findings suggest almost un-biased discrimination in this sample and that CBC-derived ratios were similar to CRP. Kurtipek et al. observed NLR as the most (AUC 0.88) and PLR (AUC 0.74) highest diagnostic discriminators of AECOPD [18], but again may be explained by greater separation between the stable and exacerbated distributions of the biomarkers (stable NLR 2.47 vs exacerbated 13.61; stable PLR 95.21 vs exacerbated 255.18). According to Yao et al., the NLR cutoff of mortality prediction is 6.24 (AUC 0.803) [17], very close to the current NLR cutoff of 6.28 which indicates the plausibility of this range. In their model, Ardestani and Naeini found that NLR was a good diagnostic performance is severity classification in AECOPD and better than CRP and with 83% and 93% sensitivity and specificity respectively at NLR cutoff 2.3, demonstrating that optimal cutoffs vary with endpoint and comparator [24]. In general, current ROC findings indicate that NLR and PLR are viable and effective biomarkers in the classification of severity, in addition to CRP.

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STRENGHTS:

The research has a number of significant strengths that make its findings more credible and useful in clinical practices. The sample size (N=142) is a fairly powered dataset to compare the inflammatory indices of the patients in the stable versus exacerbated sampling, and the balanced distribution of 71 patients in both stable and exacerbated groupings enhances comparability and removes imbalance-related bias in the group analysis. Diagnostic performance analysis also enhances the study as it yields clinically interpretable thresholds with high levels of discriminative ability (NLR cutoff: 6.28, AUC: 0.963; PLR cutoff: 175, AUC: 0.970; CRP cutoff: 25.06, AUC: 0.975) and allows risk stratification to be applied in the clinical setting.

LIMITATIONS:

Despite its strengths, there are some limitations that should be taken into account when interpreting the results of the study. To begin with, the study design and analysis is highly observational and hence restricts causal conclusions. Also, the measurement of biomarkers was evaluated in the form of group means and the presence of active infection type, effects of medications (including systemic corticosteroids), recent use of antibiotics, nutritional status, or comorbid inflammatory conditions were not thoroughly adjusted, which could affect the values of NLR, PLR, and CRP. Lastly, although the study assessed the severity classification diagnostic accuracy, multivariate models that combined clinical parameters and biomarkers were not provided, which can further explain incremental value in real-world decision-making.

CONCLUSION:

The Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) are both inflammatory markers that are very cost-effective and effective in tracking the progression and acute exacerbation of COPD. These biomarkers are strongly linked with the known indicators such as CRP and correlate with the systemic burden of inflammation in relation to progressive GOLD stages and smoking history. Interestingly, NLR is superior in terms of prognostic values to determine a risk of mortality and length of hospitalization. Considering their prognostic specificities and availability, the inclusion of NLR and PLR into the everyday clinical model can contribute greatly to the progress in patient tracking and triage. Finally, it is possible to use these ratios to make more interventions in time and to adapt the medical treatment to severe disease progression.

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